The module: Molecular, Gene and Diseases

Session 2: Lec4

Lecture Title: Haemoglobin and Myoglobin

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This Lecture was loaded in blackboard and you can find the material in:
(Lippincott's Illustrated Reviews: Cell and Molecular Biology Chapters 2,3)
For more detailed instructions, any question, or you have a case you need help in, please post to the group of session

The Learning Objectives (LO)

4. Explain the physiological roles of myoglobin and haemoglobin.
5. Contrast the oxygen-binding properties of myoglobin and haemoglobin and explain why haemoglobin is most suited to its role as an oxygen transporter.

6. Describe the major structural differences between oxygenated and deoxygenated haemoglobin and the molecular basis of cooperativity.
7. Describe the effects of CO_2, H^+, 2’3bisphosphoglycerate and CO on the binding of O_2 by Hb, and the physiological significance of these effects.
8. Appreciate that mutations in globin genes can give rise to diseases such as sickle cell anaemia or thalassemia.

LO 2.4

Haemoglobin:

Is an iron containing protein that transports oxygen (O_2) in human blood from the lungs to the tissues of the body.

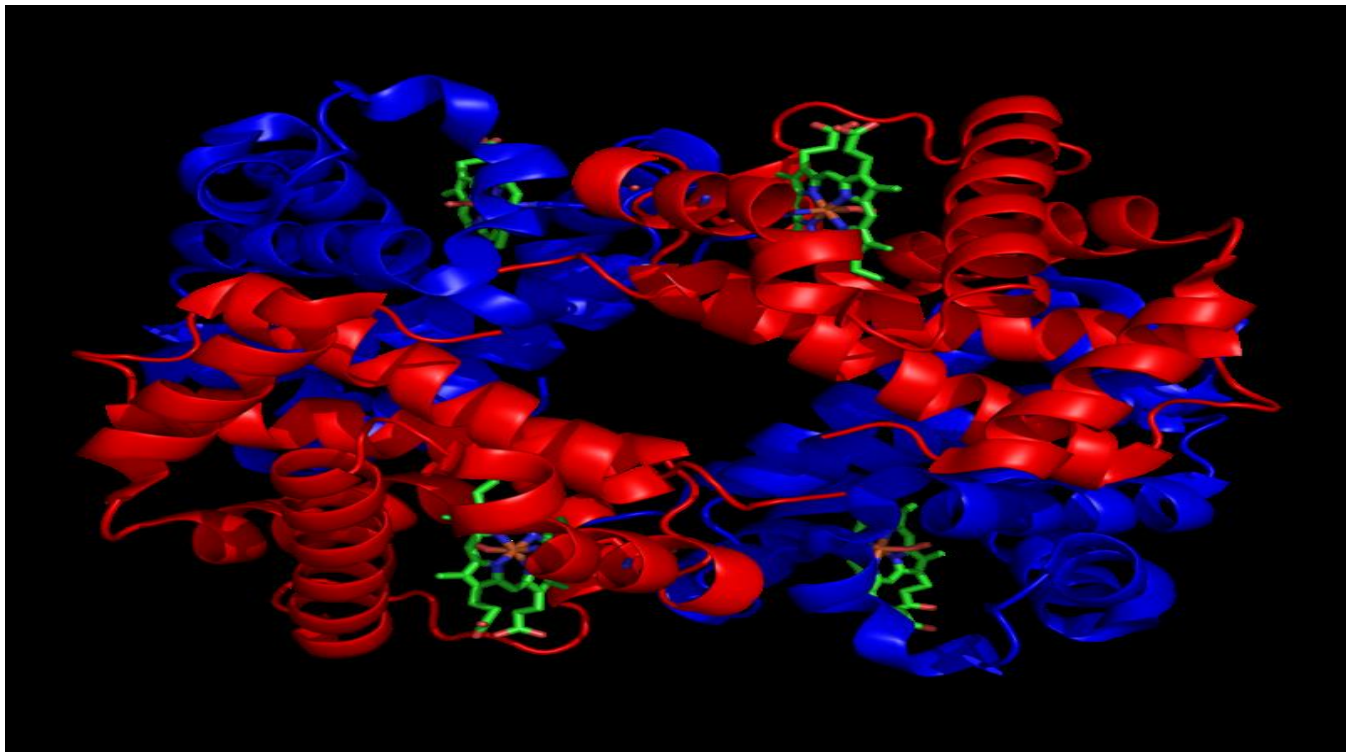
Haemoglobin = heme + globin

Structure of haemoglobin

LO 2.4

Each haemoglobin molecule is made up of four heme

(iron) groups surrounding a globin (protein) group.



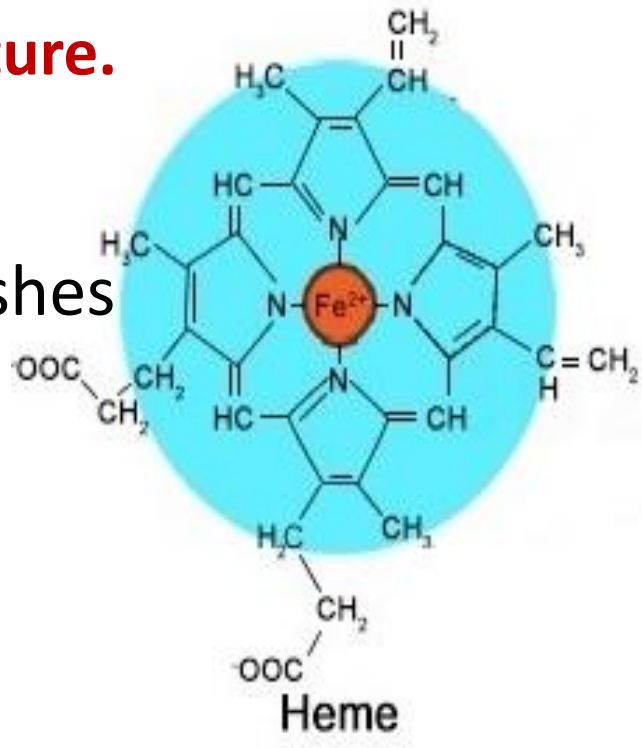
LO 2.4

Heme

- is an iron porphyrin compound.

  Porphyrin is a tetrapyrrole structure.

- Ferrous iron occupies the center of the porphyrin ring and establishes linkages with all the four nitrogens of all the pyrrole rings.



