HAEMOGLOBIN STRUCTURE AND FUNCTION

DR.OKINYI FREDRICK
CONSULTANT PATHOLOGIST
Department of Haematology and Blood Transfusion

MbChB 3

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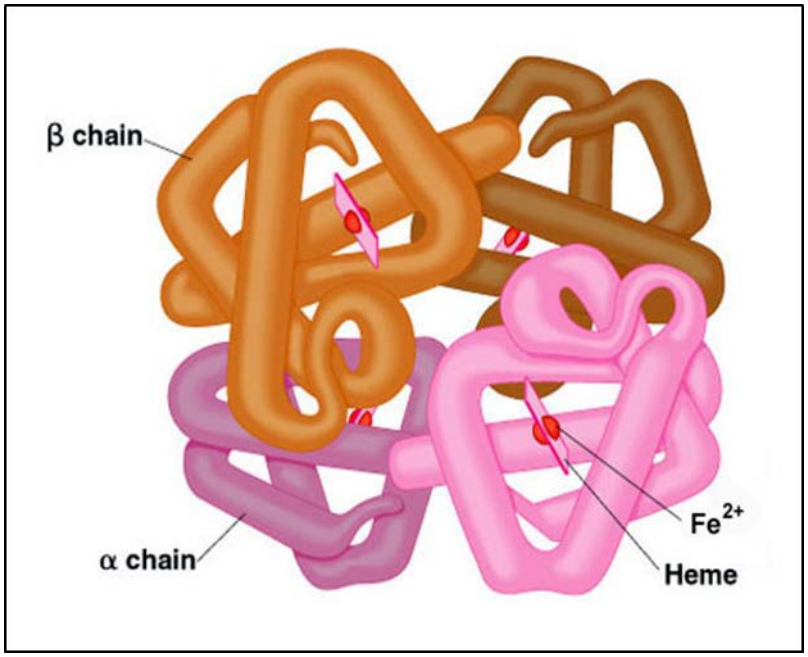
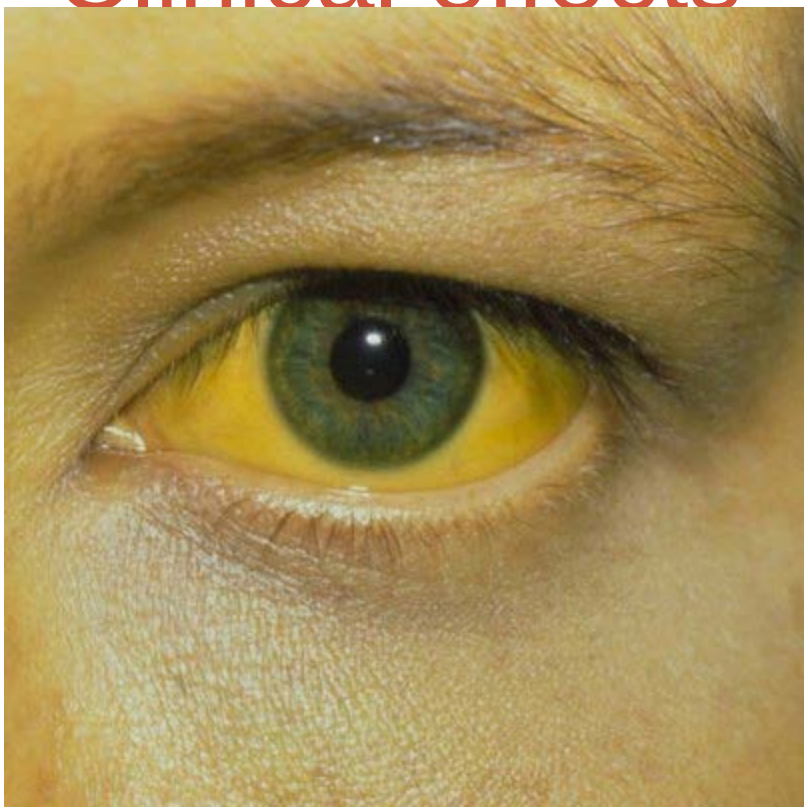
Objectives

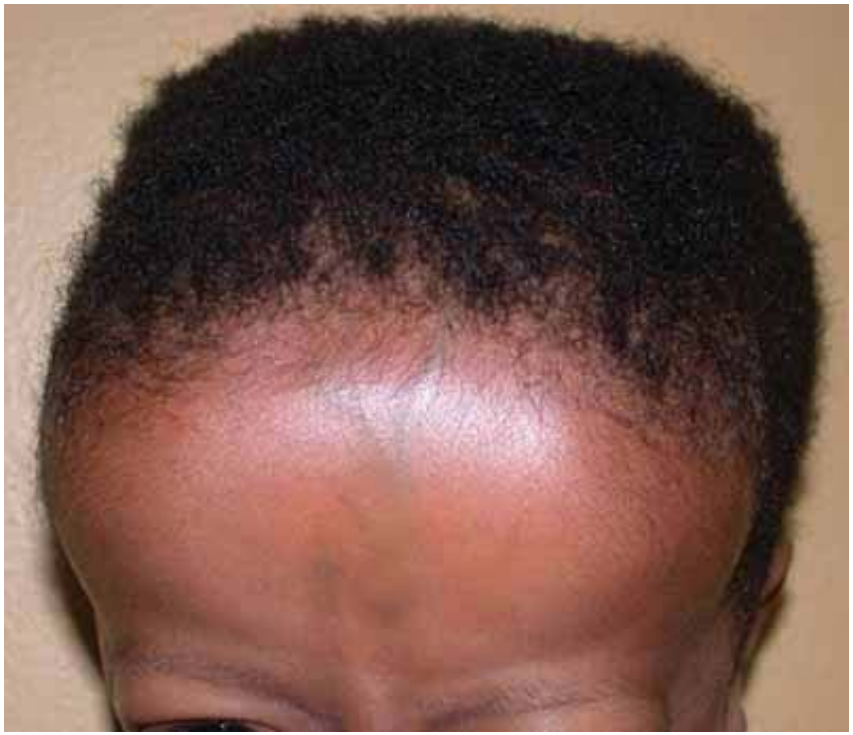
- Describe detailed structure of Haemoglobin
- Outline the changes in haemoglobin during embrology and development
- Describe the functions of Haemoglobin in the body
- List various abnormal Haemoglobin

Hemoglobin structure –Questions



Clinical effects





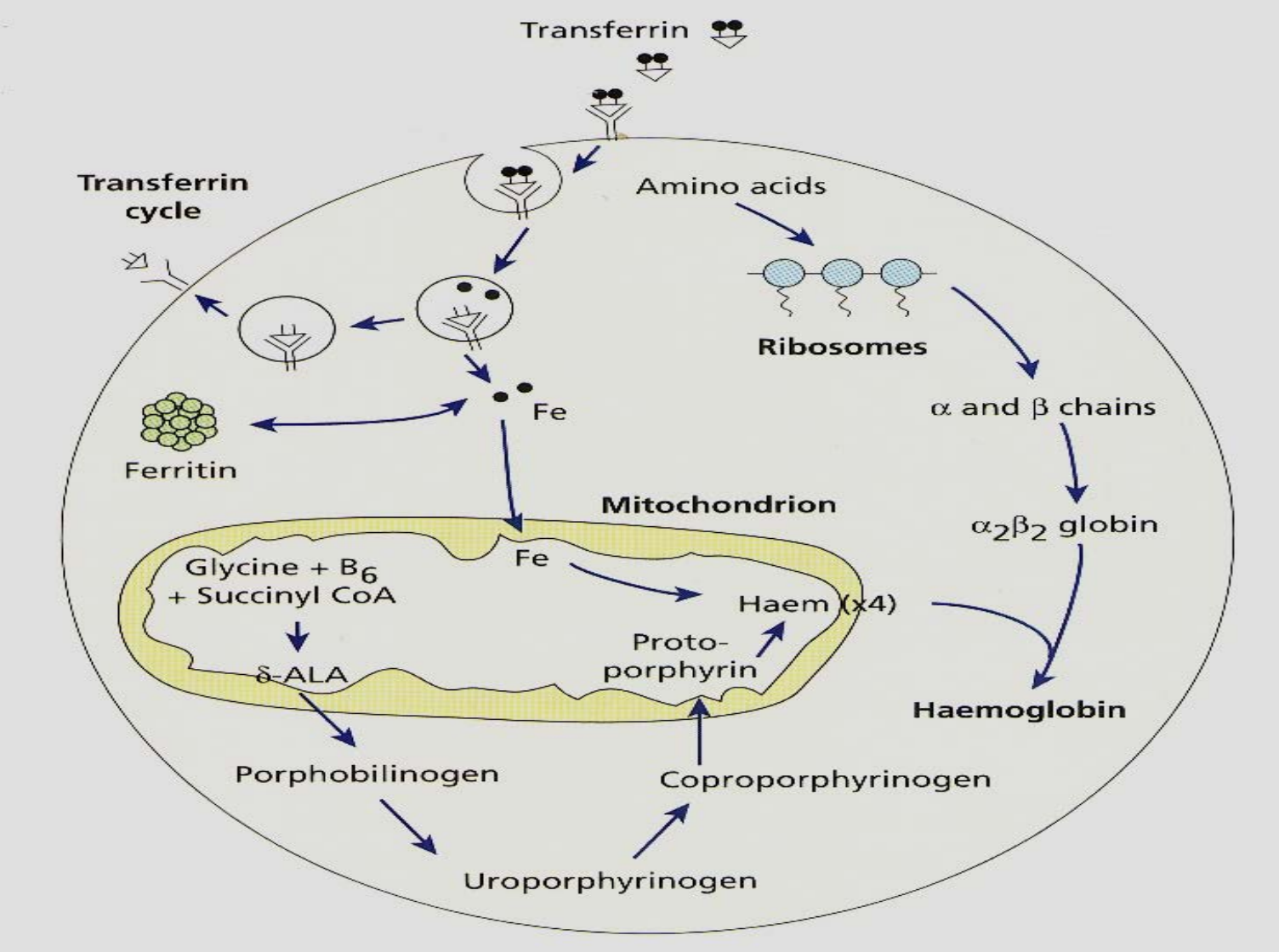
- 1.describe the structure of haemoglobin?
- 2.outline the various changes of haemoglobin during development and haemopoiesis?
- 3.Which chromosomes code for globulin chains
- 4.Review of heamoglobin metabolism-Jaundice
- 5.lists the funtions of haemoglobin and factors that affect its function in response to oxygen dissociation curve?
- 6..Whats the difference bet haemoglobin derivatives and abnormalities/types
- 7.classify the heamoglobinopathies

Introduction

- The hemoglobin are red globular proteins which have a molecular weight of about 64,500 and comprise almost one third of the weight of a red cell.
- is a **hemoprotein** only found in the cytoplasm of erythrocytes (ery)
- transports O2 and CO2 between lungs and various tissues
- normal concentration of Hb in the blood:
- It's a hemoprotein that contains heme **Hemoproteins include:**
- Hemoglobin (Hb)Myoglobin (Mb),,Cytochromes ,Catalases (decomposition of 2 H2O2 to 2 H2O and O2),Peroxidases
- physiological level varies with age ,sex, gender, geographical location
- in:
- Female: 11.5 – 16.5 g/dl
- Male: 13.5 – 18 g/dl
- Full term 13.6 – 19.6 g/dl
- 1 year: 11 – 13g/dl
- 10 – 12 years: 11.5 – 14.8g/dl

- Each rbc has 640million molecules of haemoglobin
- It has haem synthesized in the mitochondria and globulin chain which is synthesized in the polyribosomes- well cordinated.
- The synthesis starts in proerythroblast stage- 65% erythroblast and 35% reticulocyte stage
- The synthesis requires iron, vitamin B and other cofactors
- Iron is required for heme synthesis

