

血 Hematology 血



 Histology

 **Biochemistry**

 Pathology

 Pharmacology

 Physiology

 Microbiology

 Handout

 **slide 5a**

 Sheet

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 Lecture number :

 Done BY :



HETEROGENITY OF HEMOGLOBIN

- I. DEVELOPMENTAL
- II. MINOR-COMPONENT
- III. GENETIC

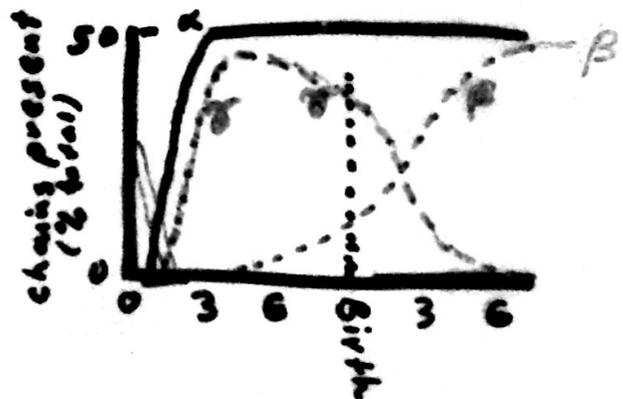
DEVELOPMENTAL

- Embryonic $\epsilon_2 \epsilon_2$
 $\alpha_2 \epsilon_2$

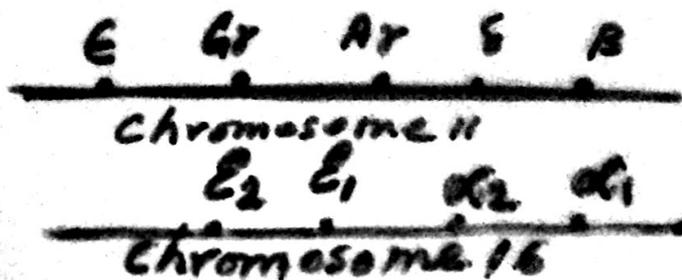
- Fetal Hb HbF

$\alpha_2 \gamma_2$
 - HbF differ from HbA a.a. sequence
 in 37 a.a.

