Haemoglobin L4

- Haemoglobin is responsible for transport of oxygen from lungs to the tissues and of carbon dioxide from tissues to the lungs. In order to achieve this gaseous exchange they contain the specialized protein haemoglobin.
- Each RBC contains approximately 640 million Hb molecules (MW 64,500 daltons). The Hb molecule is a complex structure made up of 4 subunits (monomer). Each monomer consists of a heme and a globin unit.
- The globin portion of the molecule consists of four (or two pairs of) polypeptide chains. One haem group is bound to each polypeptide chain.
- Each molecule of normal adult haemoglobin A (Hb A) (the dominant haemoglobin in blood after the age of 3–6 months) consists of four polypeptide chains, α2β2, each with its own haem group.
- Normal adult blood also contains small quantities of two other haemoglobins: Hb F and Hb A_2. These also contain α chains, but with γ and δ chains, respectively, instead of β.

  The relative proportions of different haemoglobins are:
- Adults—HbA 97%,
- HbA_2 2.5%, and
- HbF 0.5%;
- Newborns—HbF 80% and HbA 20%.

Structure of heme

Heme is a chemical structure made up of a porphyrin ring with an iron atom inserted in the center, which is attached to 4 nitrogen atoms. The porphyrin ring structure is present in hemoglobin, myoglobin, cytochrome, chlorophyll, and in many oxidases and catalases form in almost all living organisms.

All living organisms have the ability to synthesize these porphyrin structures except *Hemophilius* group of bacteria. Porphyrin structures bind with magnesium in chlorophyll, with cobalt in vit. B12 and bind with either bivalent or trivalent iron in heme. In the case Fe^{+2}**,** it is called ferrous heme; in the case Fe^{+3}, it is called ferric heme.