Synthesis of Haemoglobin

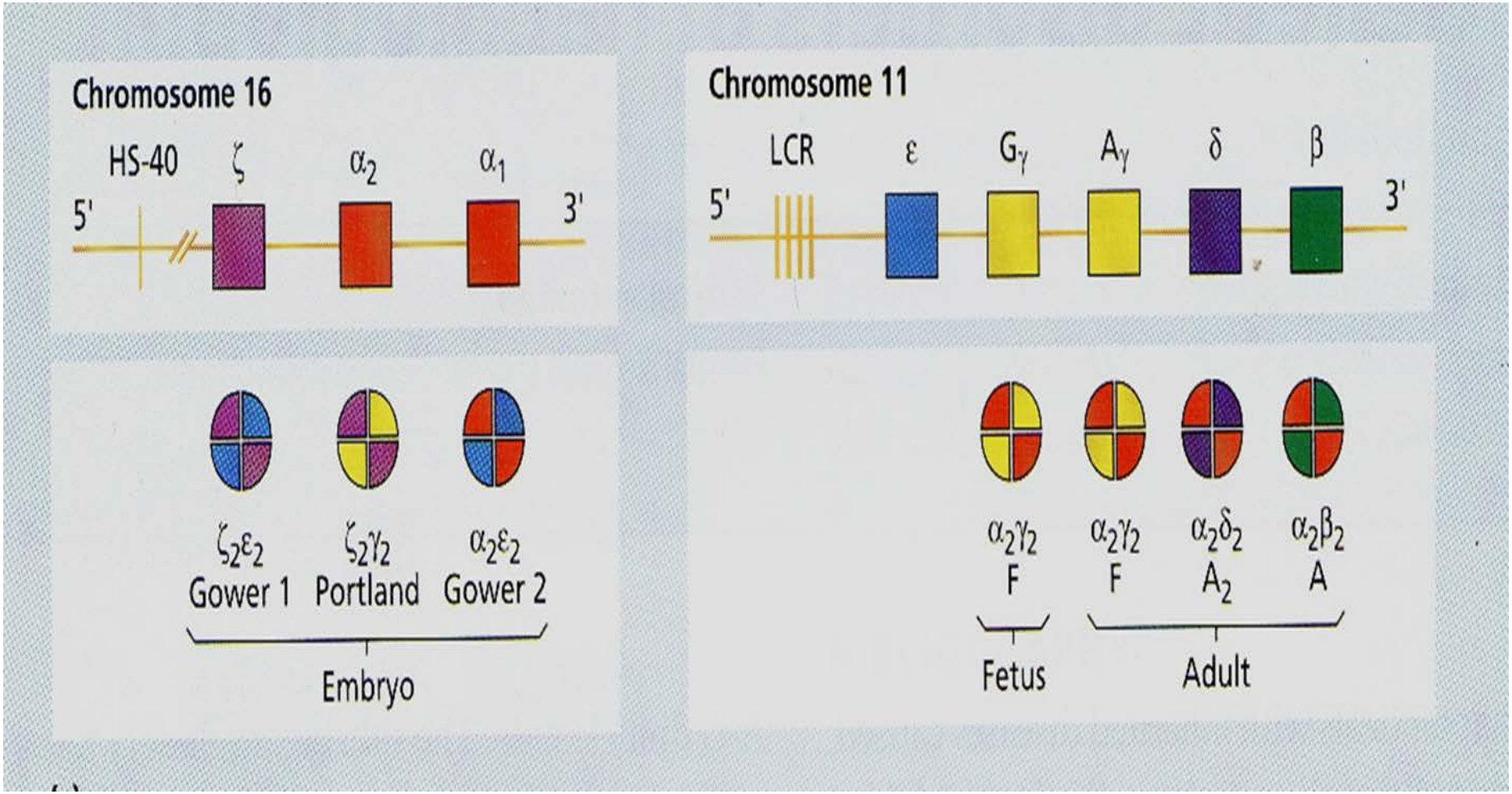


Globin synthesis, starts at 3rd week of gestation

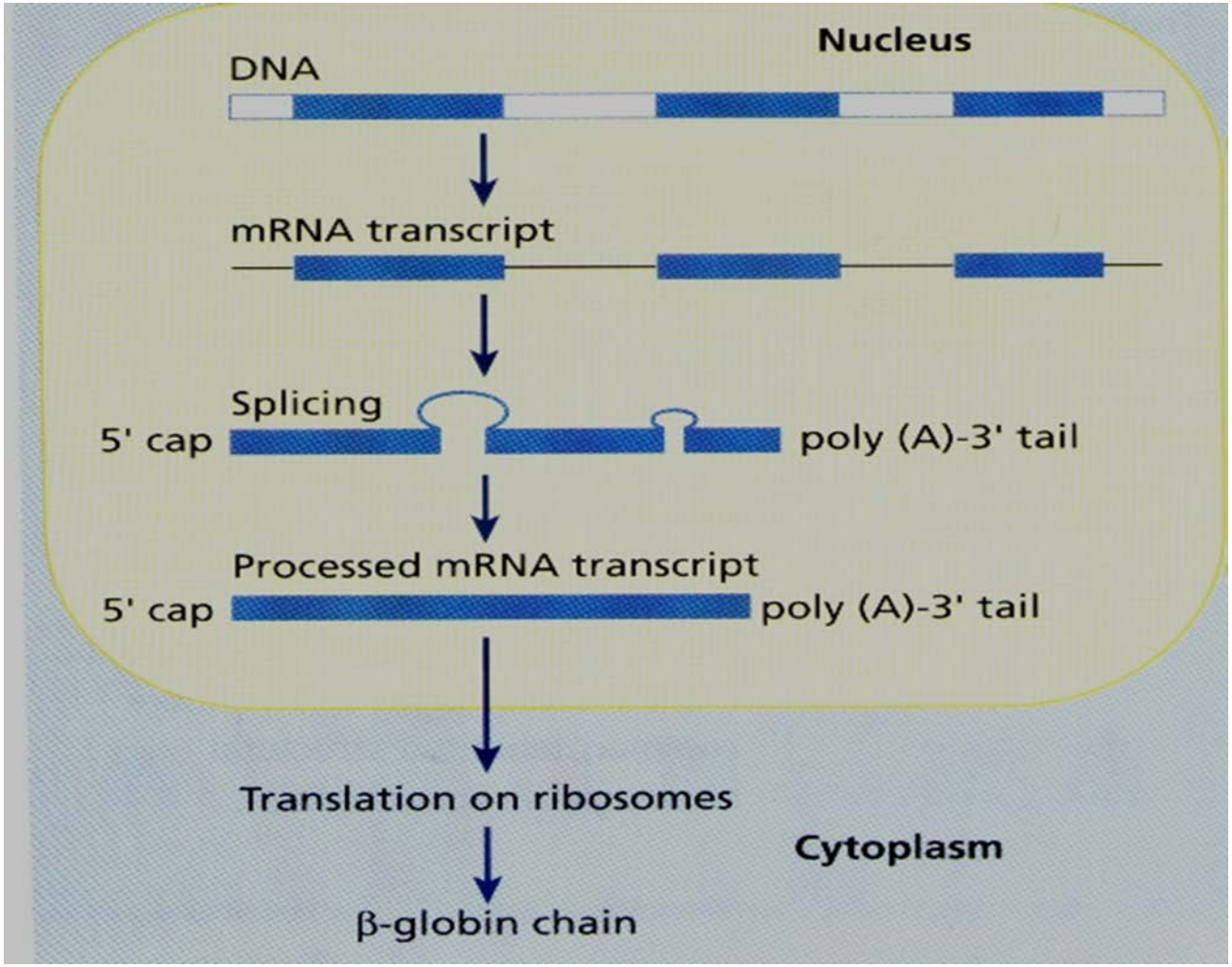
- Embryonic
  - Haemoglobin Gower I (ζ2ε2)
  - Haemoglobin Portland (ζ2γ2)
  - Haemoglobin Gower II (α2ε2)
- Fetal : HbF (α2γ2), HbA (α2β2)
- Adult : HbA, HbA2 (α2δ2), HbFVarious types of globin combines with haem to from different haemoglobin

- Eight functional globin chains, arranged in two clusters the
  - β- cluster (β, γ, δ and ε globin genes) on the short arm of chromosome 11
  - α- cluster (α and ζ globin genes) on the short arm of chromosome 16

Globulin chain/gene structure



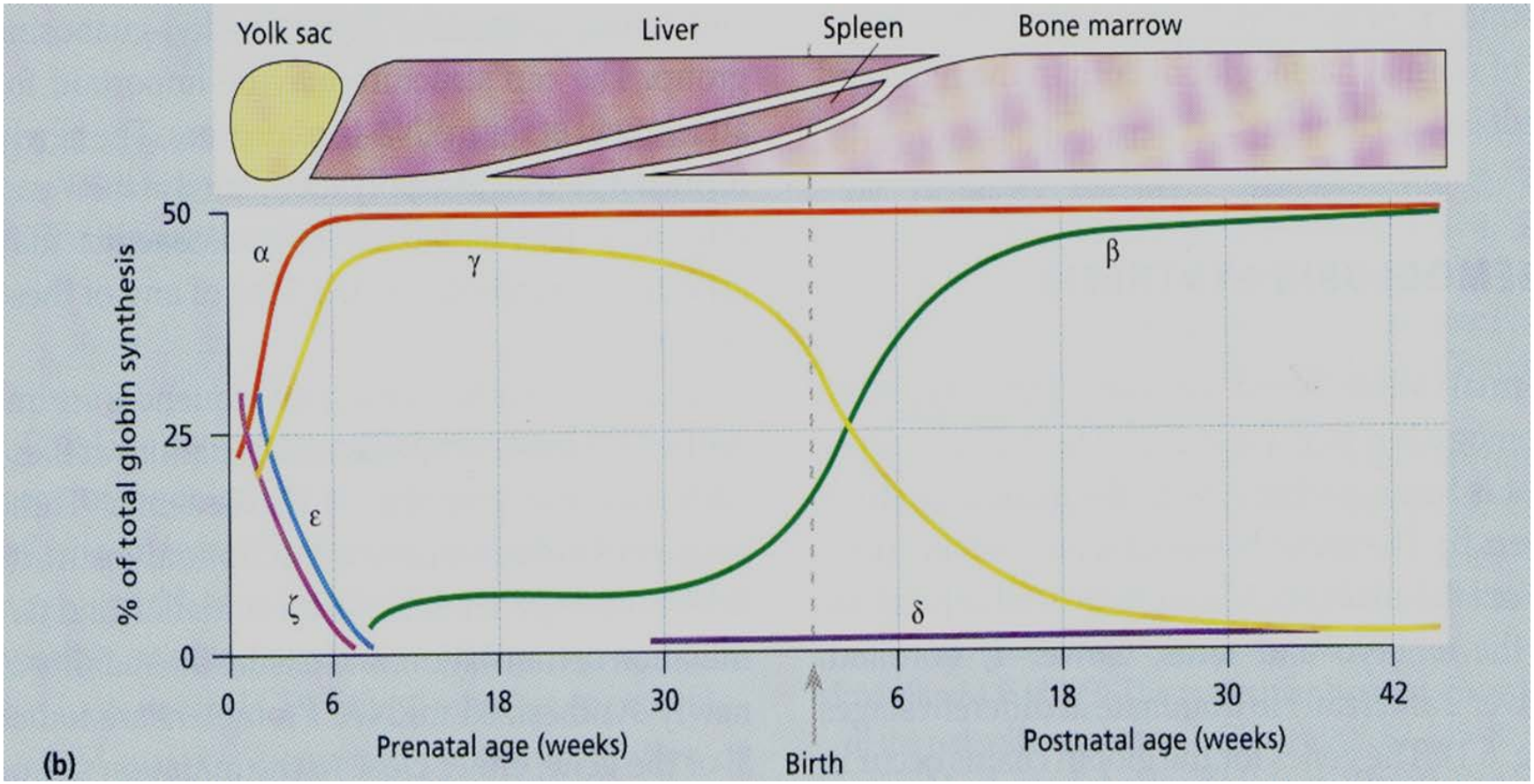
Globulin synthesis



Ontogeny of globin synthesis

Time	Region	Type of Globin Gene	Type of Hb
3 weeks of Gestation	Yolk Sac	ζ & ε	Hb Gawer1 ζ ε)2)
5 weeks of Gestation	Yolk Sac	γ&α	Hb Portland(ζ γ)2 Hb GawerII (αε)2
6-30 weeksof Gestation	Liver & spleen	α & γ& β	Hb F (α γ)2
30 weeks of Gestation	Liver	δ	Hb A2 (α δ2(
At Birth	B.M	___	HbA(α β)2

Globin chain switch



Adult haemoglobin

Adult haemoblobin

	Hb A	Hb A_2	Hb F
structure	$\alpha_2\beta_2$	$\alpha_2\delta_2$	$\alpha_2\gamma_2$
Normal %	96-98 %	1.5-3.2 %	0.5-0.8 %

4 Hierachies of globulin chain stucture

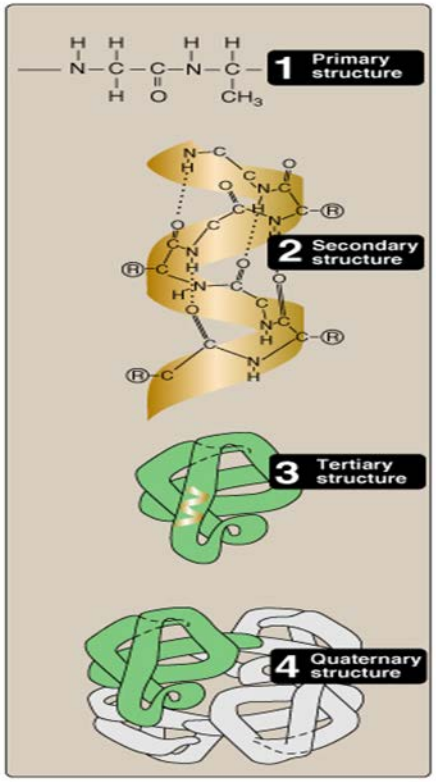


Figure 2.1

Four hierarchies of protein structure.

Structure

- Tetramer
- Conjugated protein, 68000D
- 4 haem groups
- Hb A = 2 α 141aa each & 2 ***β***146 aa each
- 10 structure – amino acid chain
- 20 structure – folding pp chain
- 30 structure – folding protein – niche H
- 40 structure – coming together 4 chains

1)Primary structure

-The primary structure of a protein refers to the linear sequence of amino acids in the polypeptide chain. The primary structure is held together by covalent bonds such as peptide bonds, which are made during the process of protein biosynthesis or translation.

The primary structure of globin refers to the amino acid sequence of the various chain types. Numbering from the N-terminal end identifies the position of individual amino acids. The identity and position of these amino acids cannot be changed without causing gross impairment to molecular function.

2)The secondary structure

- **Secondary protein structure** is the general 3-dimensional form of local segments of a protein. The most common secondary structures are **alpha helices** and **beta-pleated sheets**.
- The secondary structure of all globin chain types comprises nine non-helical sections joined by eight helical sections.
- The helical sections are identified by the letters A-H while the non helical are identified by a pair of letters corresponding to the adjacent helices e.g. NA (N-terminal end to the start of A helix), AB (joins the A helix to the B helix) etc.

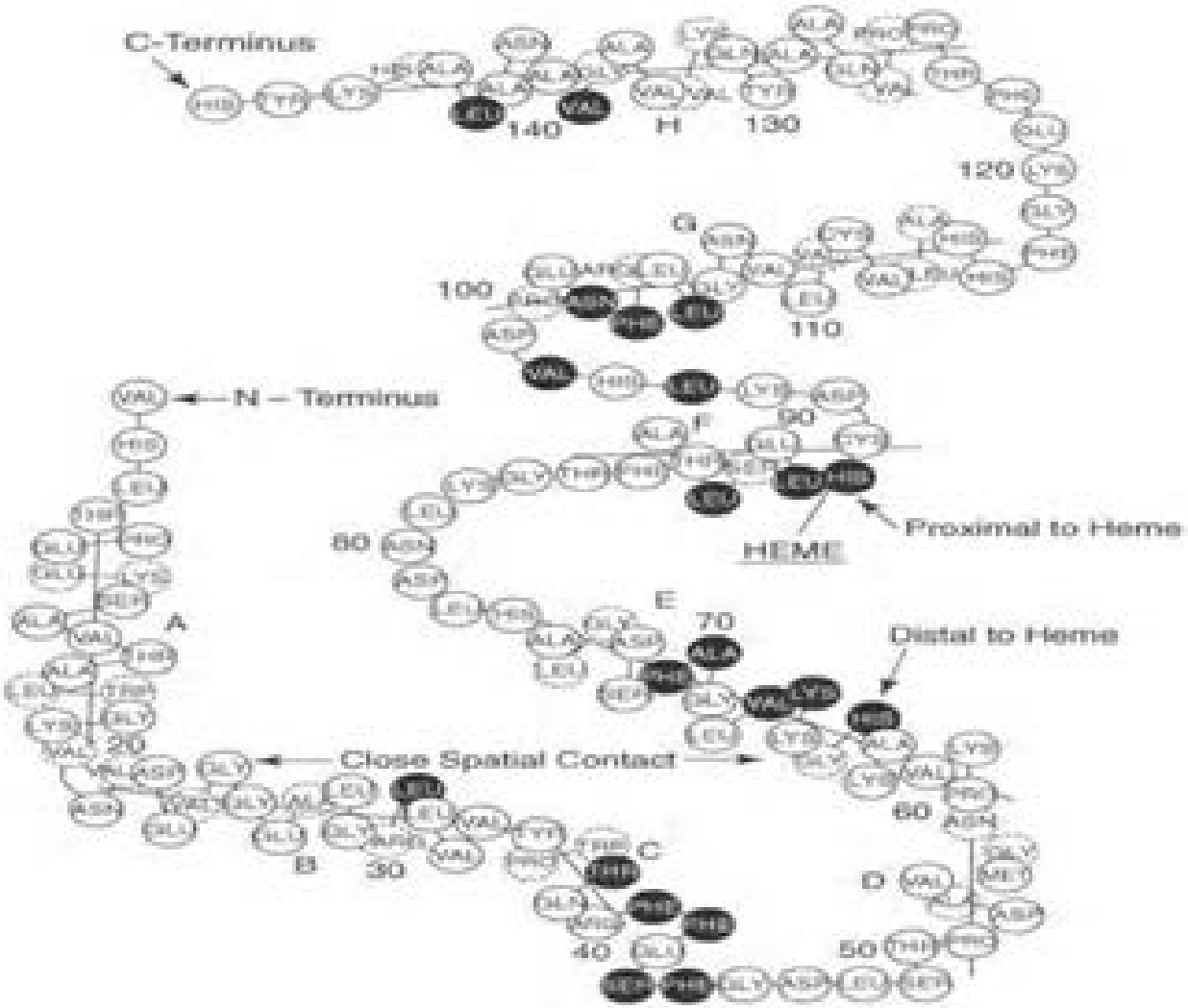


Figure 28-1 The β-globin chain, showing helical and nonhelical segments. The helical segments are labeled A through H, and nonhelical segments are designated NA for residues between the N terminus and the A helix, CD for residues between the C and D helices, and so forth. *(From Huisman THJ, Schroeder WA: New Aspects of the Structure, Function, and Synthesis of Hemoglobin. Boca Raton, FL: CRC Press; 1971.)*

3)The tertiary structure

- The tertiary folding of each globin chain forms an approximate sphere.
- The intra-molecular bonds which give rise to the helical parts of the impart considerable structure rigidity, causing chain folding to occur in the non-helical parts.
- Polar or charged side chains tend to be directed to theoutside surface of the subunit and, conversely, non-polar structures tend to be directed inwards.The effect of this is to make the surface of the molecule hydrophilic and the interior hydrophobic.

- 2- An open-toped cleft in the surface of the subunit known as **haem pocket** is created. This hydrophobic cleft protects the ferrous ion from oxidation.

- 3- The amino acids, which form the inter-subunit bonds responsible for maintaining the quaternary structure, and thus the function, of the haemoglobin molecule are brought into the correct orientation to permit these bonds to form.

- Tertiary protein structure is one step more complicated than secondary structure. Recall that secondary structures are made of alpha helices and beta-pleated sheets. These are both local structures. Tertiary structures involve packaging the secondary structures into compact globular regions called **protein domains**.
- A protein can have one or more domains. The important factor for tertiary structure is that it contains only one polypeptide.
- Tertiary protein domains are formed by combinations of **disulfide bonds**, **hydrogen bonds**, **ionic bonds**, and **non-polar hydrophobic interactions**. The type of side chain on the amino acid determines the type of interaction.