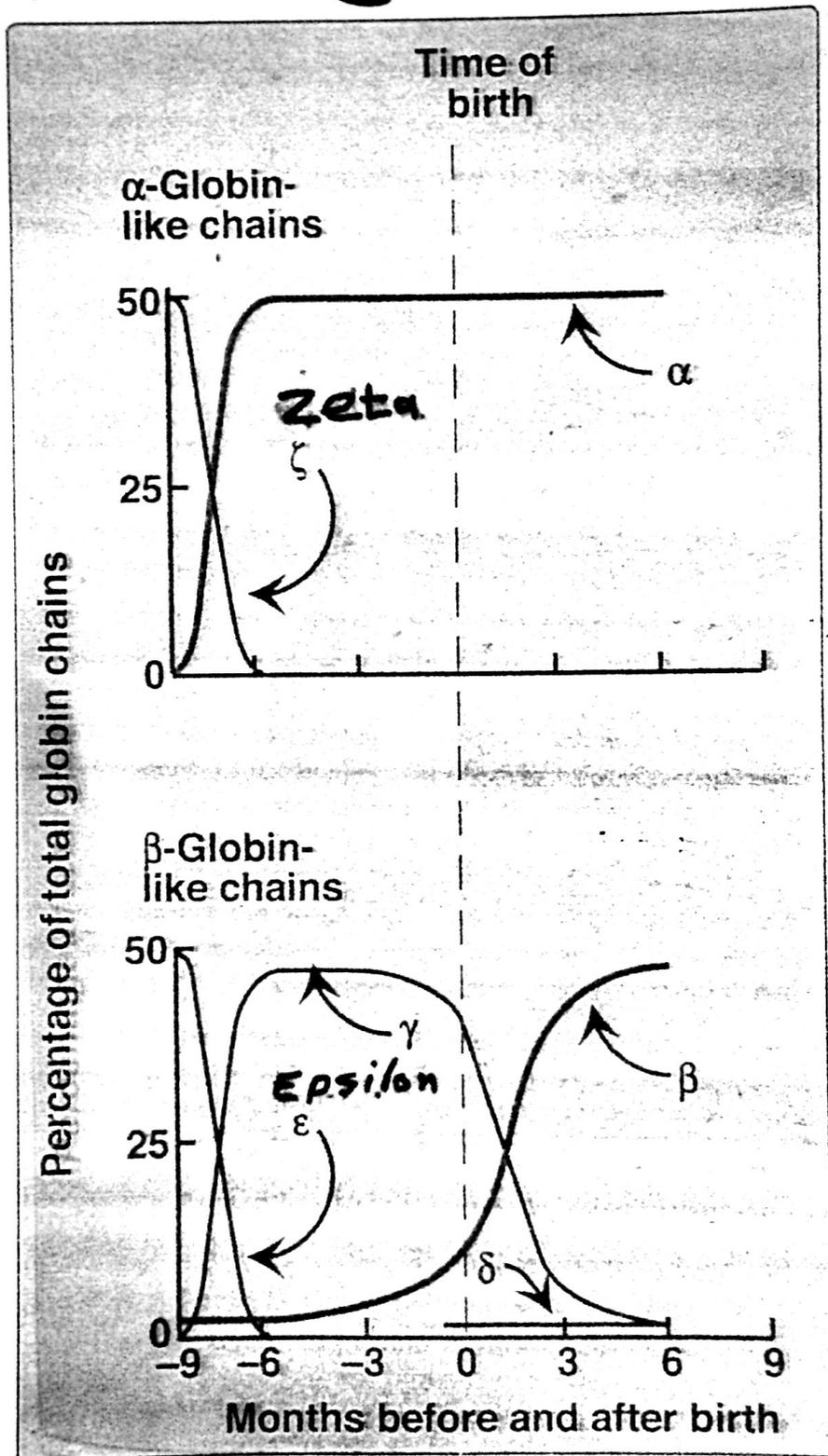
- 2,3-BPG binding
- Affinity for O₂



- Adult Hb. — HbA > 90%
 $\alpha_2^A \beta_2^A$



Developmental changes in Hemoglobin



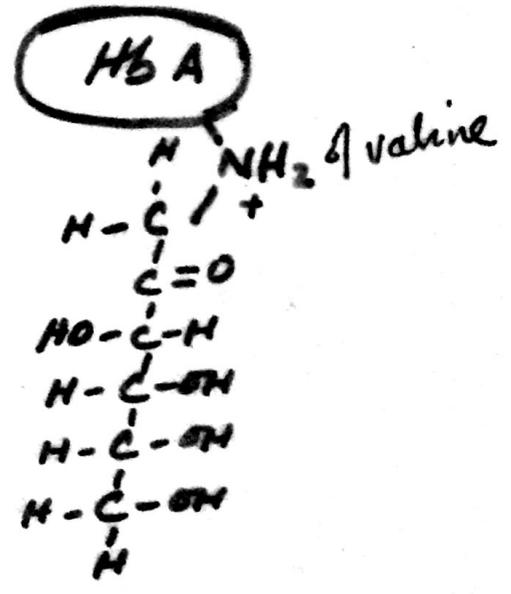
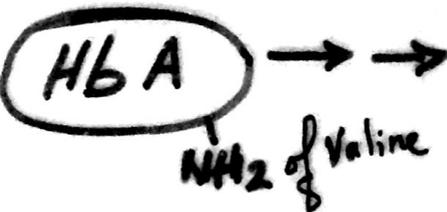
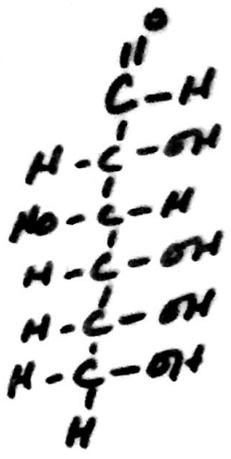
II Minor Component Hemoglobins