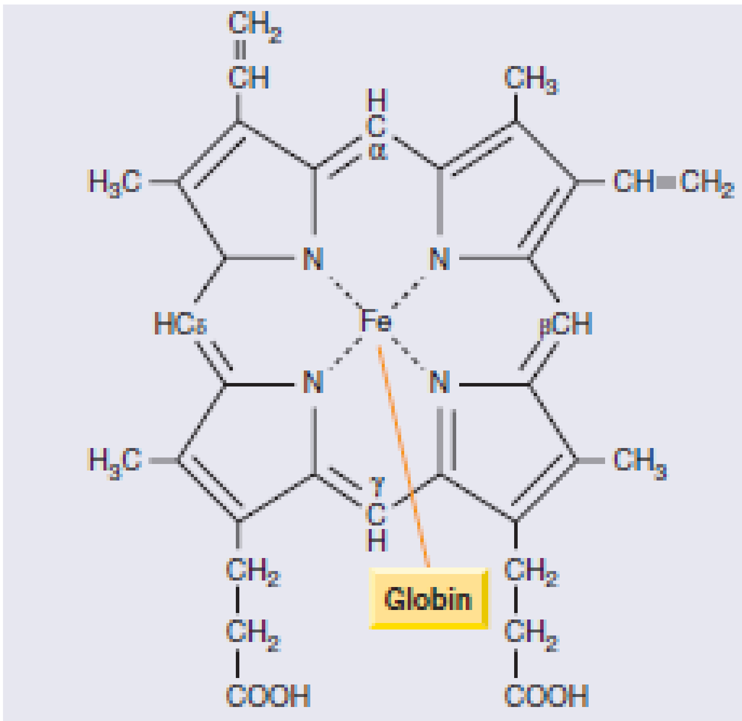
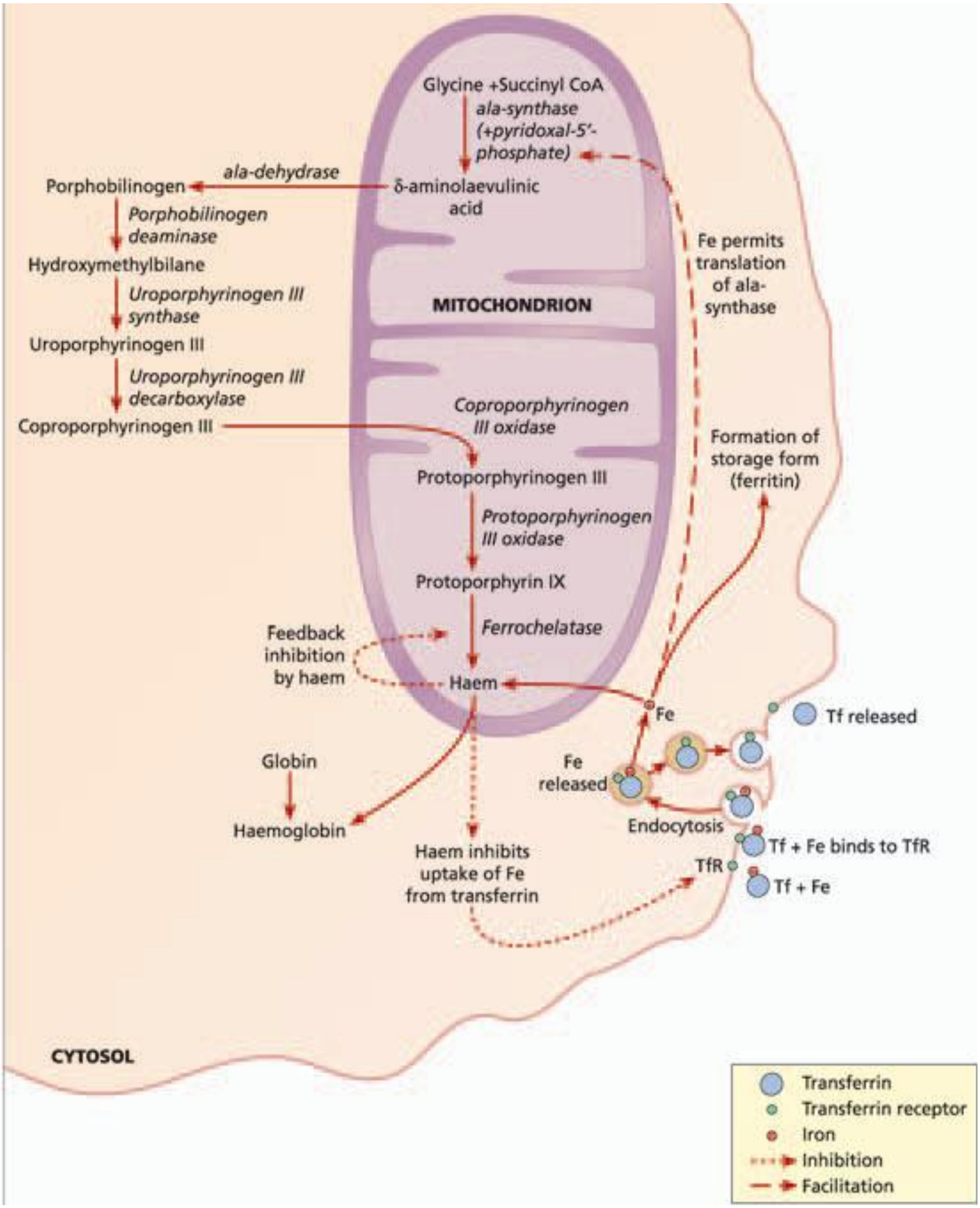