Heme

LO 2.4

Heme

- Iron attached to six coordinated bonds

  4 coordinated bonds planer

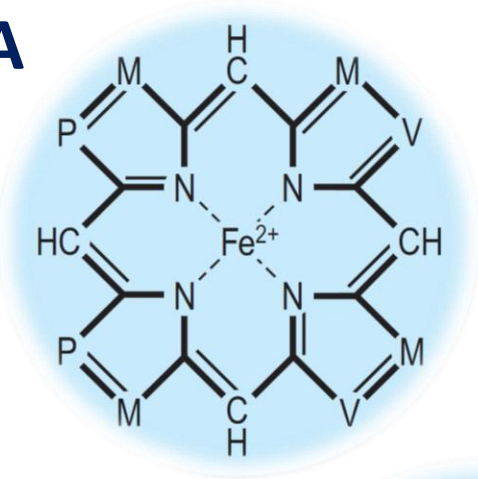
  1 coordinated bond linked to O2

  1 coordinated bond linked to Histidine A.A of α or β globin chain

- The central iron provides the reversible binding to oxygen and carbon dioxide molecules.

LO 2.4

A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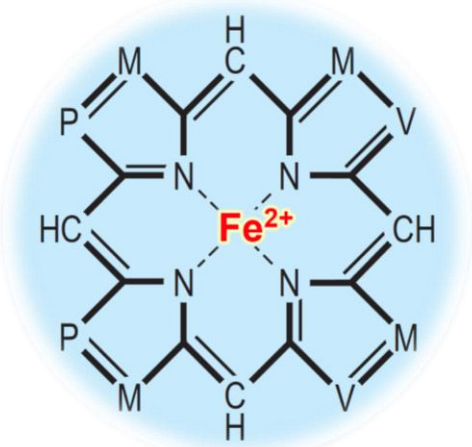
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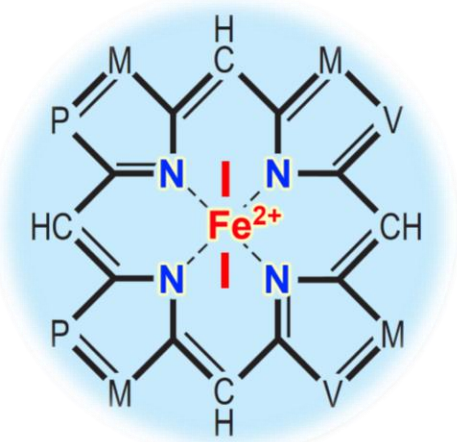
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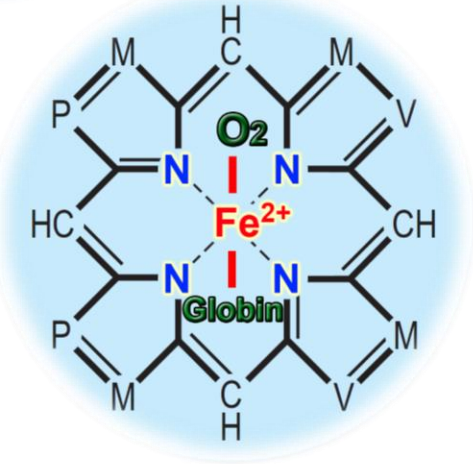
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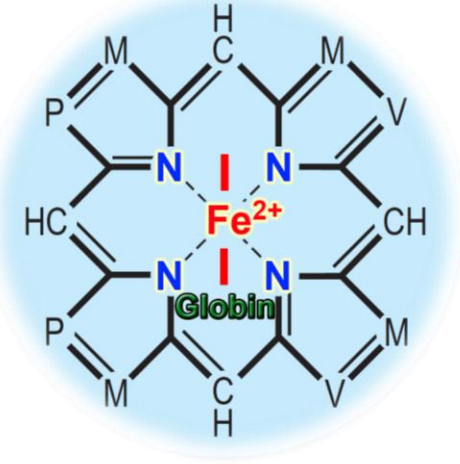
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LO 2.4

In which compounds can we find a heme group

Haemoglobin (Hb).

Myoglobin (Mb).

Cytochromes.

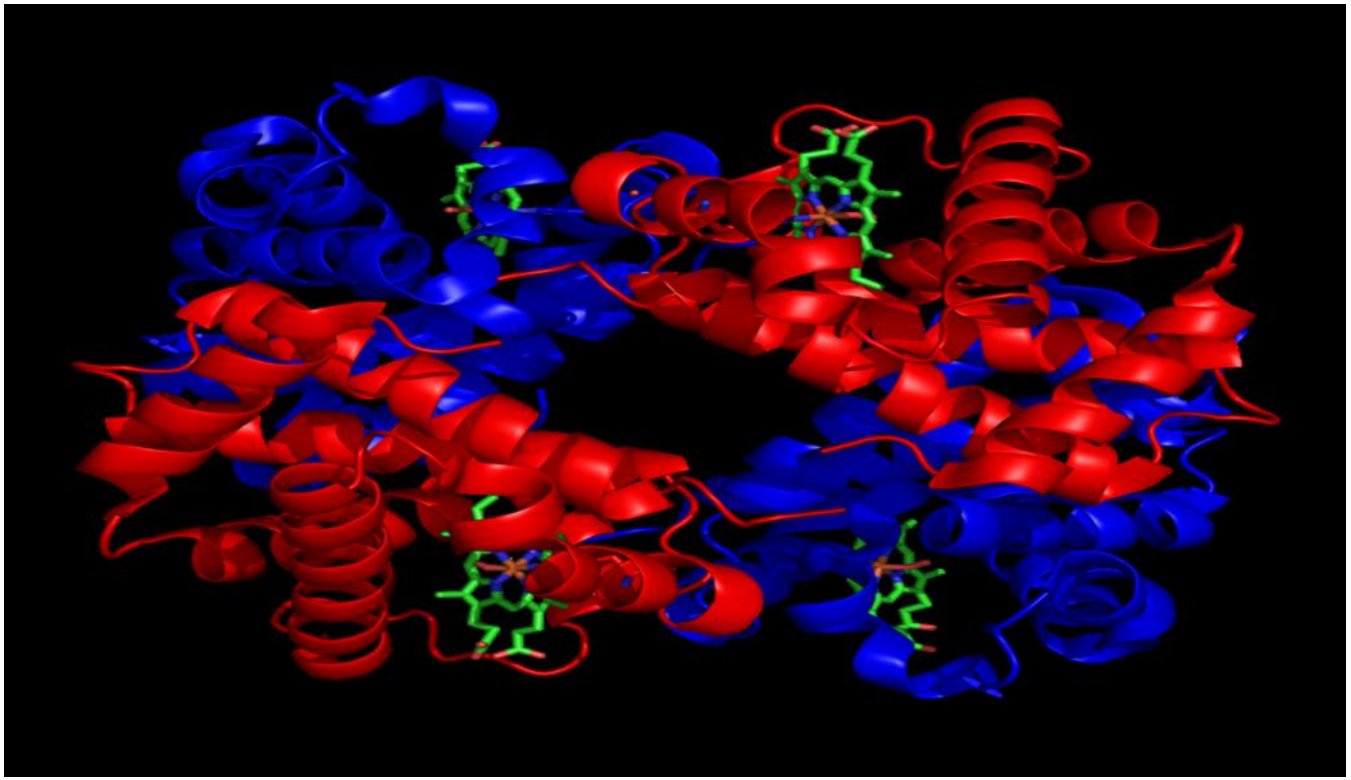
Peroxidase.