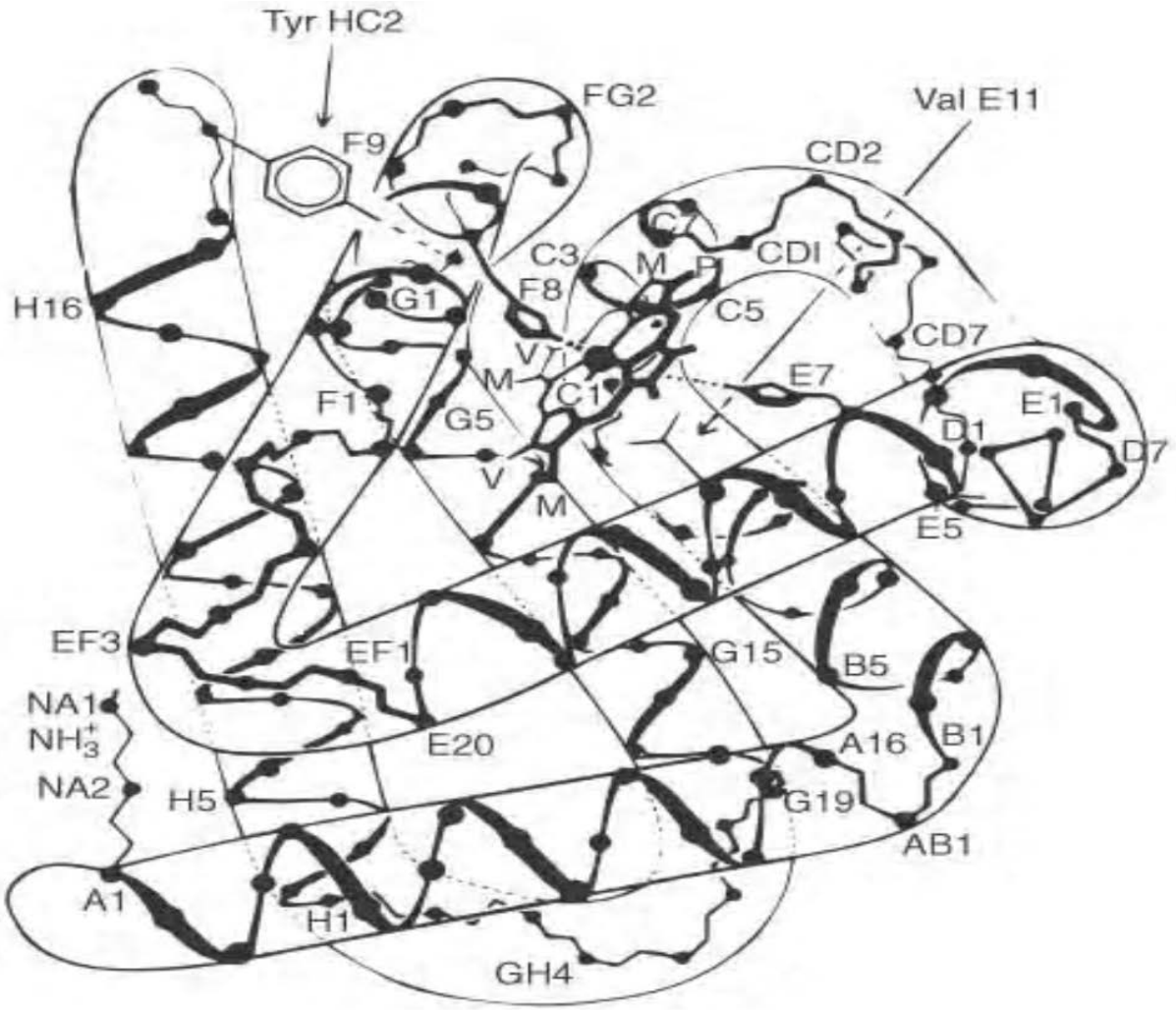


Figure 28-2 Tertiary structure of a globin chain. Globin folds into a tertiary structure such that polar or charged amino acids are located on the exterior of the molecule and the heme ring resides in a hydrophobic niche between the E and F helices. Linked to the heme are the proximal (F8) histidine and the distal (E7) histidine. *(From Perutz MF: Molecular anatomy, physiology, and pathology of hemoglobin. In Stamatoyannopoulos G, Neinhuis AW, Leder P, Majerus PW [eds]: The Molecular Basis of Blood Diseases. Philadelphia, WB Saunders, 1987, p 127.)*

4)The quartenary structure

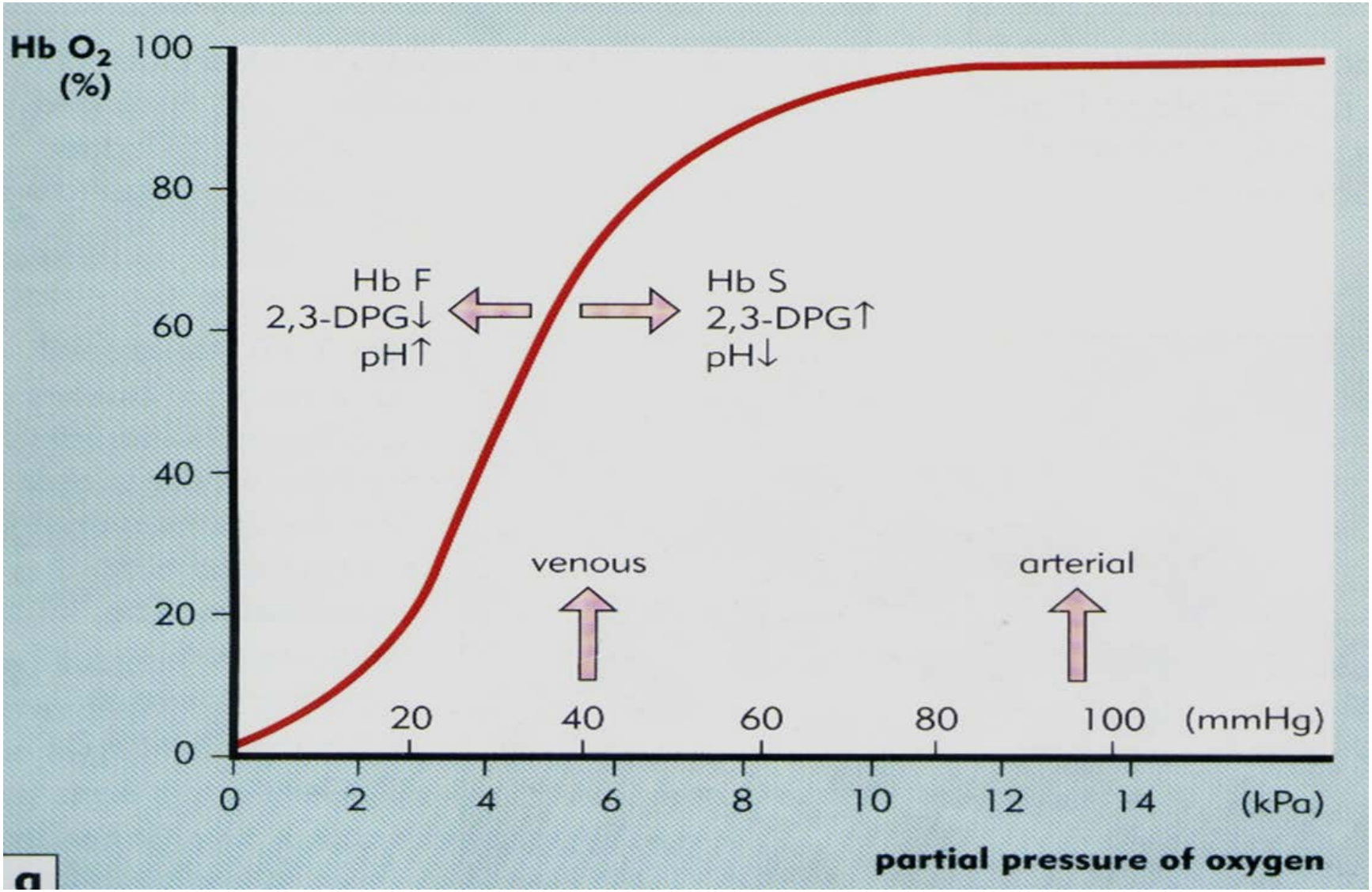
The quaternary structure of haemoglobin has four subunits arranged tetrahedrally. In adult haemoglobin- (HbA), there are different contact areas:

- α1β1 and α2 β 2 which confirms **stability** of the molecule.
- α1 β2 and α2 β1 which confirms **solubility** of the molecule.
- α1 α2 and β1 β2 which are weak bonds to permit **oxygenation and deoxygenation**

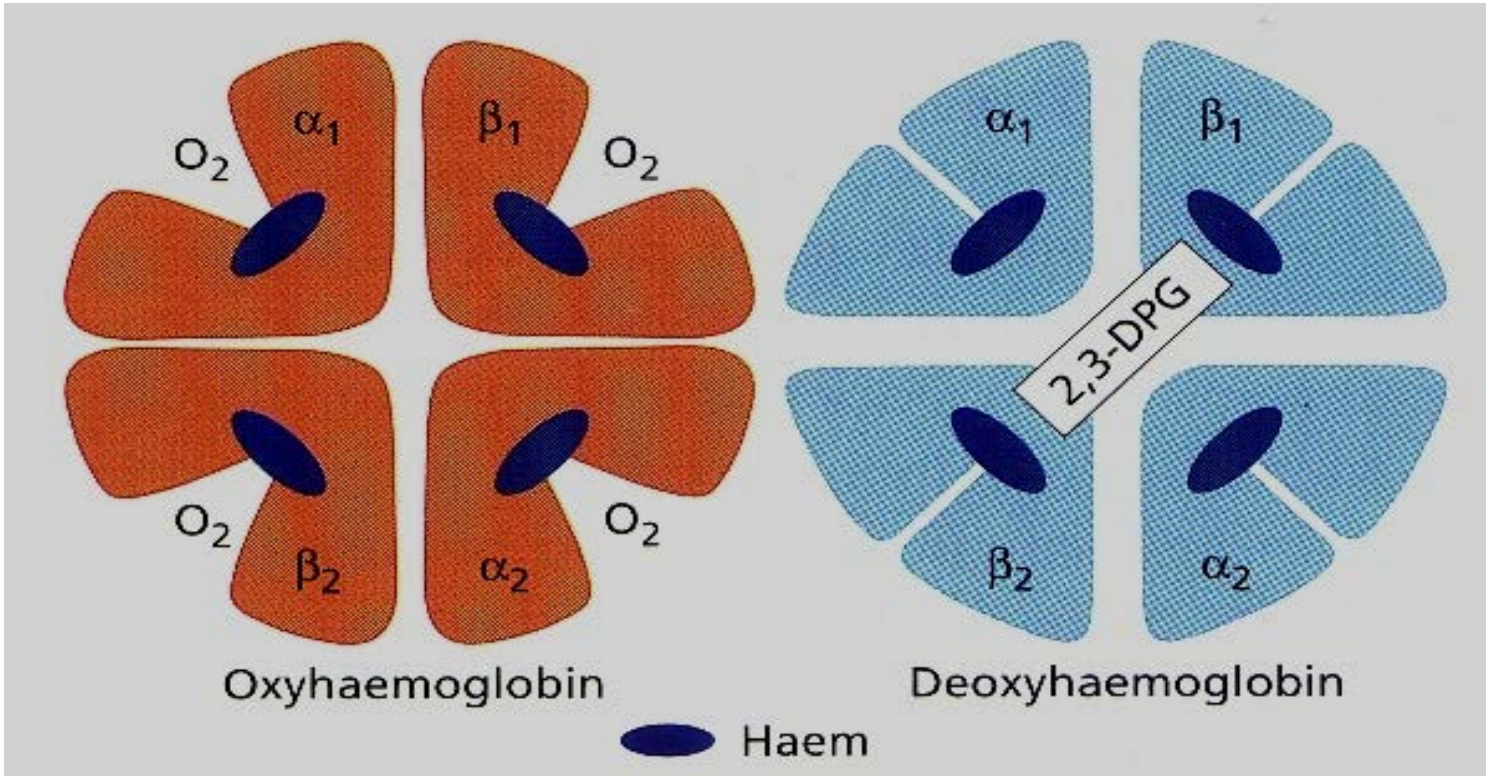
- **quaternary structure** is the arrangement of more than one protein molecule in a **multi-subunit complex**.
- Has more than one polypeptide chains- In this case, the individual peptide chains are called **protein subunits** and they cannot function on their own.

- O2 carrying capacity of Hb at different Po2
- Sigmoid shape
  - Binding of one molecule facilitate the second molecule binding
- *P* 50 (partial pressure of O2 at which Hb is half saturated with O2) 26.6mmHg
- The normal position of curve depends on
  - Concentration of 2,3-DPG
  - H+ ion concentration (pH)
  - CO2 in red blood cells
  - Structure of hb
- Right shift (easy oxygen delivery)
  - High 2,3-DPG,High H+,High CO2
  - HbS
- Left shift (give up oxygen less readily)
  - Low 2,3-DPG
  - HbF

Haemoglobin oxygen dissociation curve



Oxy & deoxyhaemoglobin



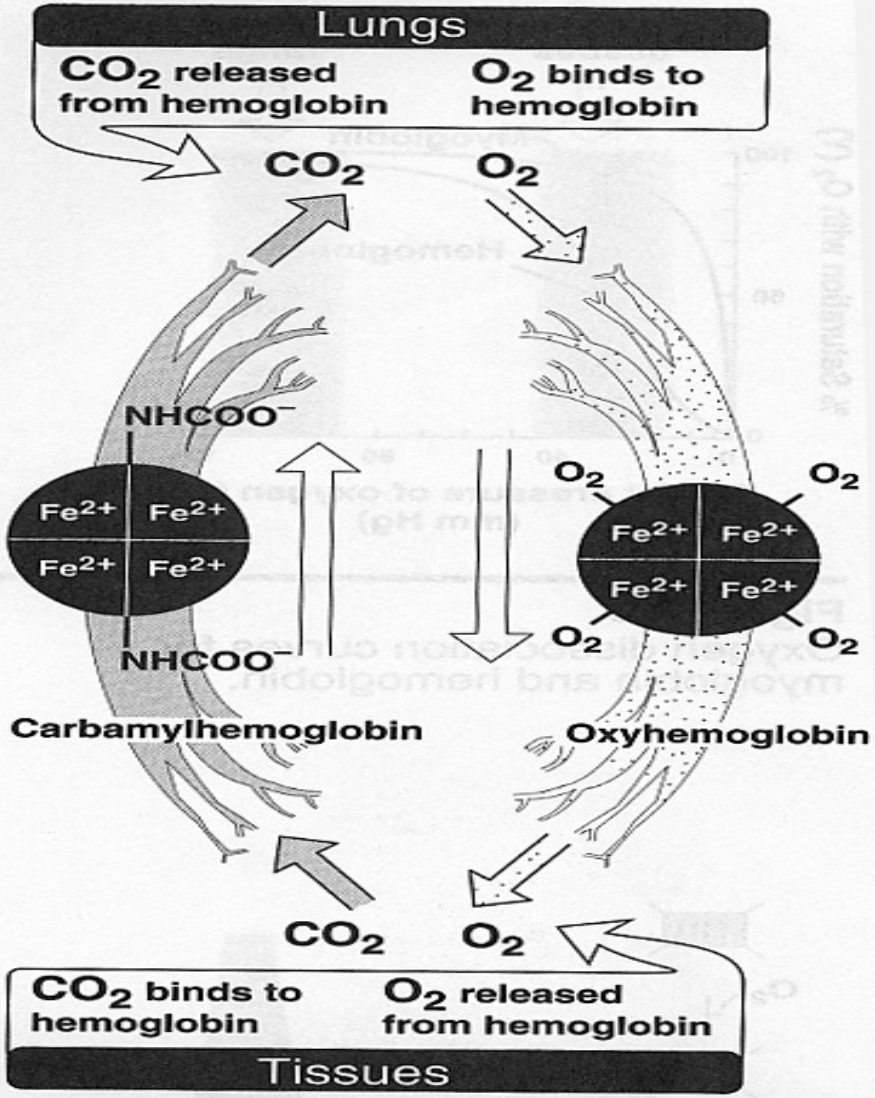


Figure 3.8
Transport of oxygen and CO_2 by hemoglobin.