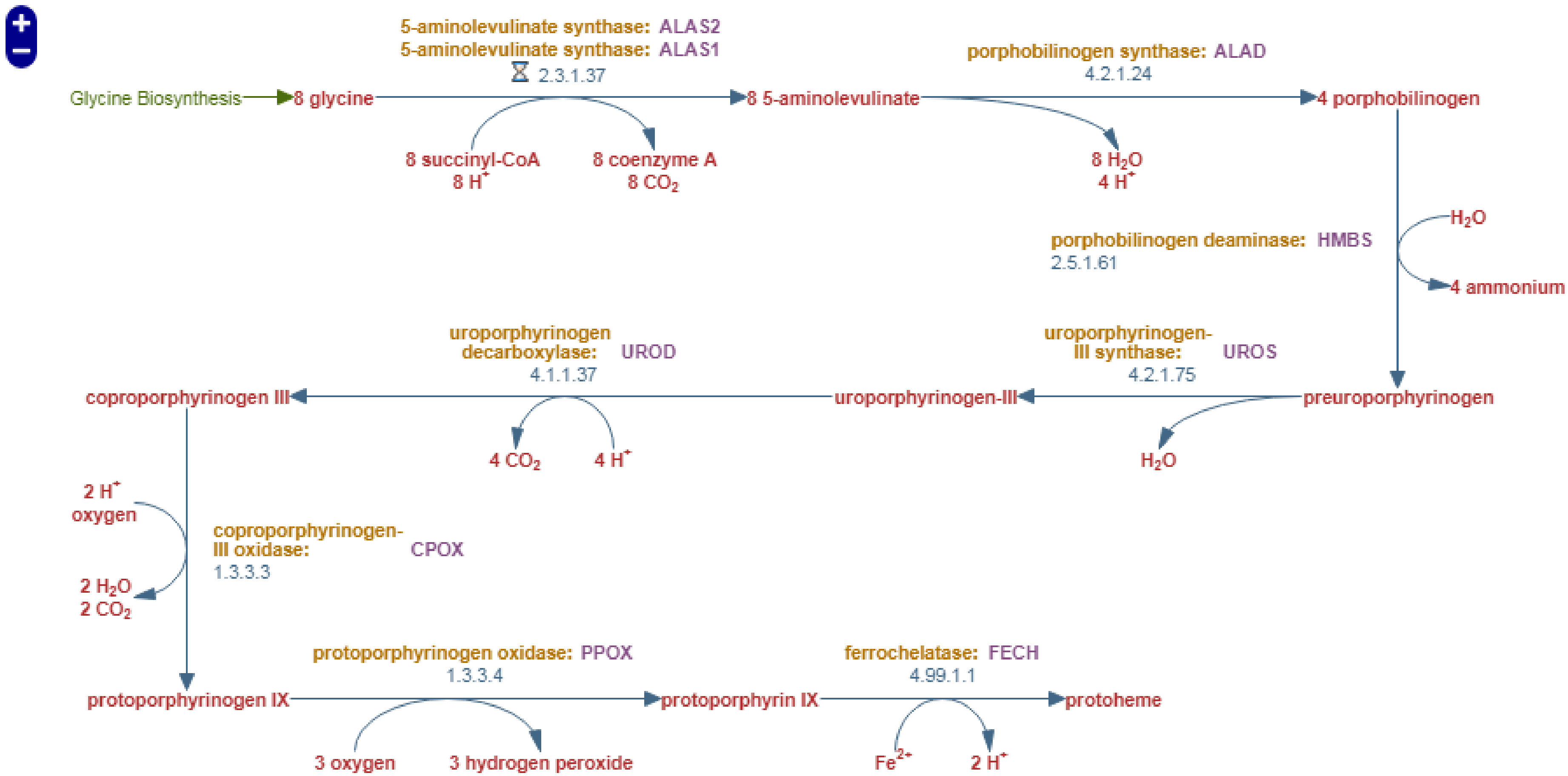