Globin:

LO 2.4

- Hb comprises two pairs of globin chains that are twisted together .
- Normal adult hemoglobin contains **141 A.A** in each alpha chain and **146 A.A** in each β chain.

- The complete haemoglobin molecule contains **four haem groups** attached to each of **four globin chains** and may carry up to four molecules of oxygen.



LO 2.4

Normal Hb types in adults

- The main type of Hb is :

1. HbA_1 ($\alpha_2\beta_2$) (97%) consisting of 2 pairs of globin chains **α (141 AA residues)** and **β (146 AA residues)**
2. HbA_2 ($\alpha_2\delta_2$) (2-3%) also found in adult but in small amount.

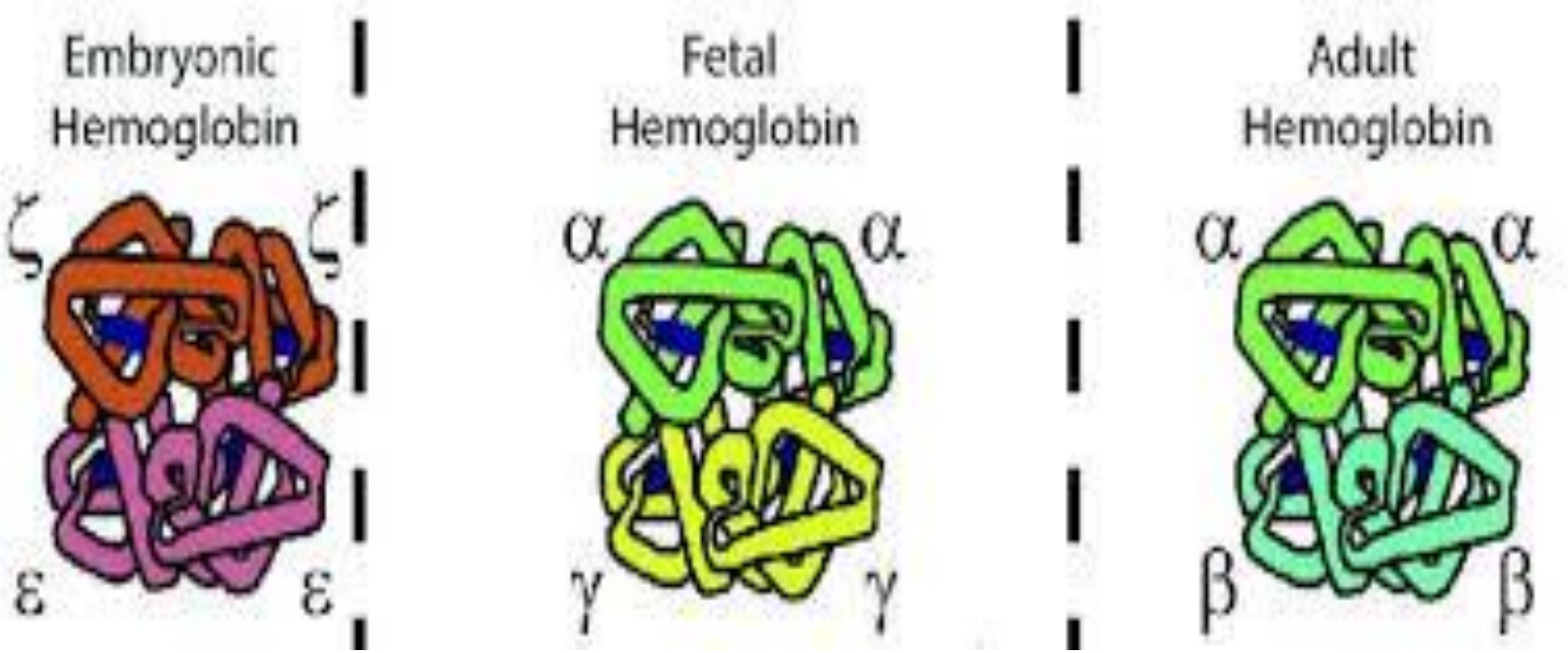
LO 2.4

3. HbF (fetal hemoglobin)($\alpha_2\gamma_2$): Is present primarily in embryonic life, and usually disappears from the circulation by the age of **6 months.**
    - HbF represents less than 1% of the Hb in adults.
    - It having a greater affinity for oxygen than adult haemoglobin.

LO 2.4

4. Gower 1 and 2: are synthesized by the embryonic yolk sac during the first month after conception.

HbE Gower1 (zeta$_2$ε$_2$), HbE Gower-2 (α$_2$ε$_2$)



LO 2.4

NORMAL HEMOGLOBIN

TYPE	COMPOSITION AND SYMBOL	% OF TOTALHEMOGLOBIN
HbA1	α2β2	97%
HbA2	α2δ2	2%
HbF	α2γ2	<1% (at birth 80%)

Haemoglobin synthesis

LO 2.4

Globin

Synthesized by ribosomes in the cytosol.