- Hb A₂ α₂ δ₂ 2.5%
appears about 12 weeks after birth

- Hb A_{1c} 5%

Glucose + N-terminal amino groups
of the β-chain (Val²)
↓ Non-enzymatic

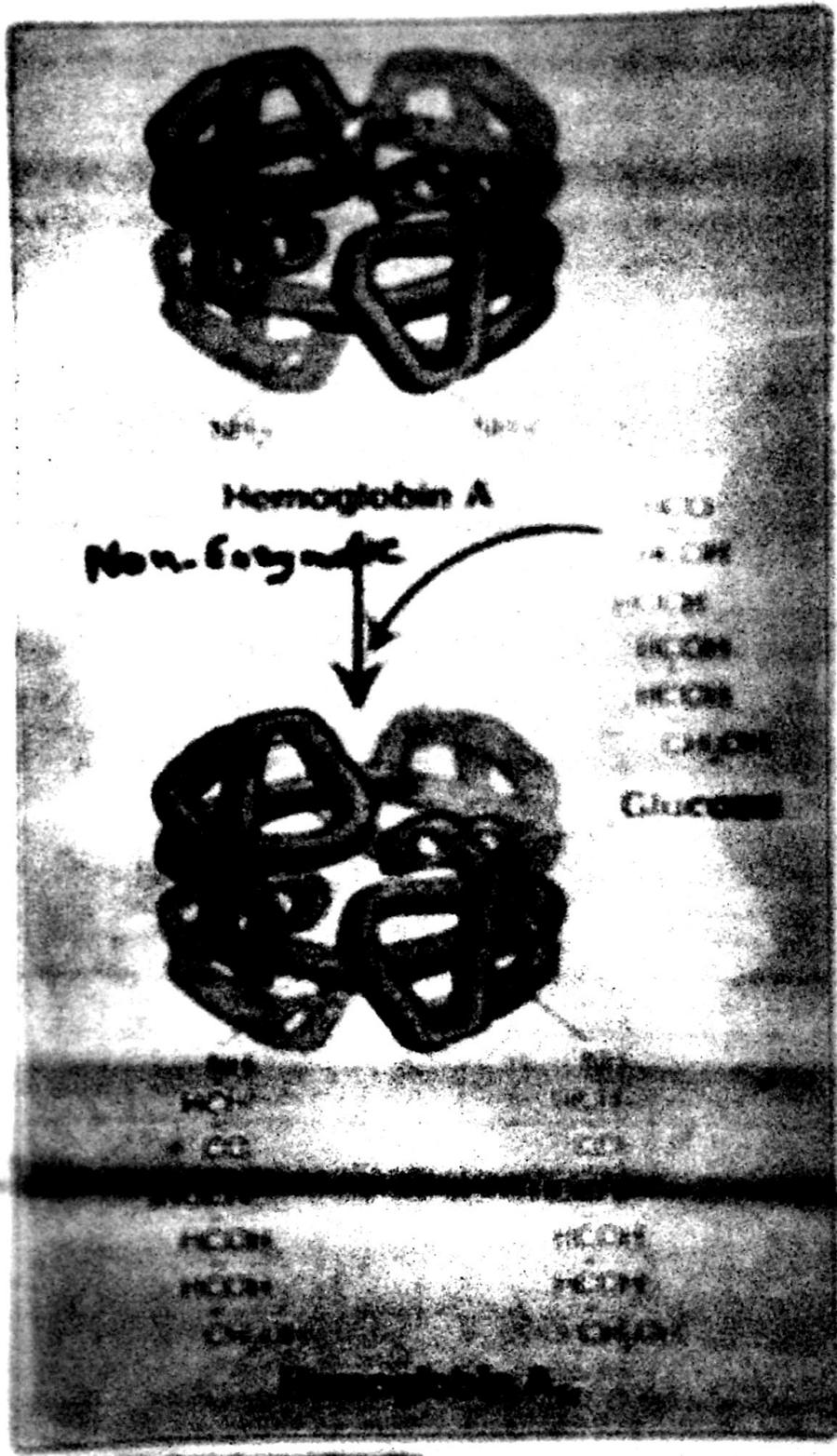
Hb A_{1c}



- Hb A_{1c} conc. is proportional to glucose conc. in blood.