Figure 2.8 The structure of haem.

Biosynthesis of heme




5-aminolevulinate synthase: ALAS2
5-aminolevulinate synthase: ALAS1
2.3.1.37
Glycine Biosynthesis
8 glycine
8 5-aminolevulinate
8 succinyl-CoA
8 H^+
8 coenzyme A
8 CO_2
porphobilinogen synthase: ALAD
4.2.1.24
4 porphobilinogen
8 H_2O
4 H^+
porphobilinogen deaminase: HMBS
2.5.1.61
H_2O
4 ammonium
uroporphyrinogen decarboxylase: UROD
4.1.1.37
uroporphyrinogen-III synthase: UROS
4.2.1.75
coproporphyrinogen III
uroporphyrinogen-III
preuroporphyrinogen
4 CO_2
4 H^+
H_2O
2 H^+
oxygen
coproporphyrinogen-III oxidase: CPOX
1.3.3.3
2 H_2O
2 CO_2
protoporphyrinogen oxidase: PPOX
1.3.3.4
ferrochelatase: FECH
4.99.1.1
protoporphyrinogen IX
protoporphyrin IX
protoheme
3 oxygen
3 hydrogen peroxide
Fe^{2+}
2 H^+

Structure of Globin

The globin portion of the hemoglobin monomer is a protein**.** The normal adult tetramer is made up of 4 polypeptide chain include two α- chains (contains141 A.A & 15.126 M.W) and two β-chains (β &γ chain contains 146 A.A & 15.886 M.W). Fetal haemoglobin (HbF), the predominant haemoglobin in fetal life, contains a pair of alpha (α) and a pair of gamma (γ) chains.

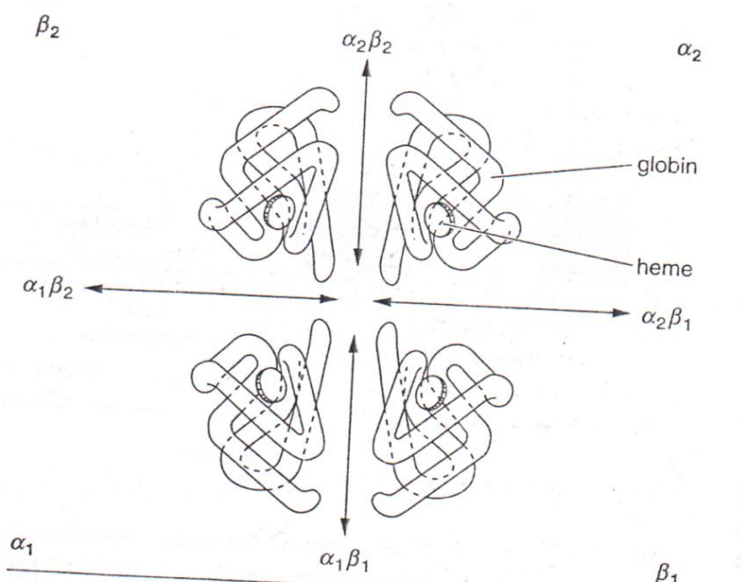


figure 5.9

The quaternary structure of hemoglobin showing the contacts between monomers.