Embryonic haemoglobins

Gower 1- zeta(2), epsilon(2)

Gower 2- alpha(2), epsilon (2)

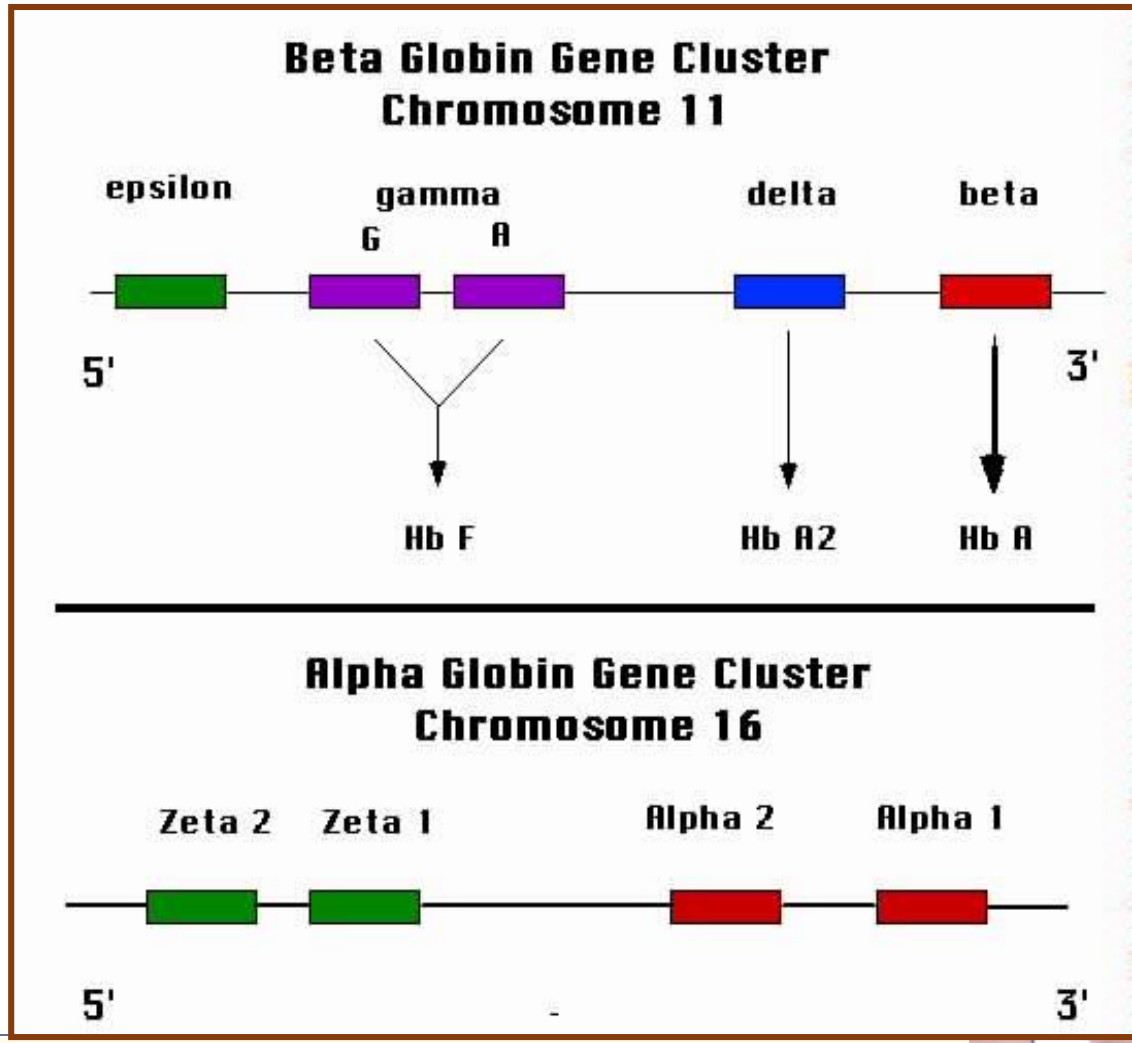
Fetal haemoglobin (HbF)

alpha(2), gamma(2

Adult haemoglobins

HBA- alpha(2), beta(2)