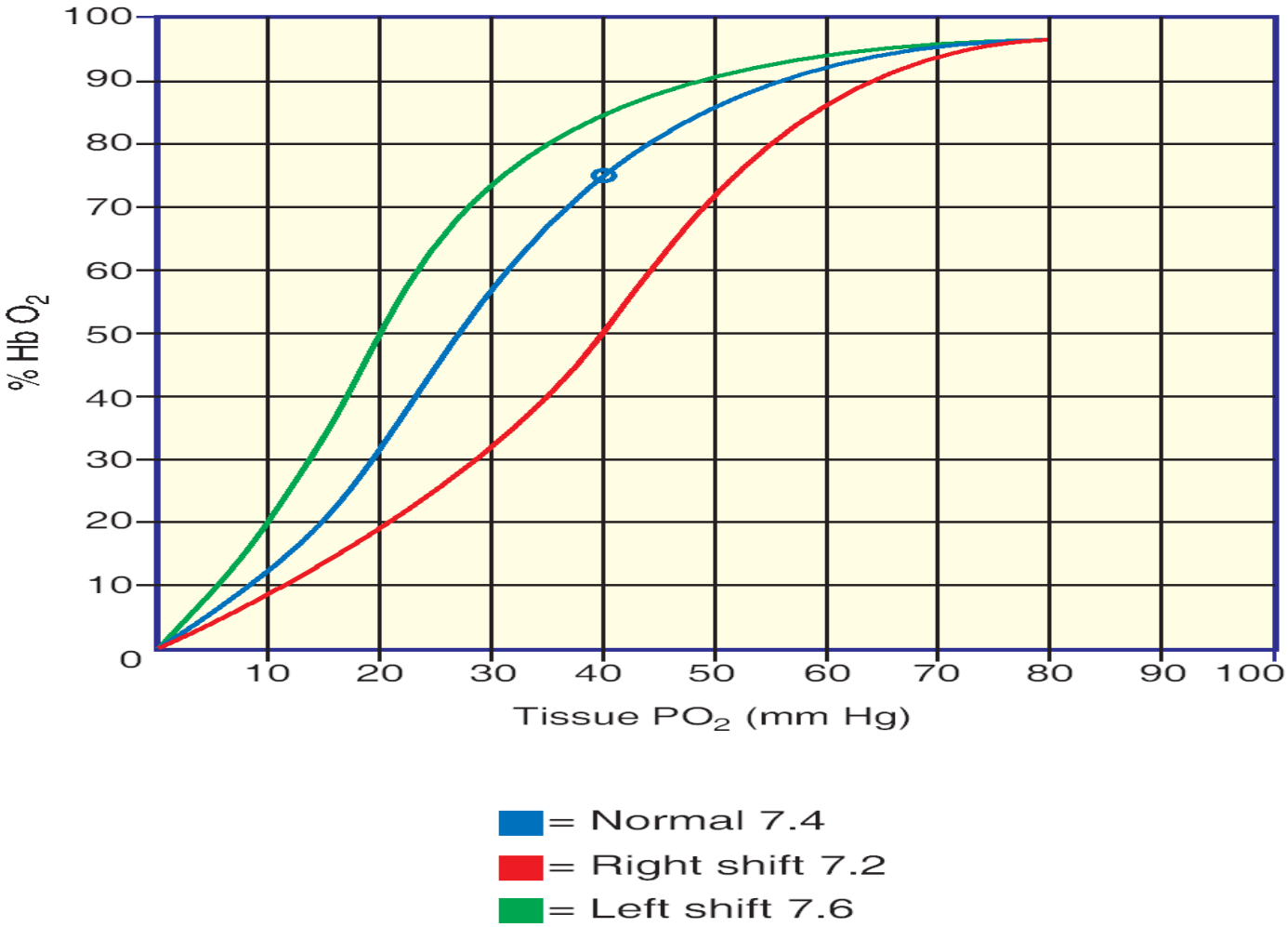
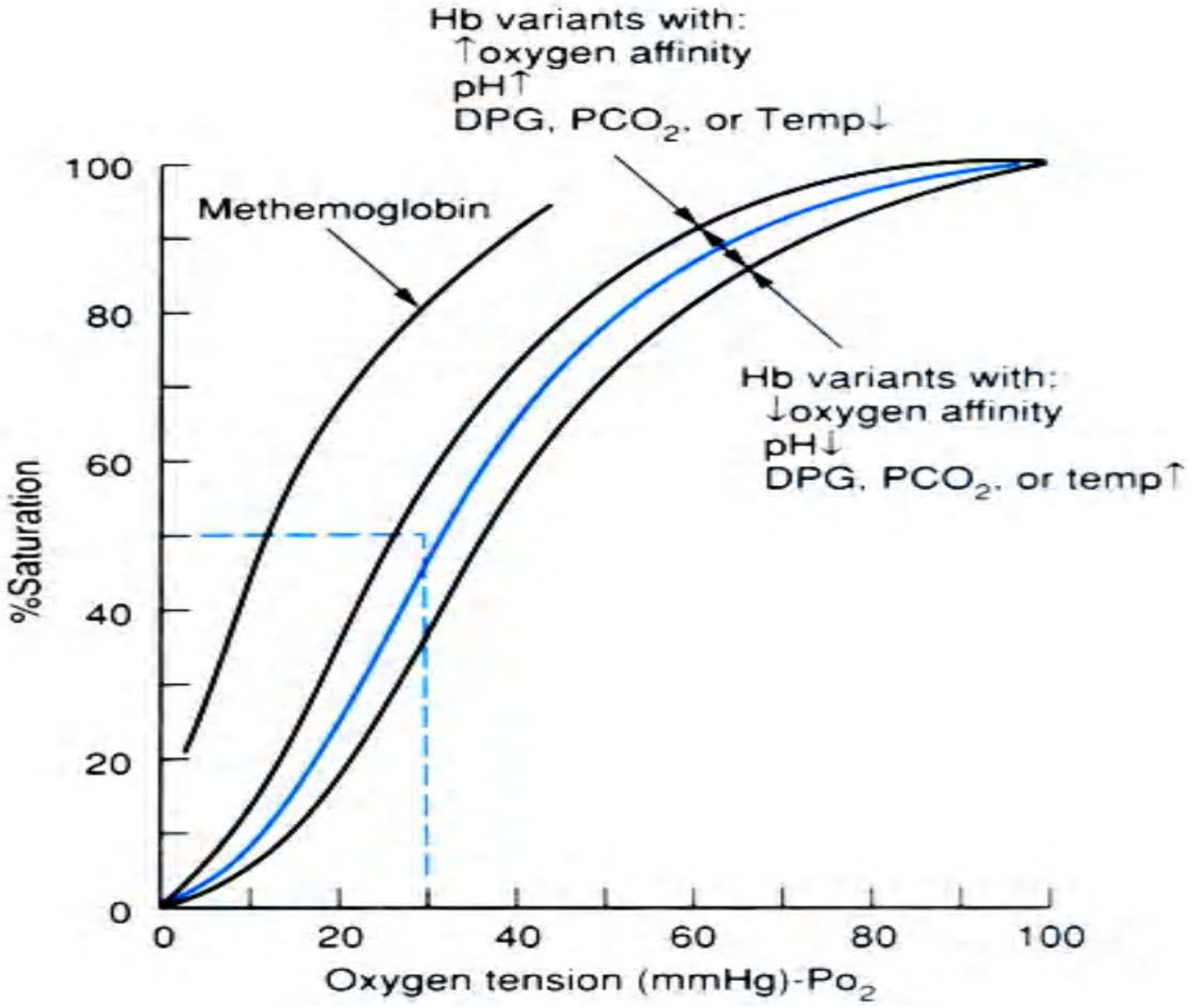
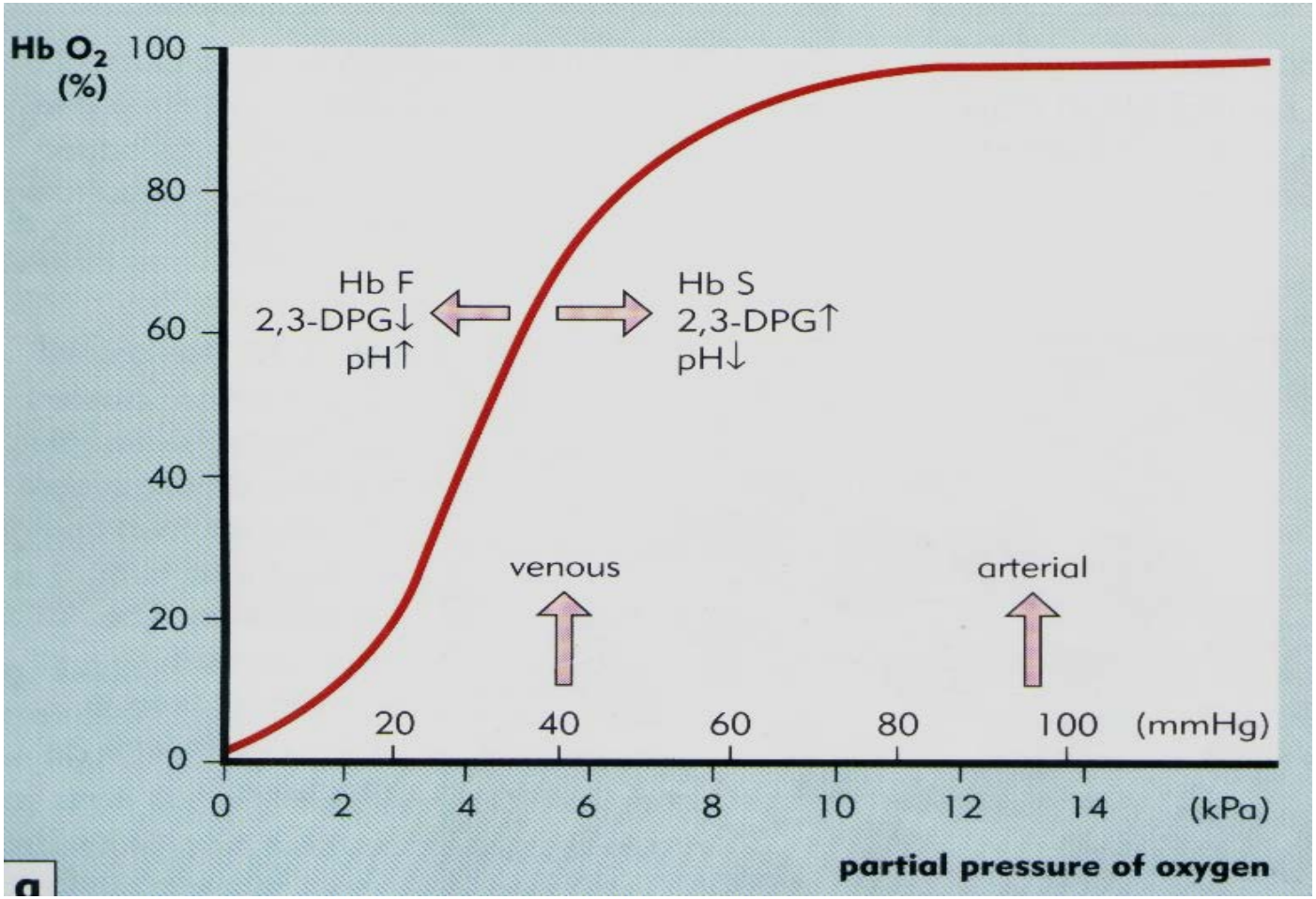


Figure 4.3 The oxygen dissociation curve. In the normal curve (blue) at 40 mm Hg, 75% of the hemoglobin molecule is saturated with oxygen, leaving 25% capable of being released to tissue. Note the right-shifted curve (red). At 40 mm Hg, hemoglobin is 50% saturated but willing to give up 50% of its oxygen to the tissues. Note the left-shifted curve (black). At 40 mm Hg, hemoglobin is 75% saturated but willing to release only 12% to the tissues.


Hb variants with:
↑oxygen affinity
pH↑
DPG, PCO_2, or Temp↓
Methemoglobin
Hb variants with:
↓oxygen affinity
pH↓
DPG, PCO_2, or temp↑
%Saturation
100
80
60
40
20
0
0
20
40
60
80
100
Oxygen tension (mmHg)-Po_2

Hb-oxygen dissociation curve



Hb-oxygen dissociation curve

- The normal position of curve depends on
  - Concentration of 2,3-DPG
  - H+ ion concentration (pH)
  - CO2 in red blood cells
  - Structure of Hb

Hb-oxygen dissociation curve

- Right shift (easy oxygen delivery)
  - High 2,3-DPG
  - High H+
  - High CO2
  - HbS
- Left shift (give up oxygen less readily)
  - Low 2,3-DPG
  - HbF

Bohr Effect

- The change in oxygen affinity with pH is known as the Bohr effect.
- Hemoglobin **oxygen affinity is reduced as the acidity increases**.
- Since the tissues are relatively rich in carbon dioxide, the **pH is lower** than in arterial blood; therefore, the Bohr effect **facilitates transfer of oxygen**.
- The Bohr effect is a manifestation of the acid-base equilibrium of hemoglobin.

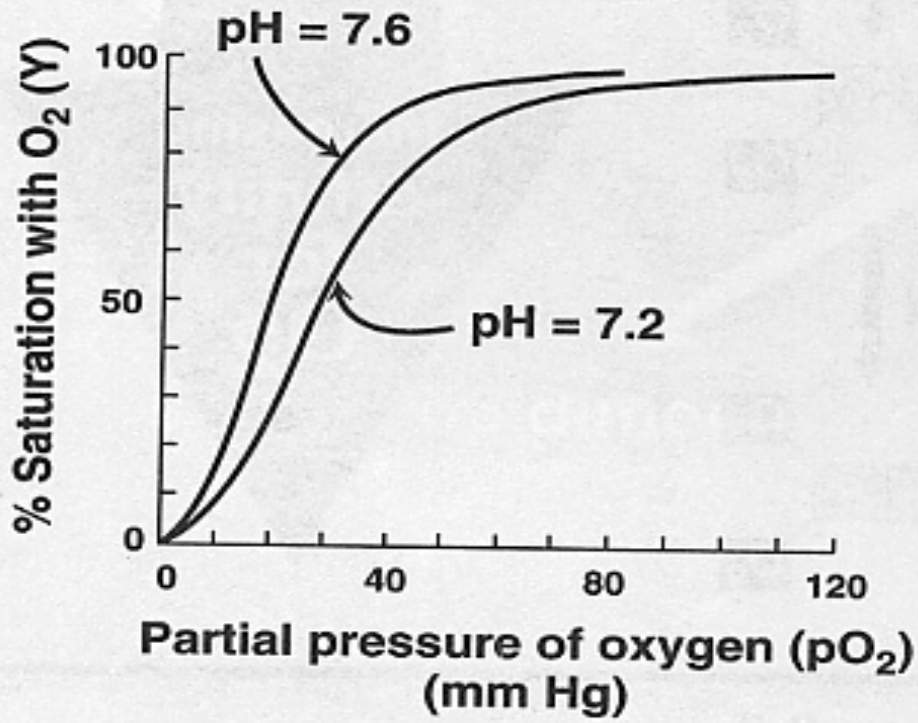


Figure 3.9
Effect of pH on the oxygen affinity of hemoglobin.