- Hb A_{1a} } G-6-P + Fru-1,6-diP
Hb A_{1b} } ~ 1%

Glycosylated (Glycated) Hb HbA1c



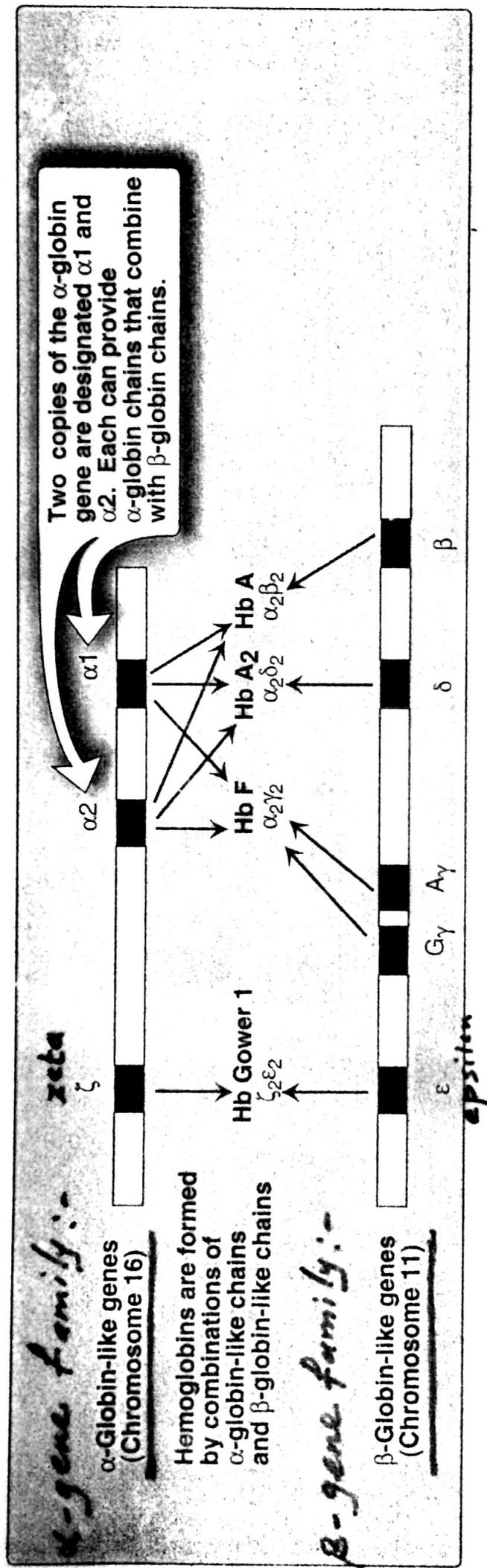
Minor Hemoglobins

3a

Normal Adult Human Hemoglobin Variants

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%– 6 %

Organization of the Globin genes



alpha-gene family:-
alpha-Globin-like genes (Chromosome 16)

Hemoglobins are formed by combinations of alpha-globin-like chains and beta-globin-like chains

beta-gene family:-
beta-Globin-like genes (Chromosome 11)

- Hemoglobinopathies
 - 1- Abnormal Hb structure
 - 2- Synthesis of insufficient quantities of normal hemoglobins

Molecular Pathology of Hemoglobin ^{56,}

- Structural changes may lead to a change in any of the following:-

- Solubility

e.g. HbS, HbC

- Methemoglobinemia

- Unstable Hb

- O₂-affinity

- The Regional changes

I. Altered Exterior

Nearly all are harmless

Exceptions:-

HbS, HbC

Africa

HbE

Ceylon &
Malaysia

; Hb Punjab

India &
Pakistan

II Altered Active site

Substitution allowing $Fe^{2+} \rightarrow Fe^{3+}$

Methemoglobinemia

e.g. HbM_{Iwate} $\alpha^{87} His \rightarrow Tyr$; $HbM_{HydePark}$ $\beta^{92} His \rightarrow Tyr$
Proximal His

also distal His

HbM_{Boston} $\alpha^{58} His \rightarrow Tyr$; $HbM_{Saskatoon}$ $\beta^{63} His \rightarrow Tyr$

III Unstable Hb

Altered tertiary structure

↳ denatured \rightarrow ppt \rightarrow Heinz bodies

- e.g. substitution of Pro to an amino acid within α -helical segment
- or: substitution by a large a.a. or small to make a contact
- or: charged or polar within domain

IV Altered Affinity

5b3

Altered quaternary structure

↓
Decreased Affinity Increased Affinity
(Lower P₅₀)

- e.g.
- Point of contacts between subunits
 - BPG binding sites
 - H⁺ binding site
e.g. Hb Cowtown P^{B146His} → leu
which is responsible for Bohr effect (50%)
which destabilize T state → ↑R & ↑affinity

Table 4.1

Amino acid substitutions in mutant hemoglobins

Mutant Hemoglobin ^a	Position Number ^b	Normal Residue	Substitution
α Chain			
G ^{Honolulu}	30	Glu	Gln
G ^{Philadelphia}	68	Asn	Lys
I	16	Lys	Glu
M ^{Boston}	58	His	Tyr
Norfolk	57	Gly	Asp
O ^{Indonesia}	116	Glu	Lys
β Chain			
C	6	Glu	Lys
D ^{Punjab}	121	Glu	Gln
G ^{San Jose}	7	Glu	Gly
E	26	Glu	Lys
S → Zurich	6	Glu	Val
	63	His	Arg

^aThe hemoglobins are often named for the cities where they were first discovered.

^bThe numbering for an amino acid position begins at the N-terminus.