HbA2- alpha(2), delta(2



Haemoglobin synthesis

LO 2.4

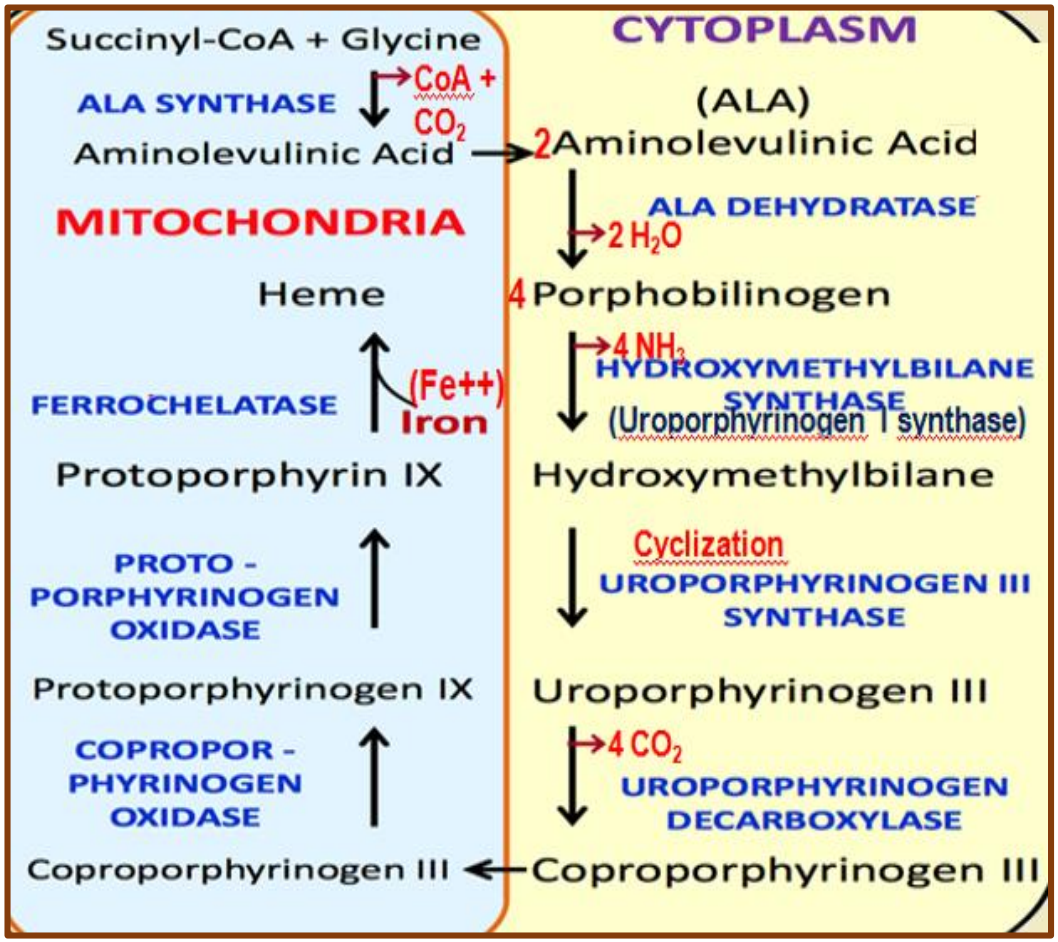
Haem

Synthesized in:
1. bone marrow.
2.liver.

In mitochondria and partly in the cytoplasm.

substrates:
Succinyl-CoA + glycine

It is an eight-step process

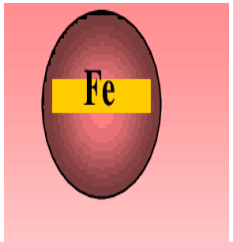


LO 2.4

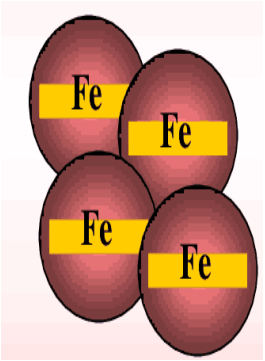
Myoglobin:

- Consists of a single polypeptide chain.
- Structurally similar to the individual globin chain of the Hb molecule.
- It can bind only to one molecule of oxygen with high affinity.
- Store oxygen inside muscle tissue to be used later on when Po_2 be very low.

Myoglobin



Haemoglobin



Haemoglobin vs Myoglobin:

LO 2.4

	HAEMOGLOBIN	MYOGLOBIN
Number of chains	4 polypeptide chains.	single polypeptide chains.
Type of structure	A tetramer.	A monomer.
Binds	Binds CO2, CO, NO, O_2 and H+.	Binds to O_2, tightly and firmly
Their presence	Systemically all over the body.	In muscles cells.
Types of curve	Sigmoid binding curve. (cooperative binding)	Hyperbolic curve.
Also known as	Hb	Mb
Role	It is oxygen carrier	It stores oxygen
Concentration in blood	High in RBC.	Low.

LO 2.5& 2.6

The Hb molecule exists in two forms:

T (tense or taut)

a) is a deoxyhaemoglobin that lacks of oxygen.

b) globin units being held tightly together by electrostatic bonds

R (relaxed)

a) is an oxyhemoglobin (fully oxygenated)

b) bonds are broken when binds to oxygen

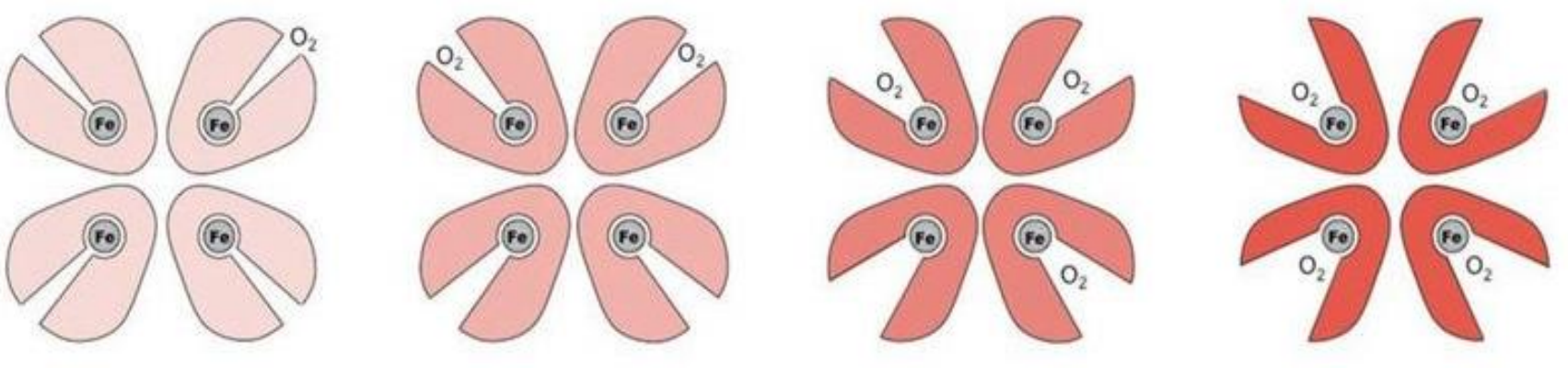
c) Hb has much higher affinity for oxygen than in T form

Cooperative binding of oxygen to Hb:

LO 2.5 & 2.6

- As each O_2 molecule attached, it alters the conformation of Hb, making it easier for others to be loaded with O_2 .