2,3-diphosphoglycerate (2,3-DPG)

- This compound is synthesized from glycolytic intermediates by means of a pathway known as the **Rapoport-Luebering shunt**.
- In the erythrocyte, 2-3-DPG constitutes the predominant phosphorylated compound, accounting for about two thirds of the red cell phosphorus.
- The proportion of 1,3-DPG pathway appears to be related largely to cellular ADP and ATP levels; when ATP falls and ADP rises, a greater proportion of 1,3-DPG is converted through the ATP-producing step.
- This mechanism serves to assure a supply of ATP to meet cellular needs.
- In the deoxygenated state, hemoglobin A can bind 2,3-DPG in a molar ratio of 1:1, a reaction leading to **reduced oxygen affinity and improved oxygen delivery to tissues.**

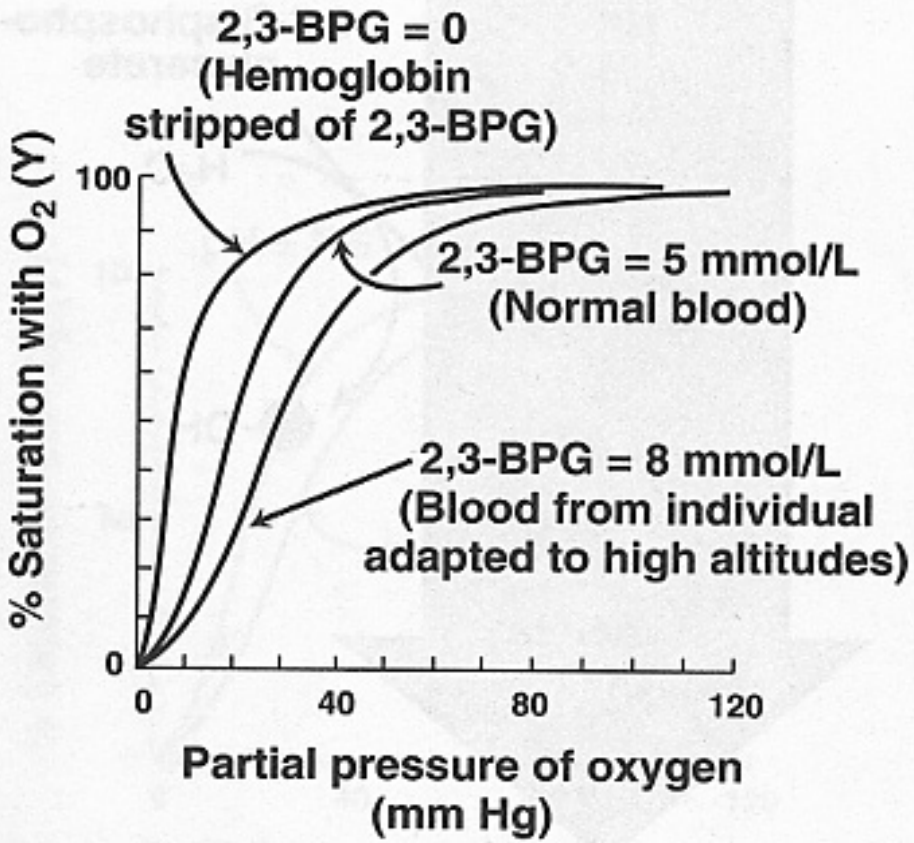


Figure 3.12
Effect of 2,3-BPG on the oxygen affinity of hemoglobin.

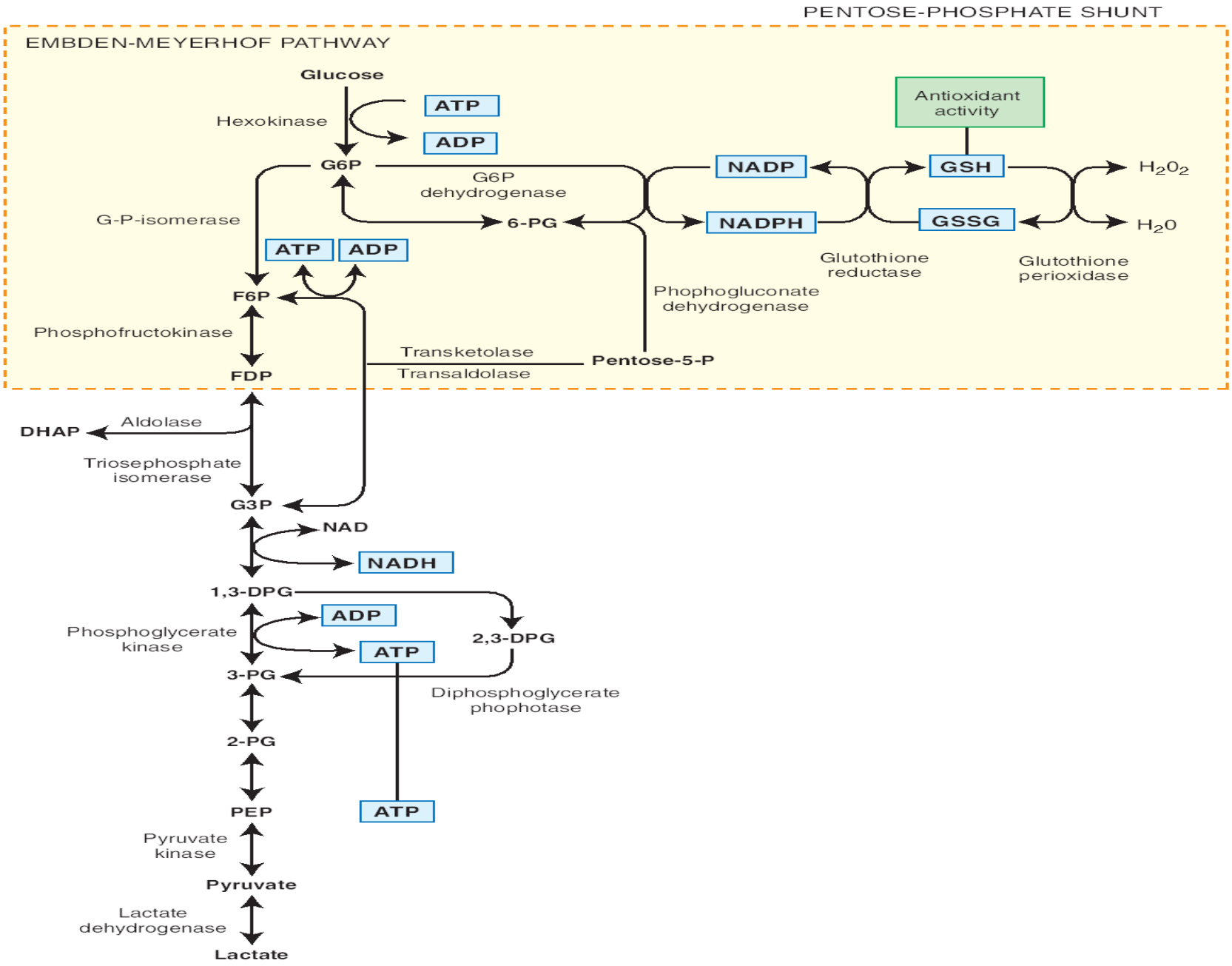
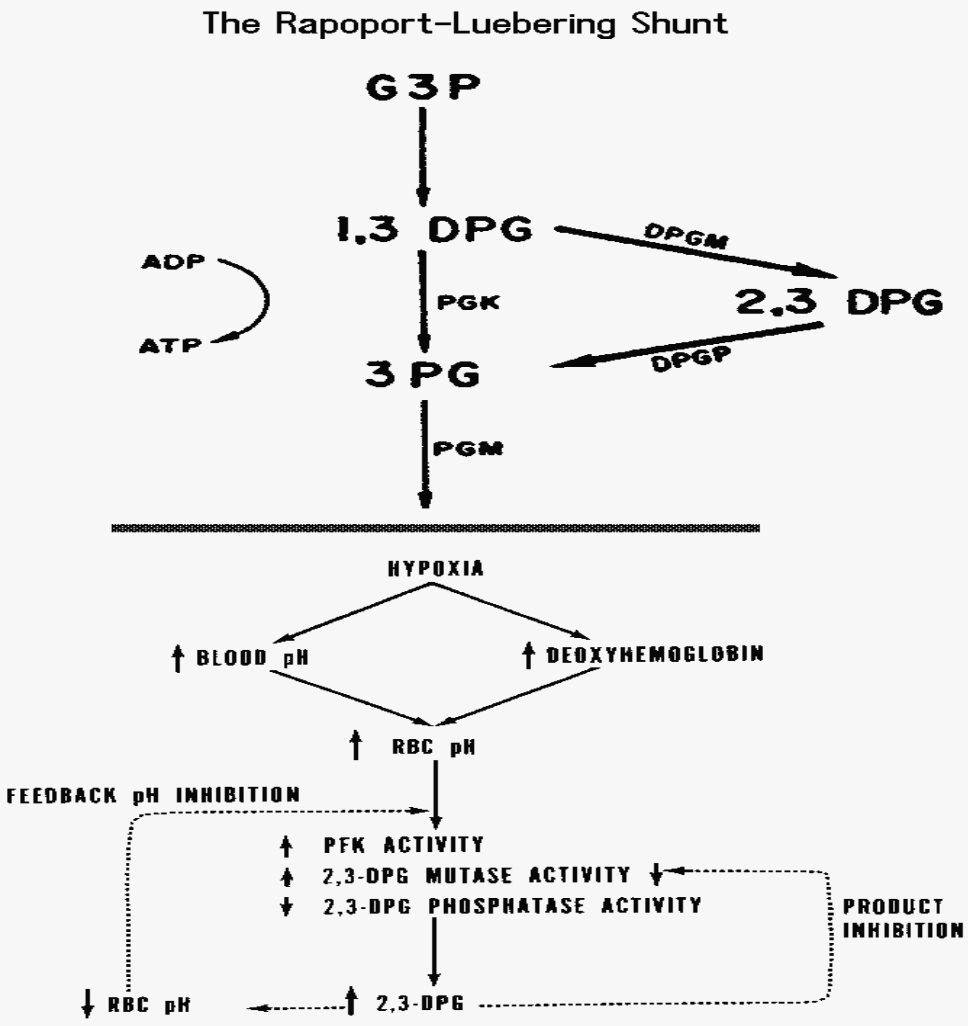


Figure 3.9 Anaerobic breakdown of glucose in red cell metabolism.



Feedback Regulation of 2,3,DPG Production

- When **oxygen is unloaded** by the hemoglobin molecule and **2,3 DPG is bound**, the molecule undergoes a conformational change becoming what is known as the ""**Tense**" or "T" form.
- The resultant molecule has a **lower affinity for oxygen**.
- As the partial pressure of oxygen increases, the 2,3, DPG is expelled, and the hemoglobin resumes its original state, known as the "**relaxed**" or "R" form, this form having a **higher oxygen affinity**.
- These conformational changes are known as "respiratory movement".
- The **increased oxygen affinity of fetal hemoglobin** appears to be related to its **lessened ability to bind 2,3-DPG**.
- The **increased oxygen affinity of stored blood is accounted for by reduced levels of 2,3-DPG**

- Changes in 2,3-DPG levels play an important role in adaptation to hypoxia. In a number of situations associated with hypoxemia, 2,3-DPG levels in red cells increase, oxygen affinity is reduced, and delivery of oxygen to tissues is facilitated.
- Such situations include abrupt exposure to high altitude, anoxia due to pulmonary or cardiac disease, blood loss, and anemia.
- Increased 2,3-DPG also plays a role in adaptation to exercise. However, the compound is not essential to life; an individual who lacked the enzymes necessary for 2,3-DPG synthesis was perfectly well except for mild polycythemia

Carbon Dioxide (CO2)

- Transport of **carbon dioxide** by red cells, unlike that of oxygen, does **not** occur by direct binding to heme.
- In aqueous solutions, carbon dioxide undergoes a pair of reactions:
- $CO_2 + H_2O \rightleftharpoons H_2CO_3$

2. $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

$\Rightarrow$

(CO2)

- Carbon dioxide diffuses freely into the red cell where the presence of the enzyme carbonic anhydrase facilitates reaction 1.
- The H+ liberated in reaction 2 is accepted by deoxygenated hemoglobin, a process facilitated by the Bohr effect.
- The bicarbonate formed in this sequence of reactions diffuses freely across the red cell membrane and a portion is exchanged with plasma Cl-, a phenomenon called the "chloride shift." the bicarbonate is carried in plasma to the lungs where ventilation keeps the pCO2 low, resulting in reversal of the above reactions and **excretion of CO2** in the expired air.
- About 70% of tissue carbon dioxide is processed in this way. Of the remaining 30%, 5% is carried in simple solution and 25% is bound to the N-terminal amino groups of deoxygenated hemoglobin, forming carbaminohemoglobin.

Methemoglobinemia

- In order to bind oxygen reversibly, the iron in the heme moiety of hemoglobin must be maintained in the **reduced** (ferrous) state despite exposure to a variety of endogenous and exogenous oxidizing agents.

- The red cell maintains several metabolic pathways to prevent the action of these oxidizing agents and to reduce the hemoglobin iron if it becomes oxidized. Under certain circumstances, these mechanisms fail and hemoglobin becomes nonfunctional.

Methemoglobinemia

- At times, hemolytic anemia supervenes as well. These abnormalities are particularly likely to occur

(1) if the red cell is exposed to certain oxidant drugs or toxins
(1) if the intrinsic protective mechanisms of the cell are defective or
(1) if there are genetic abnormalities of the hemoglobin molecule affecting globin stability or the heme crevice.

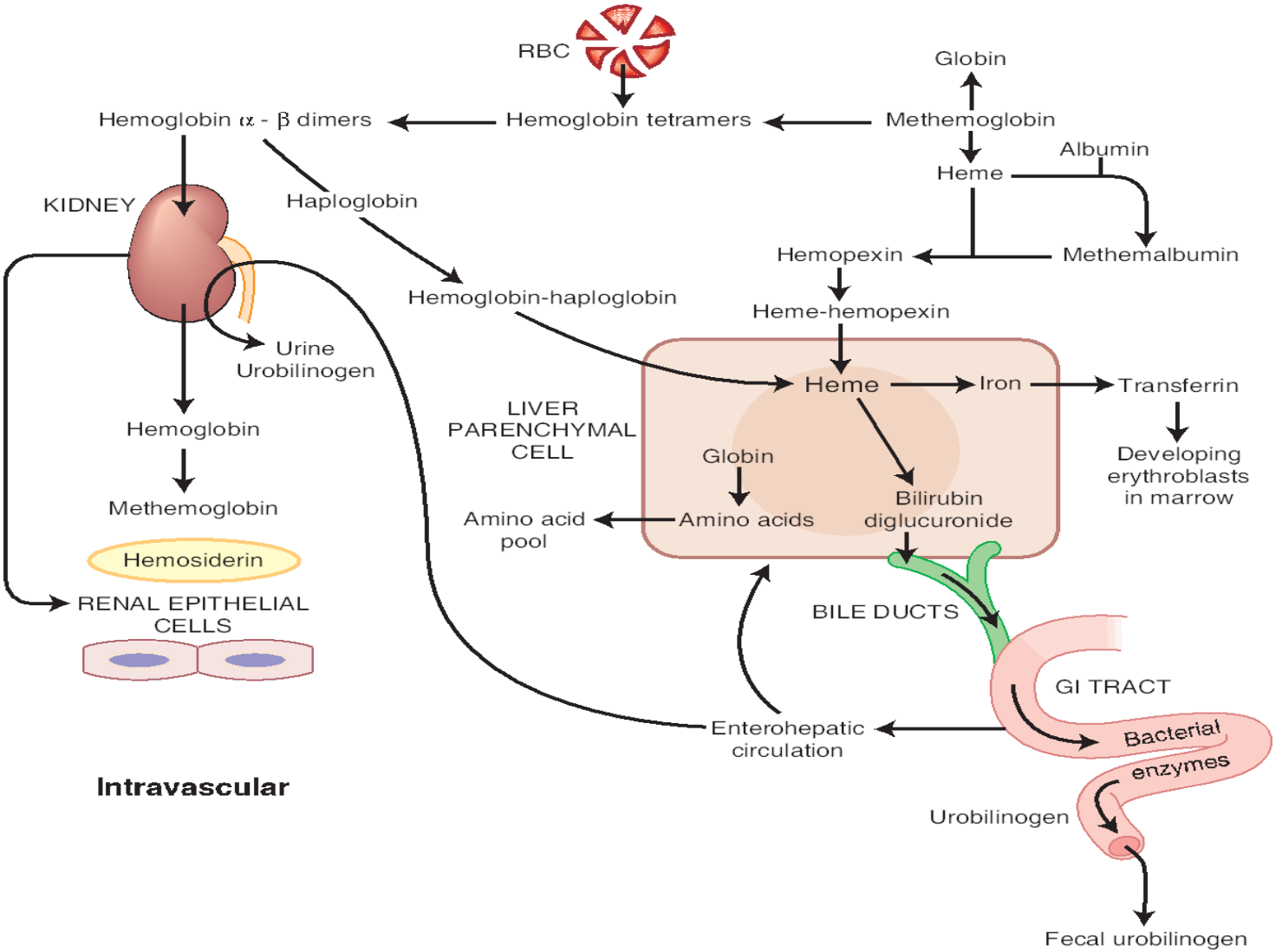


Figure 4.4 Intravascular hemolysis: increased bilirubin, decreased haptoglobin, but free hemoglobin present.