Altered Active Site:-

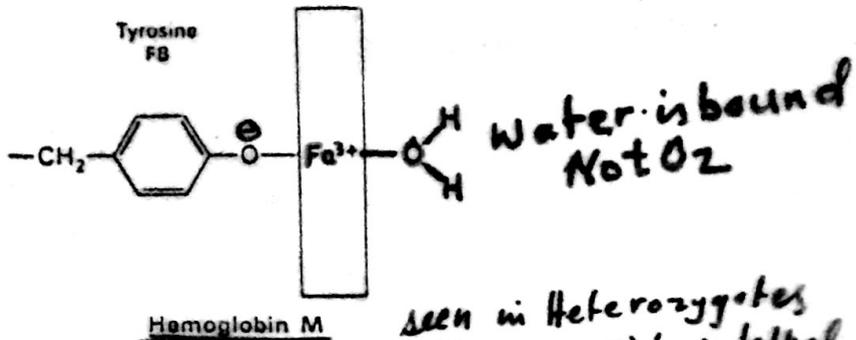
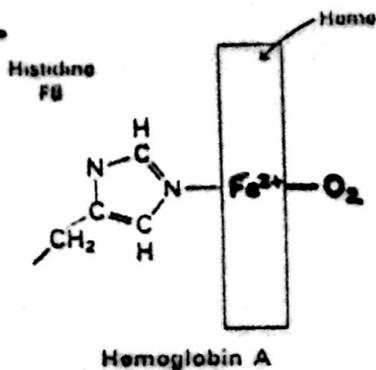


Figure 7-53
Substitution of tyrosine for the proximal histidine (F8) results in the formation of a hemoglobin M. The negatively charged oxygen atom of tyrosine is coordinated to the iron atom, which is in the ferric state. Water rather than O₂ is bound at the sixth coordination position.

Altered Tertiary Structure:-

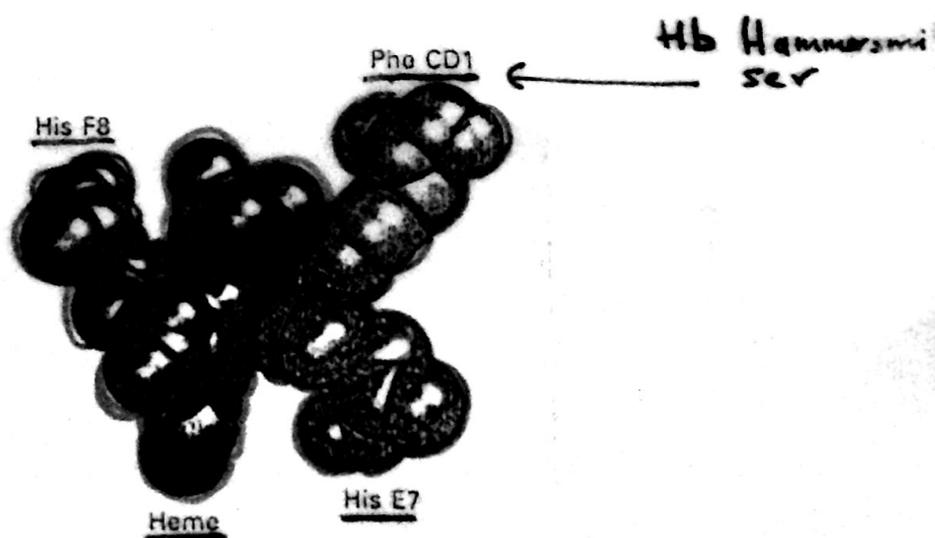
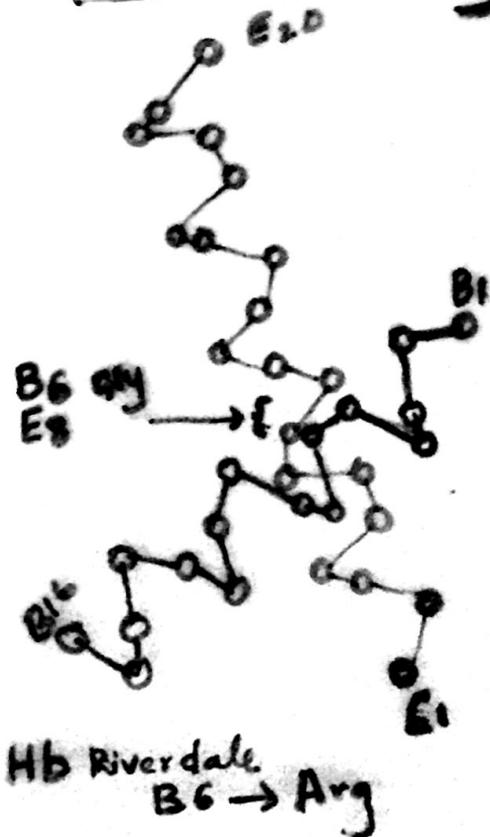


Figure 7-54
Location of phenylalanine CD1, in normal hemoglobin. The aromatic ring of this residue is in contact with the heme. In hemoglobin Hammersmith, serine replaces this phenylalanine residue; this markedly weakens the binding of heme.