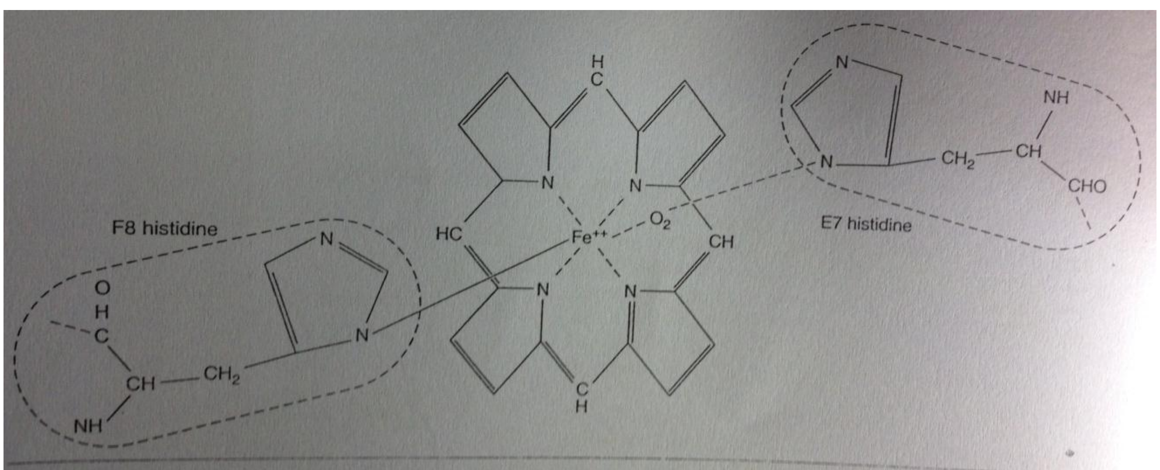


figure 5.8

The six valences of iron (Fe) in the globin monomer.

Variations in Hemoglobin

These variations may be classified under two broad headings; normal and abnormal variations.

Normal hemoglobin Variations

Normal hemoglobin variations fall into three categories: **embryonic**, **fetal**, and **adult**.

There are three kinds of **embryonic** hemoglobin:

Gower 1, which is made up of two ζ- and two ε-chains or (ε4);

Gower 2, composed of two α and two ε-chains;

Portland, which has two ζ- and two γ-chains. These hemoglobins occur early in gestation and are soon replaced by.

Fetal hemoglobin (HbF), which consists of two α - and two γ-chains. Before birth, this fetal type is gradually replaced by **adult hemoglobin (HbA),** of which there are two types:

HbA1, made up of two α and two β-chains; and

HbA2, which consists of two α - and two δ-chains. The most important of these is HbA1, which accounts for about 97% of the total HbA. Two other variations of Hb made up of normal globin chains occur in certain disorders are known as

HbH (β4) and

Hb Barts (γ4).