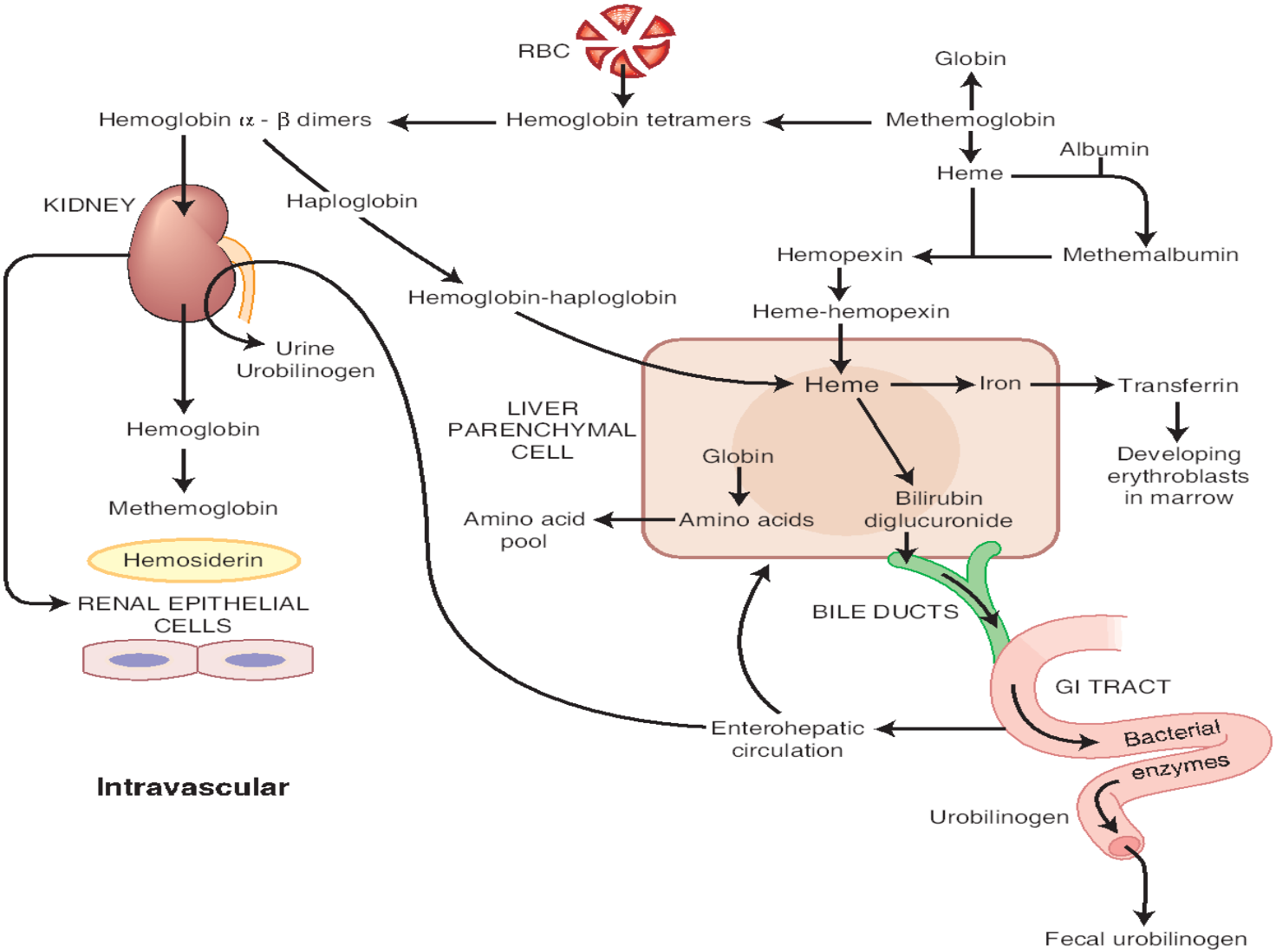


Figure 4.4 Intravascular hemolysis: increased bilirubin, decreased haptoglobin, but free hemoglobin present.

Abnormalities in the hemoglobin/types

- **Adult Hb (Hb A)** = 2 α and 2 β subunits
- **HbA1** is the major form of Hb in adults and in children over 7 months.
- **HbA2** (2 α, 2 δ) is a minor form of Hb in adults. It forms only 2 – 3% of
- a total Hb A.

- **Fetal Hb (Hb F)** = 2 α and 2 γ subunits

- in fetus and newborn infants Hb F binds O2 at lower tension than Hb A → **Hb F has a higher affinity to O2**

After birth, Hb F is replaced by Hb A during the first few months of life.

- **Hb S** – in β-globin chain Glu is replaced by Val

= an abnormal Hb typical for sickle cell anemia

Haemoglobinopathies

- Qualitative and quantitative -affects
- 1.Oxygen transport
- 2.Carbon dioxide transport
- 3.Acid- base balance
- -Qualitative
- 1. Hb S – 6th B, glutamate – Valine
- 2 - Hb C - 6th B, glutamate – Lysine
- 3 - Hb E - 26th B, glutamate – Lysine
- 4 – Others – Hb J nyanza, Hb Lepore

- Others;-

1, Koln, Sydney

– Increased oxygen affinity eg Hb C.town

2 – Reduced oxygen affinityeg Hb Kansas

3 – Unstable Hb eg Hb Zurich

4 – M Hbs – Fe 3+

- Quantitative

Thalassaemias;-

1 – Major – alpha

- - beta

2 – Minor – alpha

- - beta

Derivatives of haemoglobin

- **Oxyhemoglobin** (oxyHb) = Hb with O2
- **Deoxyhemoglobin** (deoxyHb) = Hb without O2
- **Methemoglobin** (metHb) contains **Fe3+** instead of Fe2+ in heme groups
- **Carbonylhemoglobin** (HbCO) – **CO binds to Fe2+** in heme in case of CO poisoning or smoking. CO has 200x higher affinity to Fe2+ than O2.
- **Carbaminohemoglobin** (HbCO2) - CO2 is non-covalently bound to globin chain of Hb. **HbCO2 transports CO2 in blood** (about 23%).
- **Glycohemoglobin** (HbA1c) is formed spontaneously by nonenzymatic reaction with Glc**.** People with DM have more HbA1c than normal (› 7%). Measurement of blood HbA1c is useful to get info about long-term control of glycemia.

Abnormal Hb (contd)

- Others;-

1 – Increased oxygen affinity eg Hb C.town

2 – Reduced oxygen affinityeg Hb Kansas

3 – Unstable Hb eg Hb Zurich, Koln, Sydney

4 – M Hbs – Fe 3+

Structure and function of haemoglobin

HAEMOGLOBIN STRUCTURE AND FUNCTION

- **Haemoglobin is a tetramer**
- **Composed of 4 polypeptide chains (2α and 2β) and 4 haem groups**
- **Each globin chain is attached to a haem group**

Structure of haemoglobin

- **Highly complex and viewed at 4 levels**

PRIMARY STRUCTURE

- **Sequence of amino acids in the polypeptides that constitute the globin chain**

SECONDARY STRUCTURE

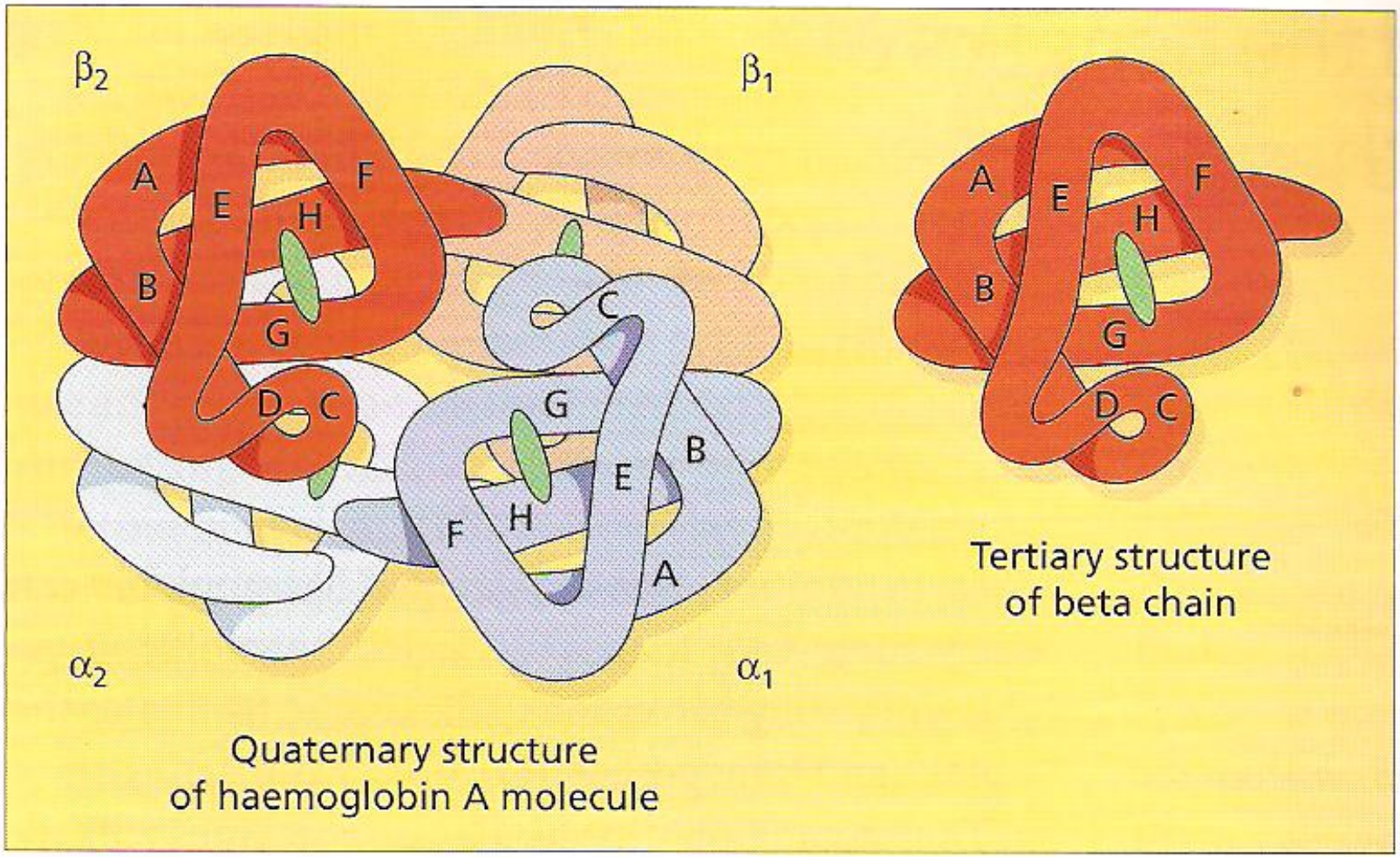
- **Helical conformation of the polypeptide chain**
- **There are 8 helical segements designated from A-H**
- **Iron of haem is bound to histidine at the 8^{th} position of F helical segement**
-

TERTIARY STRUCTURE

- **Refers to the three dimensional arrangement of the coiled globin chain and has a haem containing pocket between the E- H helices**

QUATERNARY STRUCTURE

- **Relationship between the four globin chains**
- **Bonds between polypeptide chains allow for chains to slide on each other and at same time maintain stability**


β2
β1
A
E
F
H
B
G
C
D
C
G
B
E
H
F
A
α2
α1
Quaternary structure
of haemoglobin A molecule
A
E
F
H
B
G
D
C
Tertiary structure
of beta chain

STRUCTURE OF HAEM

- **Each heme molecule consists of protoporphyrin with an iron (Fe^{++})**
- **Protoporphyrin is a tetrapyrrole which is a complex structure made up of 4 pyrrole rings**

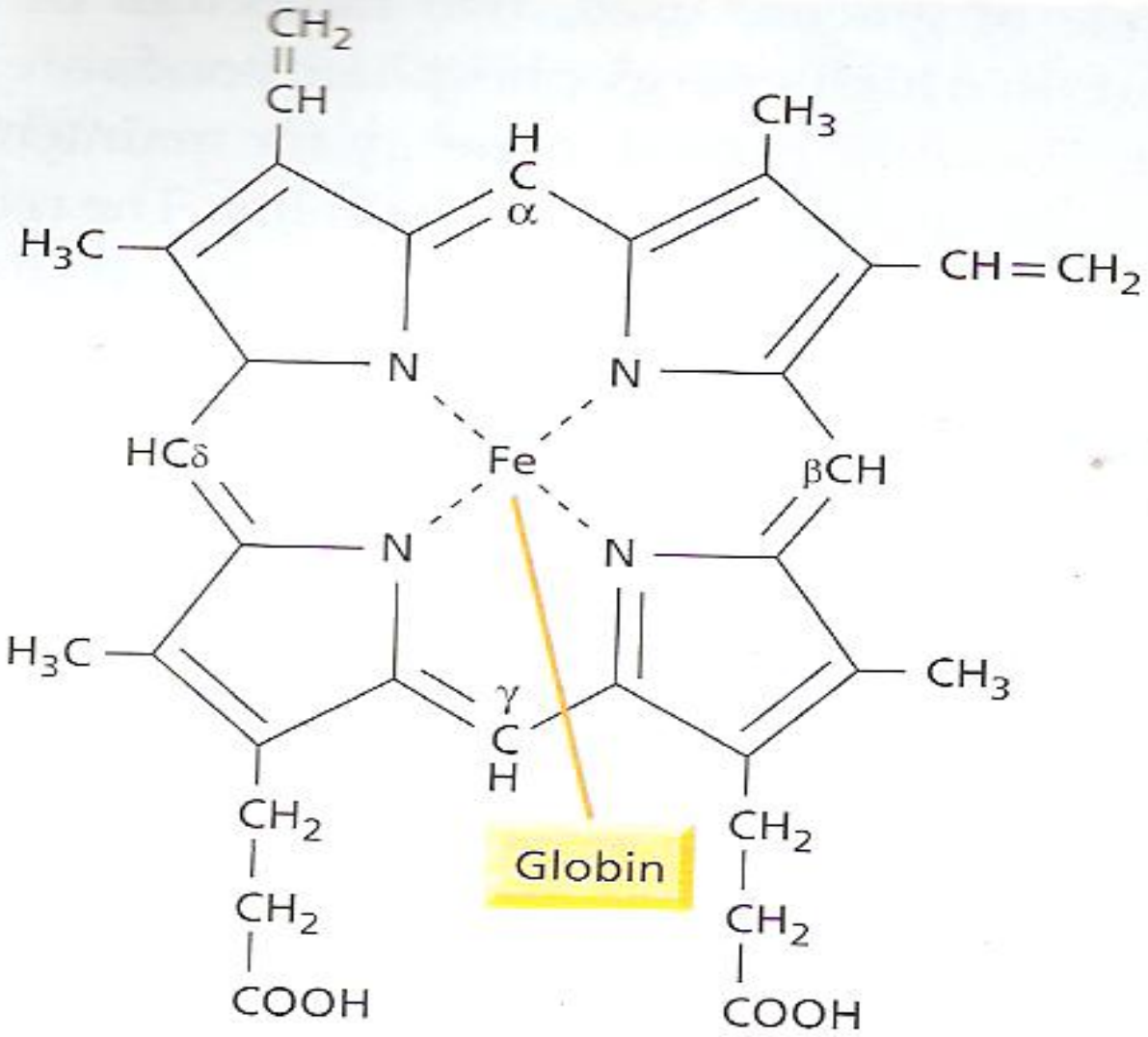


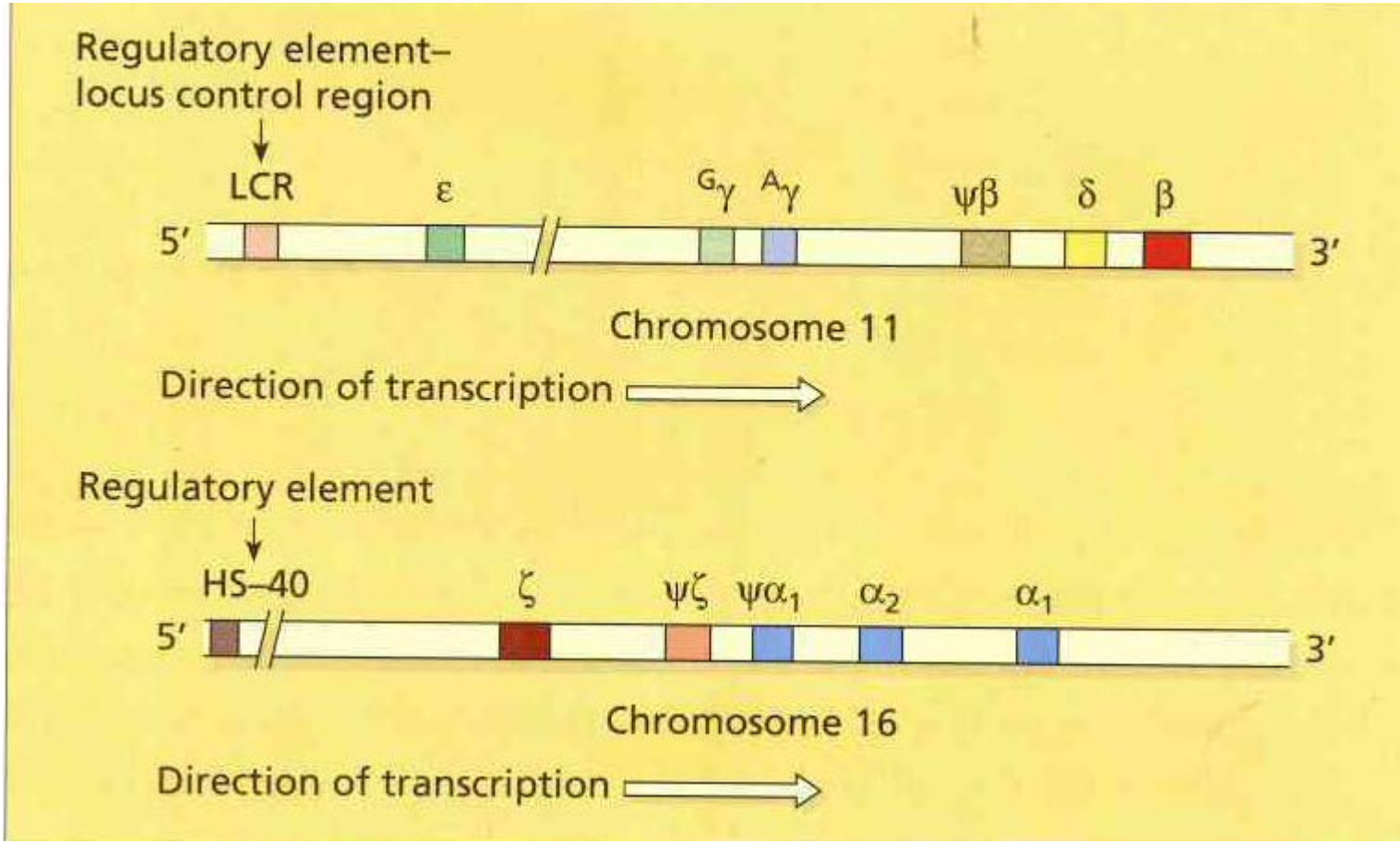
Fig. 2.7 The structure of haem.