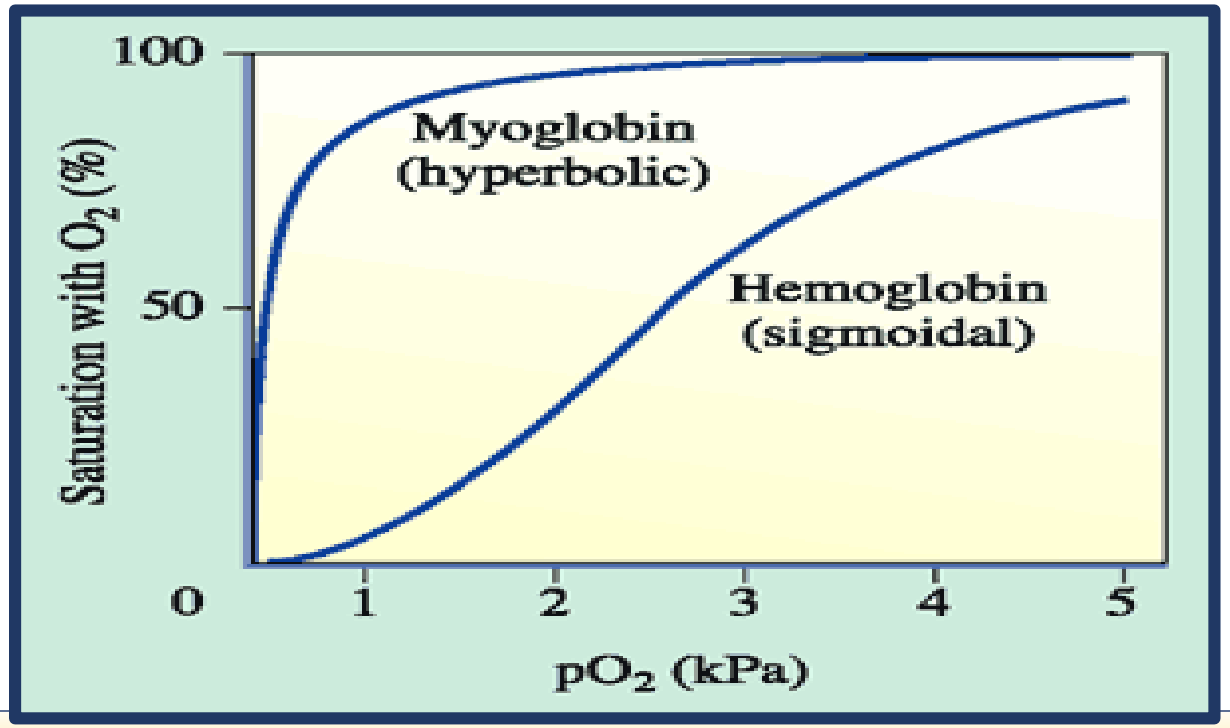
- Conversely, as each O_2 molecule is released, the change in Hb makes it easier for other molecules to be unloaded.



Oxygen Dissociation Curve

LO 2.5& 2.6

- Is a curve that plots the proportion of hemoglobin in its saturated form on the vertical axis against the prevailing oxygen tension on the horizontal axis.



LO 2.5&2.6& 2.7

FACTORS THAT AFFECT OXYGEN DISSOCIATION CURVE OF HB

shift the oxygen dissociation curve to the **right** (low affinity of Hb to O_2) (Bohr effect)

- ↑ temperature
- ↑ PCO_2
- ↓ pH
- ↑ 2,3 DPG

shift the oxygen dissociation curve to the **left** (high affinity of Hb to O_2) (Haldane Effect)

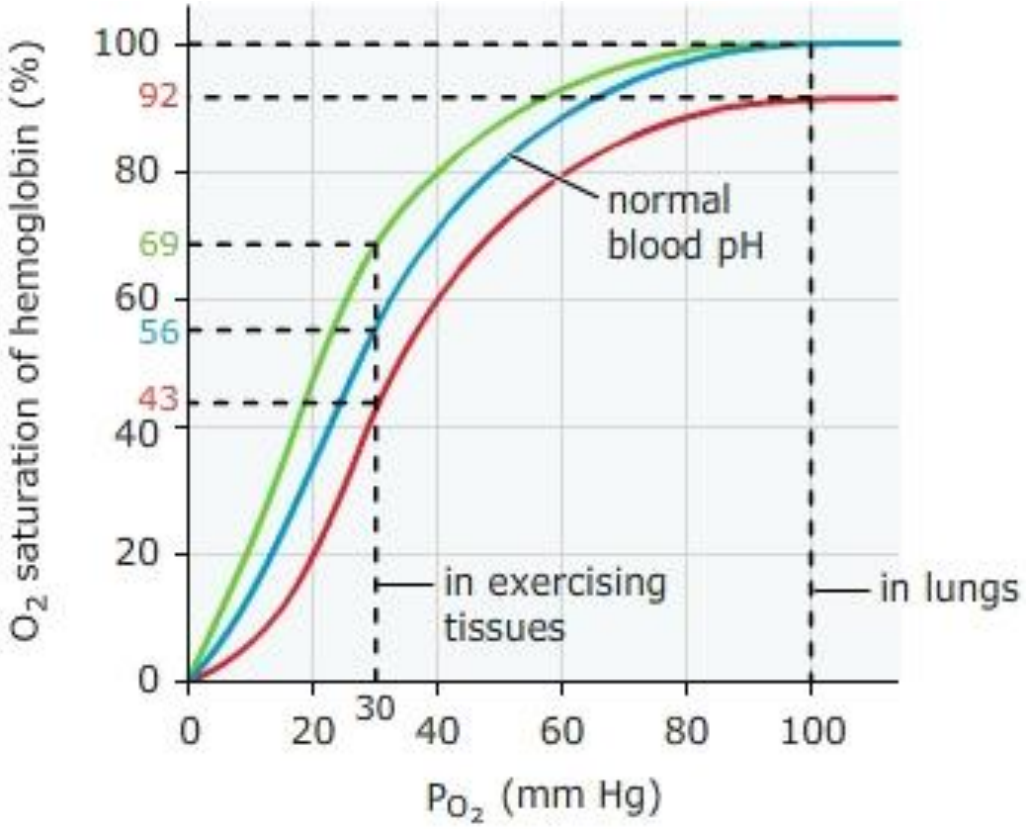
- ↓ temperature.
- ↓ PCO_2
- ↑ pH
- ↓ 2,3 DPG
- ↑ CO poisoning

LO 2.5& 2.6& 2.7

(Bohr effect)

Is a decrease in the O_2 affinity of a Hb in response to:

- ↑ temperature
- ↑ PCO_2
- ↓ pH
- ↑ 2,3 DPG



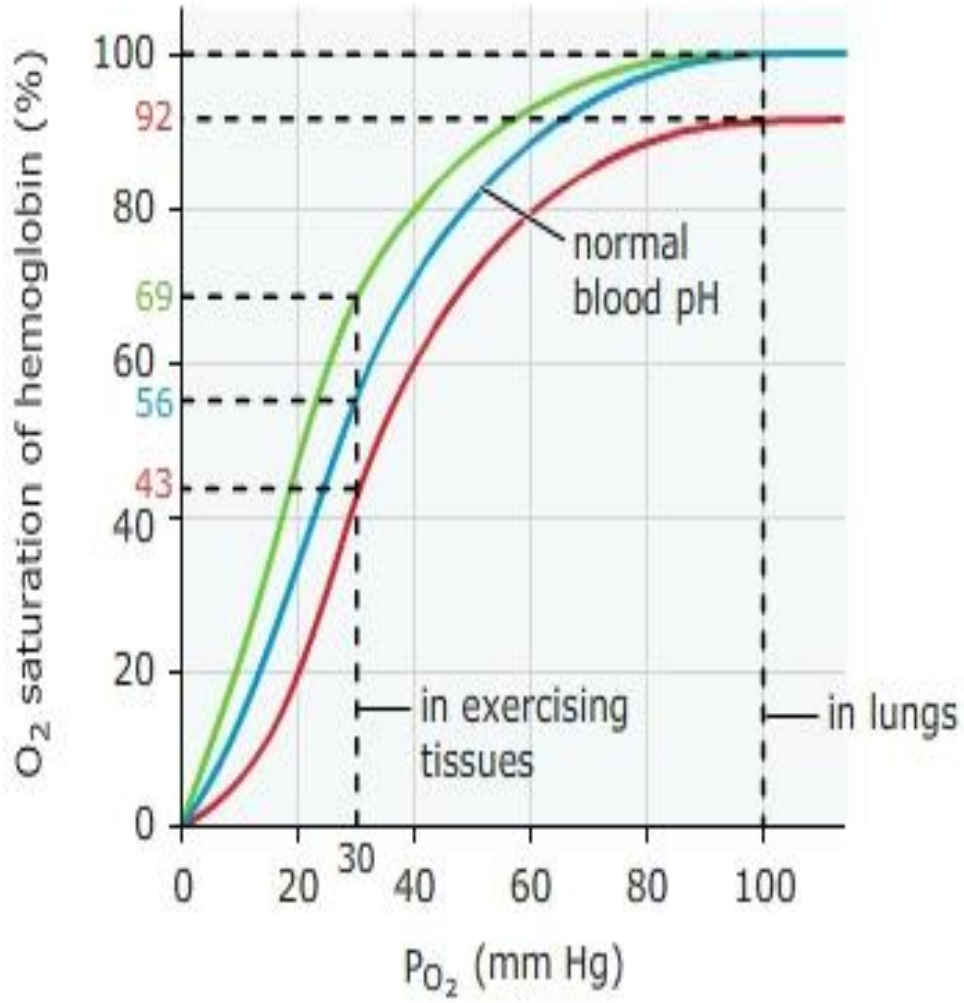
2,3 DPG: Is a special intermediate of glycolysis in erythrocyte that plays a role in liberating O_2 from Hb.

LO 2.5& 2.6& 2.7

(Haldane Effect)

Is an increase in the O_2 affinity of Hb promotes the release of PCO_2 in response to:

- ↓ temperature.
- ↓ PCO_2
- ↑ pH
- ↓ 2,3 DPG
- ↑ CO poisoning



LO 2.6 & 2.7

Why 2,3-BPG decreases the oxygen affinity of Hb ?

Explain why patient with CO Poisoning has cherry red or pink cheek appearance.?

LO 2.6 & 2.7

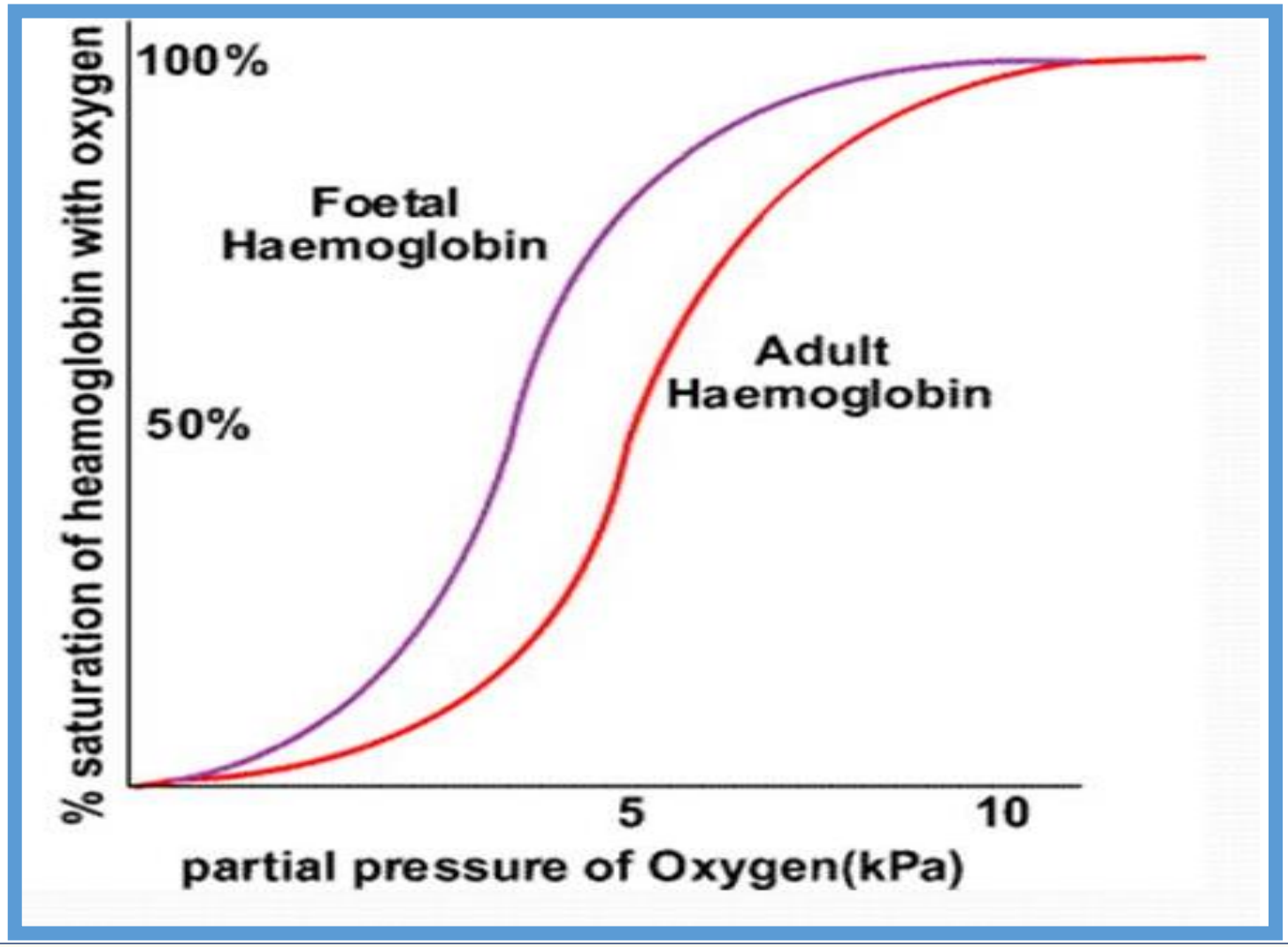
2,3-BPG decreases the oxygen affinity of Hb by binding to deoxyhaemoglobin but not to oxyhaemoglobin. This binding stabilizes the taut form of deoxyHb.