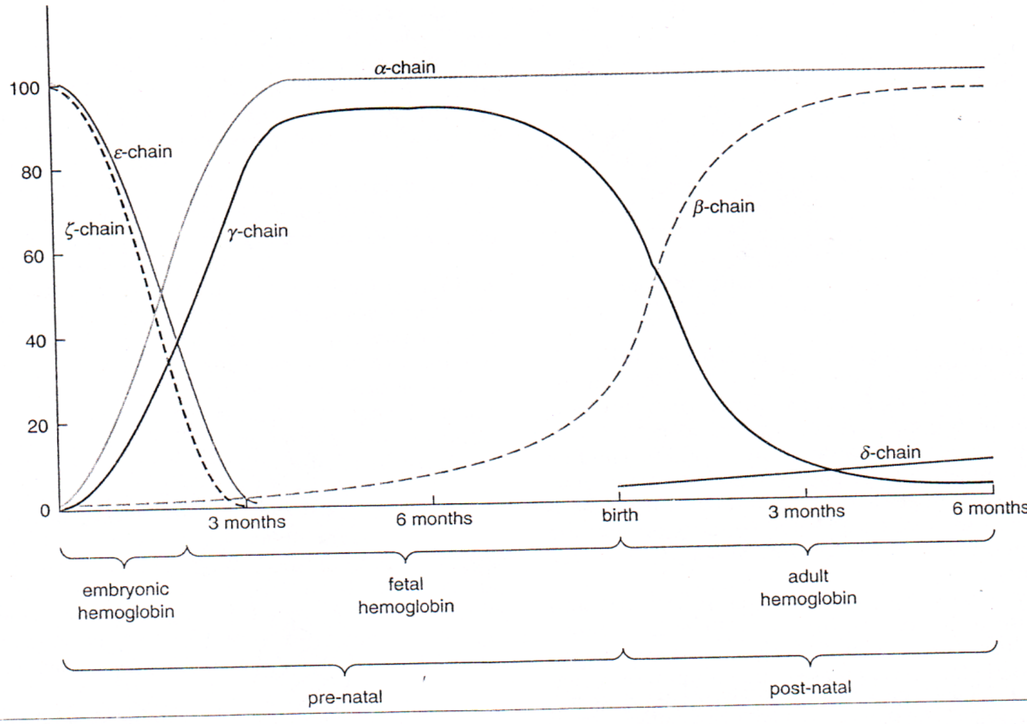


Figure 5.10

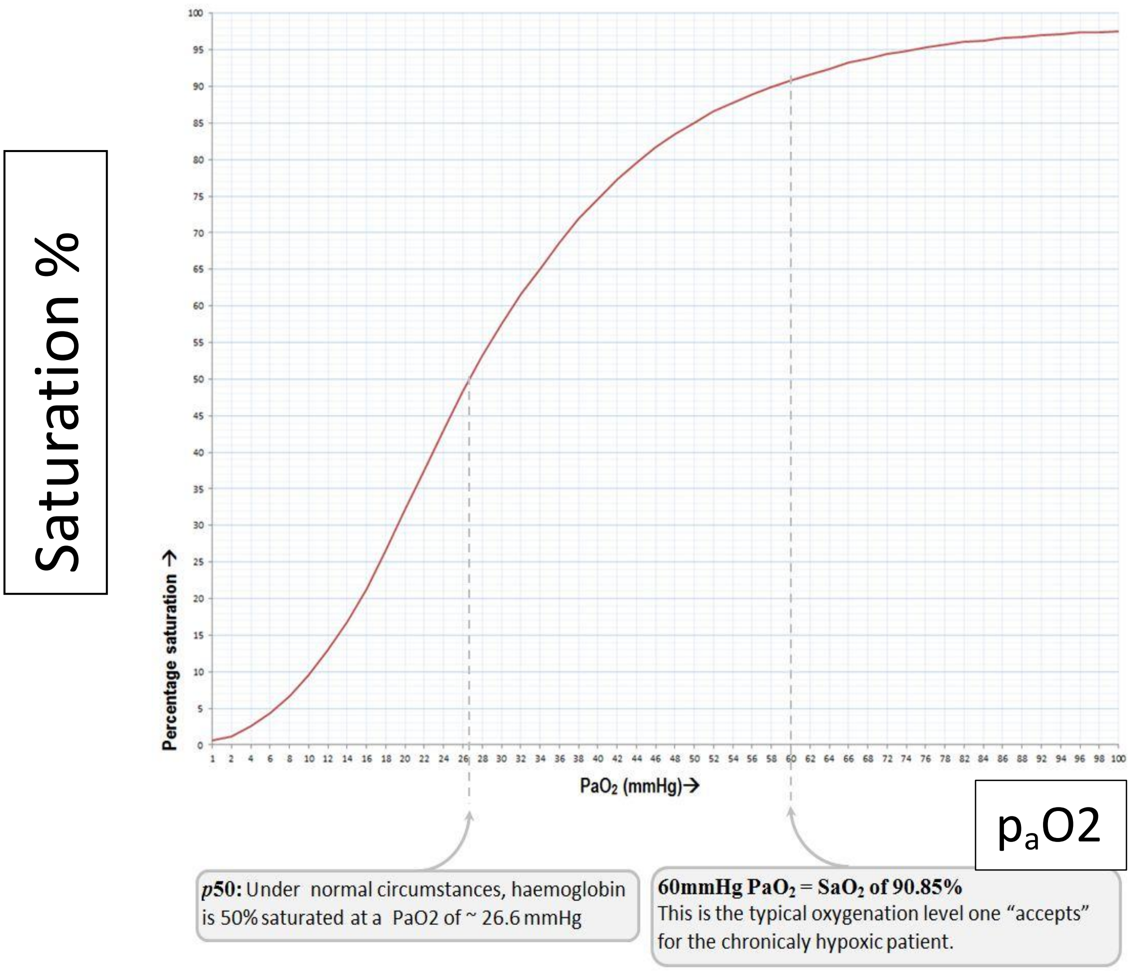
The relative rates of globin chain synthesis during embryonic, fetal, and neonatal life.
From D. L. Rucknagel, *Clinical Obstetrics and Gynecology,* 12:49, 1969. Copyright © 1969 J. B. Lippincott Company, Philadelphia, PA. Reprinted by permission of the publisher and the author.