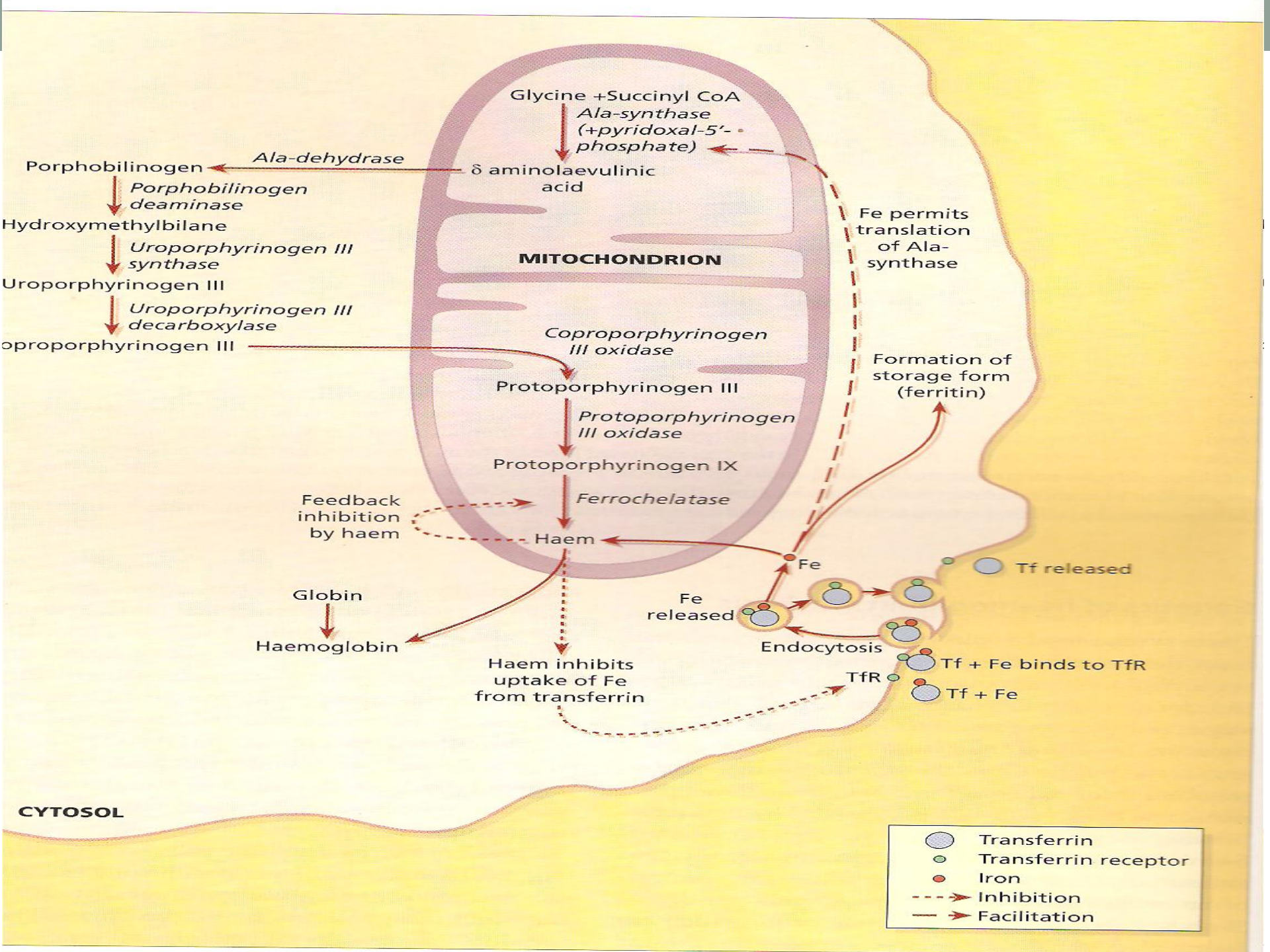
Synthesis of haem

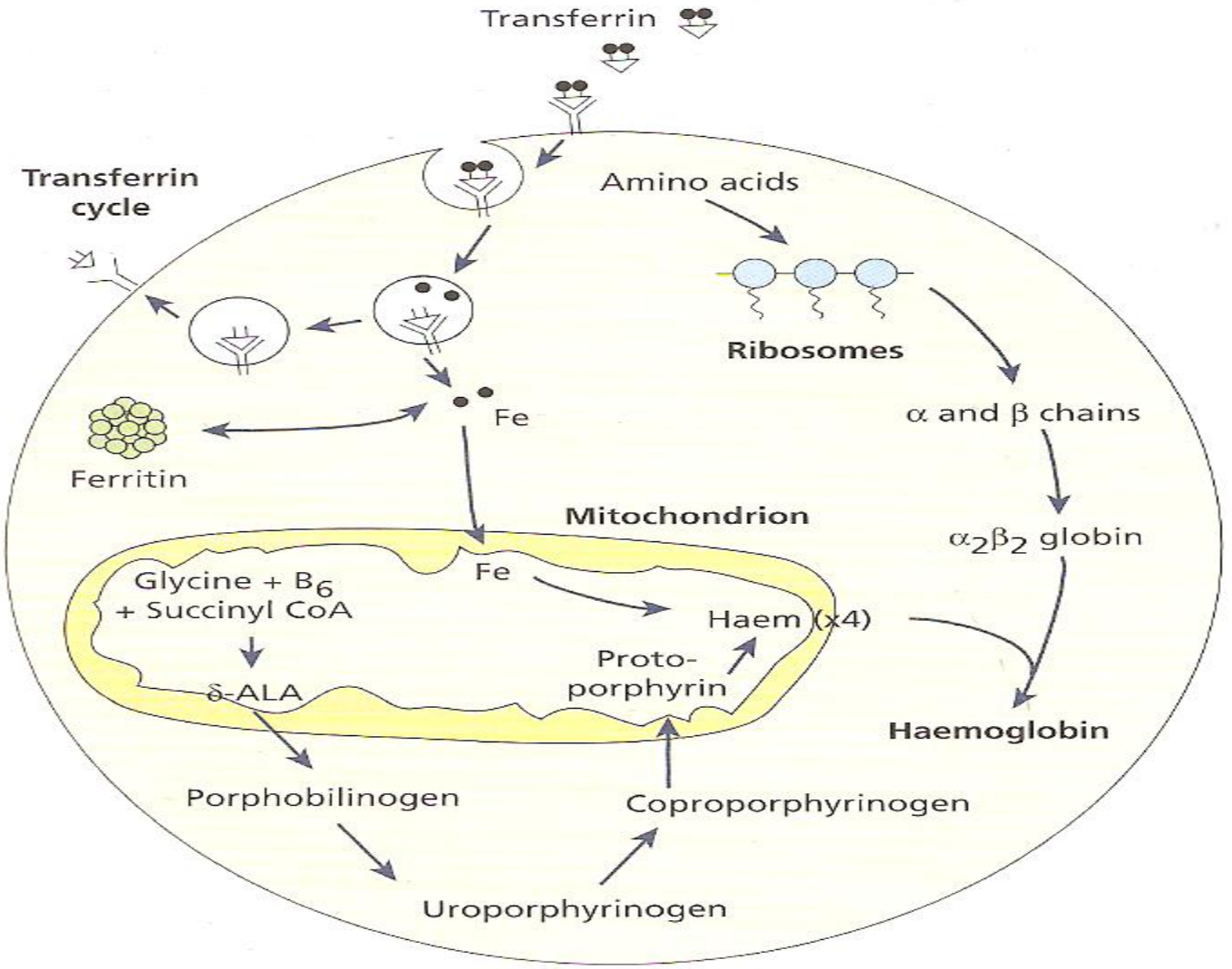
-
- **Heme is synthesized from glycine and succynl CoA**
- **The first step is condensation of Glycine and succynl CoA to form δ amino laevulanic acid with the help of enzyme aminolaevulinic acid synthetase. This step takes place in the mitochondrion.**
- **δ aminolaevulinic acid moves into the cytosol**
- **Two molecules of δaminolevulinic acid combine to form porphobilinogen**

- **Four molecules of porphobilinogen in turn combine to form uroporphyrinogen III**
- **Utophorphyrinogen III is then modified in two further steps to form Coprophorphinogen III.**
- **Coprophorhinogen III enters the mitochondrion where it is converted to Protoporphyrin.**
- **The final stage is combination of ferrous (Fe^{2+}) to form haem.**

- **Globin chain synthesis is under the control of genes located on chromosomes 11 (α chains) and chromosome 16 (β chains). Synthesis in the cytoplasm on ribosomes.**


Regulatory element–
locus control region
LCR
ε
Gγ
Aγ
ψβ
δ
β
5′
3′
Chromosome 11
Direction of transcription
Regulatory element
HS–40
ζ
ψζ
ψα1
α2
α1
5′
3′
Chromosome 16
Direction of transcription


Glycine +Succinyl CoA
Ala-synthase
(+pyridoxal-5'-phosphate)
δ aminolaevulinic acid
Ala-dehydrase
Porphobilinogen
Porphobilinogen deaminase
Hydroxymethylbilane
Uroporphyrinogen III synthase
Uroporphyrinogen III
Uroporphyrinogen III decarboxylase
Coproporphyrinogen III
Coproporphyrinogen III oxidase
Protoporphyrinogen III
Protoporphyrinogen III oxidase
Protoporphyrinogen IX
Ferrochelatase
Haem
MITOCHONDRION
Fe permits translation of Ala-synthase
Formation of storage form (ferritin)
Feedback inhibition by haem
Fe
Tf released
Fe released
Endocytosis
Tf + Fe binds to TfR
TfR
Tf + Fe
Globin
Haemoglobin
Haem inhibits uptake of Fe from transferrin
CYTOSOL
Transferrin
Transferrin receptor
Iron
Inhibition
Facilitation


Transferrin
Transferrin cycle
Amino acids
Ribosomes
Fe
Ferritin
α and β chains
Mitochondrion
$\alpha_2\beta_2$ globin
Glycine + B_6 + Succinyl CoA
Fe
Haem (x4)
Proto-porphyrin
δ-ALA
Haemoglobin
Porphobilinogen
Coproporphyrinogen
Uroporphyrinogen

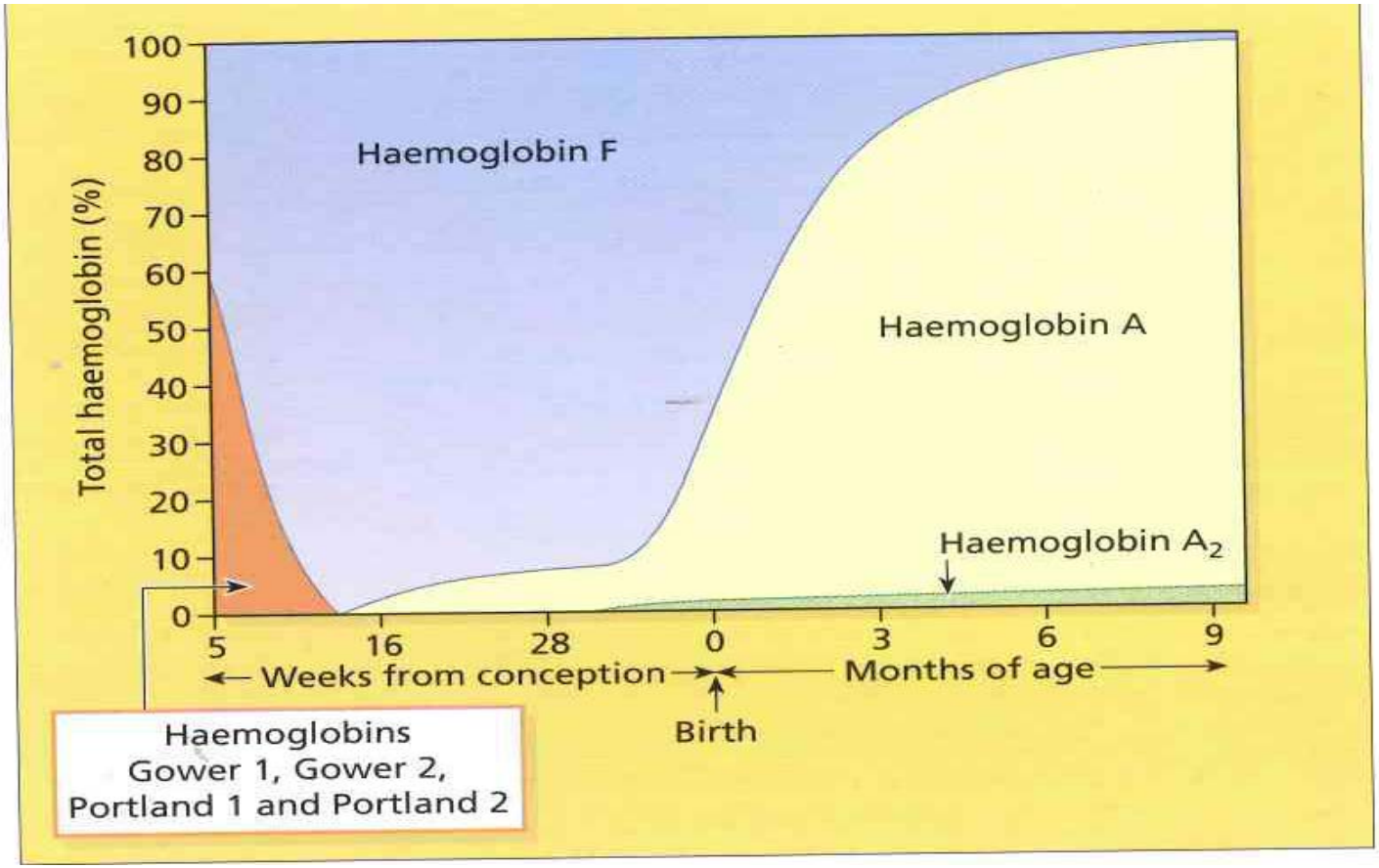
- **Variants of haemoglobin include Haemoglobin A, A2, F, Gower I, Gower II and Portland**
- **Adults Hb A 97% Hb A2 2.5% and Hb F 0.5%**
- **Newborns HbF 80% and Hb A 20%**
- **Hb A is the principal haemoglobin of adults 1 pair of alpha (α) chains and one pairs of beta (β) chains $\alpha 2 \beta 2$**
- **Foetal haemoglobin (Hb F) is the predominant haemoglobin in foetal life and contains a pair of alpha (α) and a pair of gamma (γ) chains**