When CO binds to one or more of the haem sites, Hb shifts to the relaxed form causing the remaining haem sites to bind oxygen with high affinity

LO 2.6 & 2.7

Why Hb F has high oxygen affinity than Hb A ?

LO 2.6 & 2.7


% saturation of heamoglobin with oxygen
100%
50%
Foetal
Haemoglobin
Adult
Haemoglobin
5
10
partial pressure of Oxygen(kPa)

LO 2.6 & 2.7

1) Hb F having **γ subunits** that allows to bind more strongly to oxygen

2) **2,3-BPG** interacts much more with **Hb A than Hb F**. because the **adult β subunit** has more **positive charges** than the **fetal γ subunit**, which attract the negative charges from 2,3-BPG.

Due to the preference of 2,3-BPG for Hb A, Hb F binds to oxygen with high affinity.

LO 2.8

Haemoglobin abnormality (haemoglobinopathy):

Is a variant form of **Hb** that is often inherited and may cause a blood disorder in

- **heme production**
  - **Porphyria**
- **globin synthesis**
  - **Structure**
    - **Sickle cell disease**
  - **production**
    - **Thalassaemia**

LO 2.8

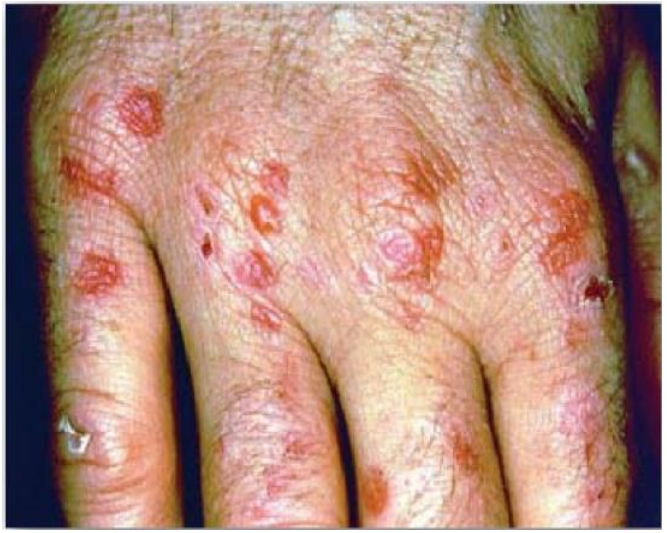
Porphyria

- Is a group of disorders caused by abnormalities in the chemical steps that lead to heme production.

- The most common types of porphyria are:

a) Acute intermittent porphyria (AIP).

b) Porphyria Cutanea Tarda (PCT)



LO 2.8

Sickle Cell Anaemia.

Caused by a mutation in the β-globin gene that changes the sixth amino acid from **Glutamic acid (charged AA)** to **valine (nonpolar AA)**.

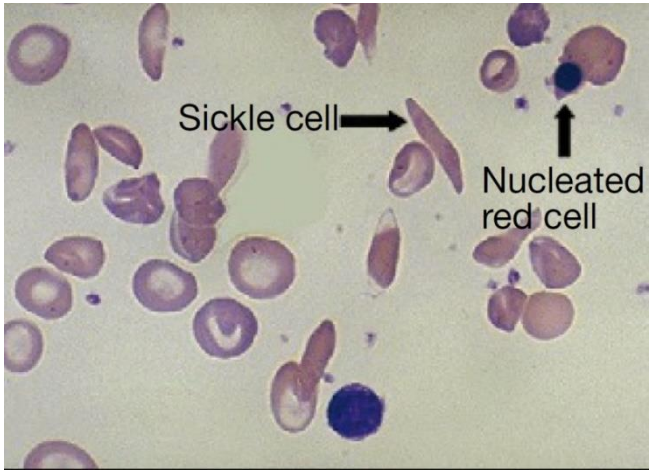
a) **Homozygotes** only produce **abnormal β-chains** that make **HbS**.

b) **Heterozygotes** produce a **mixture of normal and abnormal β-chains** that make normal HbA and HbS **(HbAS),**

LO 2.8

Sickle Cell Anaemia.

When HbS is deoxygenated, the molecules of Haemoglobin polymerize to form **pseudocrystalline** structures known as '**tactoids**'. These distort the red cell membrane and produce a characteristic of **sickle-shaped cells**.



LO 2.8

Thalassaemia

There is a reduced **rate of production** in one or more of the globin chains. Which results in imbalanced globin chain synthesis.

α-Thalassaemia.

defect in the synthesis of α globin chain.

β-Thalassaemia

defect in the synthesis of β globin chain.

α-Thalassaemia.

LO 2.8

- Single-gene mutation (-α/αα) → Clinically silent
- Two-gene mutation (-α/-α) or (αα/--) → microcytic anemia
- Three-gene mutation (--/-α); HbH disease → β chains precipitate as β4 tetramers (HbH). → Moderately severe
- Four-gene mutation (--/--) (hydrops fetalis) → forming γ4 tetramers (Hb Bart's) → Incompatible with life

LO 2.8

β-Thalassaemia.

mutations in the β-globin gene

↓

generation of a stop codon in mRNA

↓

termination of globin chain synthesis

↓

variable reduction in β globin output

LO 2.8

Types of β-Thalassaemia.

1. Thalassaemia major (Cooley's Anemia). — severe transfusion-dependent
2. Thalassaemia intermedia — Intermediate in severity
3. Thalassaemia minor — The symptomless carrier state


Thank
You