Box 1.1: Normal haemoglobin variants

- Hb Gower I: $\zeta_2\varepsilon_2$
- Hb Gower II: $\alpha_2\varepsilon_2$
- Hb Portland: $\zeta_2\gamma_2$

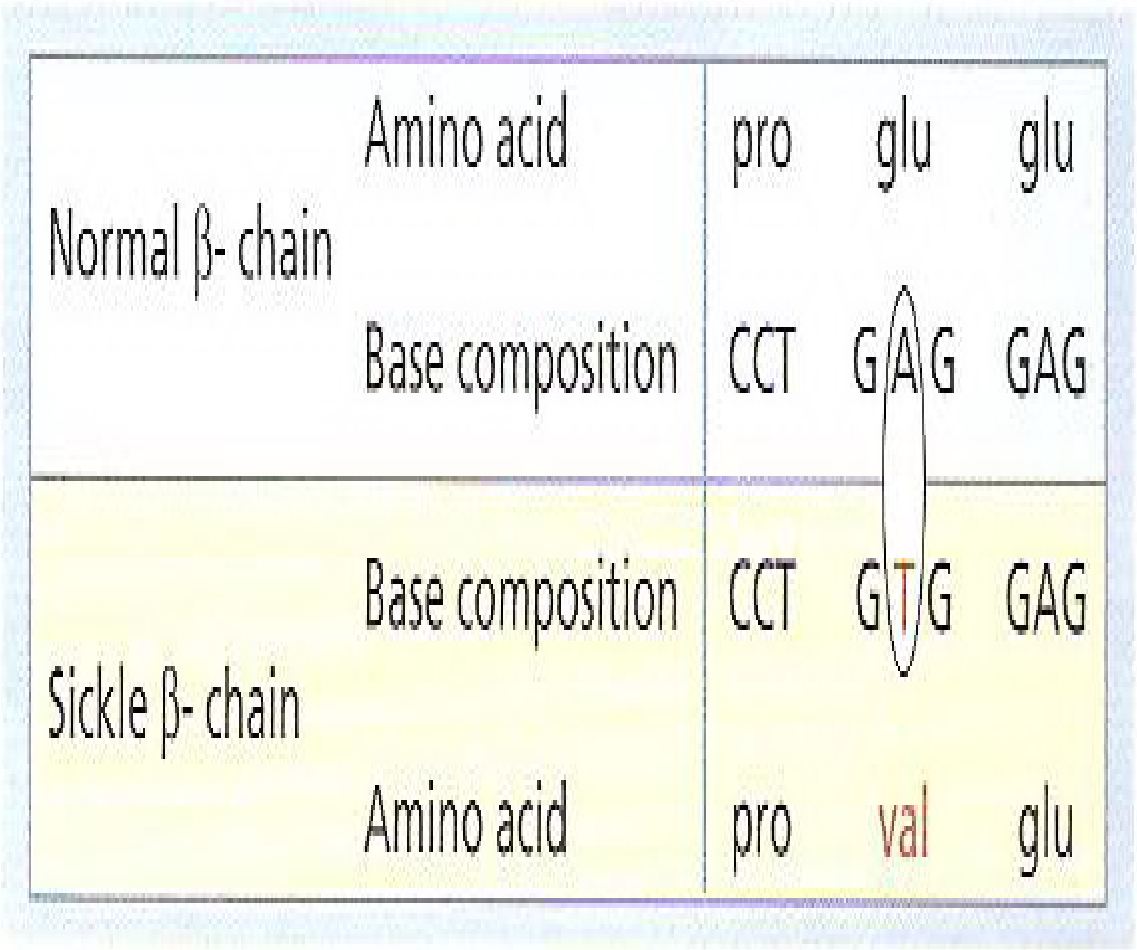
The above three haemoglobins are embryonic haemoglobins

- HbF: $\alpha_2\gamma_2$: Predominates in foetal life
- HbA: $\alpha_2\beta_2$: Predominates in adult life
- HbA2: $\alpha_2\delta_2$


Total haemoglobin (%)
100
90
80
70
60
50
40
30
20
10
0
Haemoglobin F
Haemoglobin A
Haemoglobin A_2
5
16
28
0
3
6
9
Weeks from conception
Months of age
Birth
Haemoglobins
Gower 1, Gower 2,
Portland 1 and Portland 2

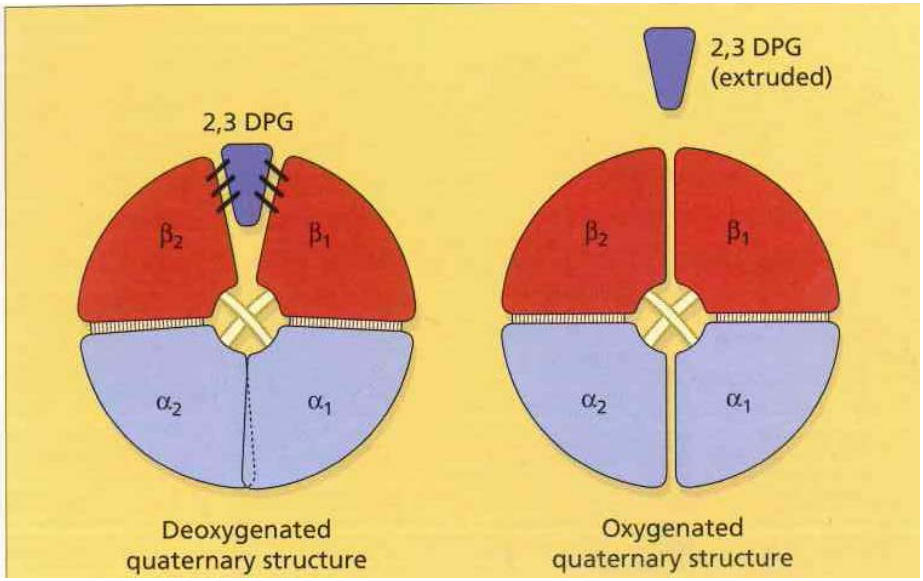
Abnormal haemoglobins

- **Over 350 abnormal haemoglobins have been described**
- **Sickle cell haemoglobin : substitution of glutamic acid by valine on position 6 of the b chain.**
- **Thalassemia: defective production of alpha or beta chains.**

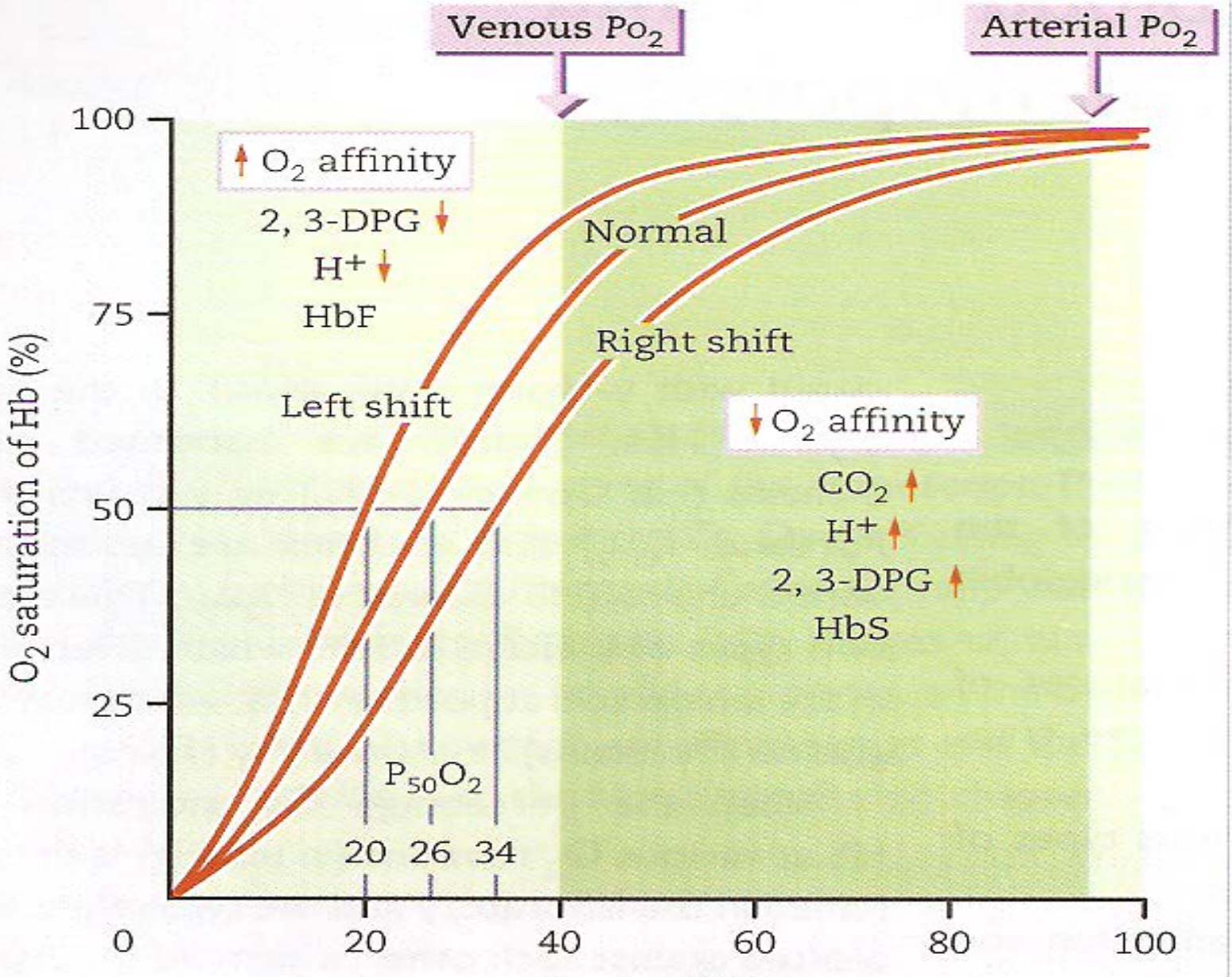

Normal β- chain
Amino acid
pro
glu
glu
Base composition
CCT
GAG
GAG
Sickle β- chain
Base composition
CCT
GTG
GAG
Amino acid
pro
val
glu

Haemoglobin Function

- **Red cells carry oxygen from the lungs to the tissues and carbon dioxide from tissues to lungs**
- **As the haemoglobin molecule loads and unloads oxygen the individual globin chains in the haemoglobin molecule move on each other**
- **When oxygen is unloaded the b chains are pulled apart permitting entry of the metabolite 2,3 Diphosphoglycerate (2,3 DPG) resulting in lower affinity of the molecule for oxygen**
- **This movement is responsible for the sigmoid form of the haemoglobin oxygen dissociation curve.**


2,3 DPG
(extruded)
2,3 DPG
β2
β1
α2
α1
β2
β1
α2
α1
Deoxygenated
quaternary structure
Oxygenated
quaternary structure

OXYGEN DISSOCIATION CURVES



- **The P_{50} (partial pressure at which oxygen is half saturated with oxygen) of normal blood is 26.6 mmHg**
- **With increased affinity for oxygen the curve shifts to the left (P_{50} falls)**
- **With decreased affinity (P_{50} rises) and curve shifts to the right**

ABNORMAL HEMOGLOBIN

Objectives

At the end of this lecture

- Describe the hemoglobinopathies
- The epidemiology- geographical area, age , gender, physiological status.
- The causes and genetics defects
- The laboratory and clinical features in investigations.

- Hereditary anemia include disorders of the structure or synthesis of hbn, enzymopathies that providethe RBC with energy or protect it from chemical damage, and membranopathies.
- Inherited diseases of Hb, hemoglobinopathies

Hemoglobinopathies

- Thalassemia genetics
- Hb sytnthesis
- Hb a, A2, F
- Hb Electrophoresis
- Hb constant-spring
- Hb Bart's
- Hb H, Lepopre, E S C SC disease

Hemoglobinopathies

- Decrease, lack of, or abnormal Hb
- May be severe hemolytic anemia
- Abnormal Hb
- Hb electrophoresisi is important in making diagnosis

Classification and inheritance

- The common sickling disorders consist of the homozygous state for the sickle cell gene ie sickle cell anemia, and the compound heterozygous state for sickle celll genee and that for either Hb C (another chain variant) or thalassemia(termed Hb SC disease or sickle cell thalassemia).
- The sickle cell mutation results in a single amino acid substitution in the globin chain; heterozygotes have one normal(A) and one affected chain (S) gene and produce about 60% hb A and 40% Hb S.; homozygotes produce mainly Hb S with small amounts of hb F.
- Compound heterozygotes for Hb S and Hb C produce almost equal amounts of each variant, whereas those who inherit the sickle cell gene from one parent and thalassemia from the other make predominantly sickle Hb.

Sickling Syndromes

- Hb SS
- HB SC DISEASE
- Hb S/ thalassemia
- Hb S/ thalassemia
- Hb SD

Othe Hb Pathies

- At the end of this lecture
- Hb C ()'b6 Glu- Lys in Westeern Afric
- Hb SC disease
- Hb E

Sickle Cell trati (Hb A and Hb S)

- Less than half the Hb in each RBC IS HB S
- occasionall renal pappillary syndromes

Complication

- Hand and foot syndrome
- Painful crises
- Aplastic crisis
- Splenic sequestration crisis
- Hepatic sequestration crisis
- Lung or brain syndromes
- Gall stones
- Progressive chronic renal failure

Sickle Cell Anemia(homozygous Hb S)

- Anemia
- Gall stones

Pathophysiology

The amino acid substitution in the globin chain causes RBC sickling during deoxygenation, leading to increased rigidity and aggregation in the microcirculation. These changes are reflected by a hemolytic anemia and episodes of tissue infarction.

- Common complications are
  - hemolytic crisis leading to jaundice
  - Sequestration crisis leading to infarctive changes in microcirculation (acute chest syndrome or abdominal pain)
  - hemiparesis due to neurological strella

Geograqphical Distribution

- The sickle cell gene is spread widely in Africa and in countries with African immigrants

Clinical Features

Diagnosis

- Sickle cell anemia should be suspected in any patient of appropriate racial group with a hemolytic anemia.
- It can be confirmed by a sickle cell test, although this does not distinguish between heterozygotes and homozygotes.
- A definitive diagnosis requires Hb electrophoresis and the demonstration of the sickle cell trait in both parents.

Thalassemias

Are classified as thalassemias depennding on which globiun chain is affected

Distribution

Like sickle cell anemia, it is thought to be common due to protection of carriers from malaria.

Diagnosis

- Heterozygotes of thalassemia are asymptomatic, have hypochromic microcytic red cells with a low MCHC and MCV, and have a mean Hb A2 level of about twice normal.
- Sickle cell anemias and Thalassemias are microcytic hypochromic anemias.
- Therefore rule out Iron deficiency and other differentials.

Lab investigations

- Complete Blood Count
- Peripheral Blood Film
- Osmotic fragility
- Hb Electrophoresis
- PCR (DNA analysis)

Thalassemia

- Described by Dr. Thomas Cooley and DR. Pear Lee- 1925
- Osmotic fragilty test 1920's
- Familial pattern recognised 1930's
- Alkali denaturation test for Hb F, Hb ElP
- Coulter model
- RBC indices
- Histogram, DNA analysis, PCR

SUMMARY OF HEMATOLOGIC PARAMETERS

- RBC
- Hb
- Hct
- MCV
- MCH
- MCHC
- RDW
- ZPP/FEP
- HbA2

SUMMARY OF HEMATOLOGIC PARAMETERS IDA

- RBC low
- Hb low
- Hct low
- MCV low
- MCH low
- MCHC low
- RDW high(different sizes)
- ZPP/FEP high
- HbA2 normal

Diagnosis

- PBF
- Sickling test(metabisulfite)
- Demonstrate sickling Hb
- Sickle crisis in low O2 condition
- b6 glu-val substitution
- Prevalent in East Africa
- solubility Test

Perl's stain contains potassium ferrocyanide

A thal Lab Changes

- Hair on end