Table 5.1 Summary of Normal Human Hemoglobins

Hemoglobin	Structure	Co
A	$\alpha_2\beta_2$	Cc
A_{1c}	α_2 (β-NH-glucose)$_2$	Cc
A_2	$\alpha_2\delta_2$	Cc El
F	$\alpha_2\gamma_2$	Pr
		Fa
		In
Gower 1	ϵ_4 or $\zeta_2\,\epsilon_2$	Pr Fu
Gower 2	$\alpha_2\epsilon_2$	Pr Fu
Portland	$\zeta_2\gamma_2$	Pr Fu
H	β_4	Fc Lc N
Barts	γ_4	Tı M
		N

Oxygen dissociation curve

- The S-shaped curve produced when the percentage saturation of haemoglobin with oxygen is plotted against the partial pressure of oxygen (pO_2), which is a measure of the oxygen concentration in the surrounding medium.



- The steep rise of the curve indicates the high affinity of haemoglobin for oxygen: a small increase in pO_2 results in a relatively sharp increase in the percentage saturation of haemoglobin with oxygen. Therefore in the lungs, where the pO_2 is high, the blood is rapidly saturated with oxygen.

- Conversely, a small drop in pO_2 results in a large drop in percentage saturation of haemoglobin. Thus in tissues that utilize oxygen at a high rate, where the pO_2 is low, and oxygen readily dissociates from haemoglobin and is released for use by the tissues.

Forms of O_2 in Blood

In the blood, O_2 is carried in two forms:

1- Dissolved O_2

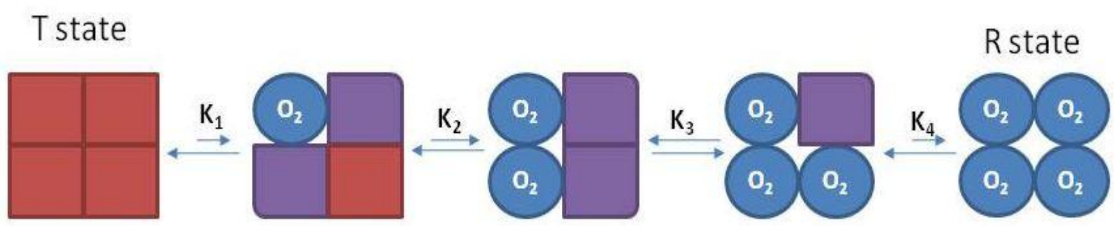
2- O_2 bound to hemoglobin (called O_2- hemoglobin).

PO_2 of the blood.	% saturation	
10	25%	
20	35%	
25	50%	(P50)
30	60%	
40	75%	(mixed venous blood)
50	85%	
60	90%	
80	96%	
100	98%	(≈ 100% arterial blood)

- The O_2-hemoglobin dissociation curve has a sigmoidal shape. Thus, rather than a linear relationship between percentage saturation (%) and PO_2, the percentage saturation increases steeply between a PO_2 of zero and 40 mm Hg, then increases less steeply between 40 and 60 mm Hg, and then is nearly flat between 60 and 100 mm Hg.
- **Why the O_2-hemoglobin dissociation curve has a sigmoidal shape.**
- The sigmoidal shape results from positive cooperativity of O_2 binding to hemoglobin. As each successive O_2 binds, it increases the affinity for the next O_2. Binding of the first O_2 increases the affinity for the second O_2, etc. Affinity for the

fourth (last) O_2 is the highest, which corresponds to the portion of the curve where % saturation is near or at 100%.

- Each gram of haemoglobin can combine with 1.34 mL of oxygen.

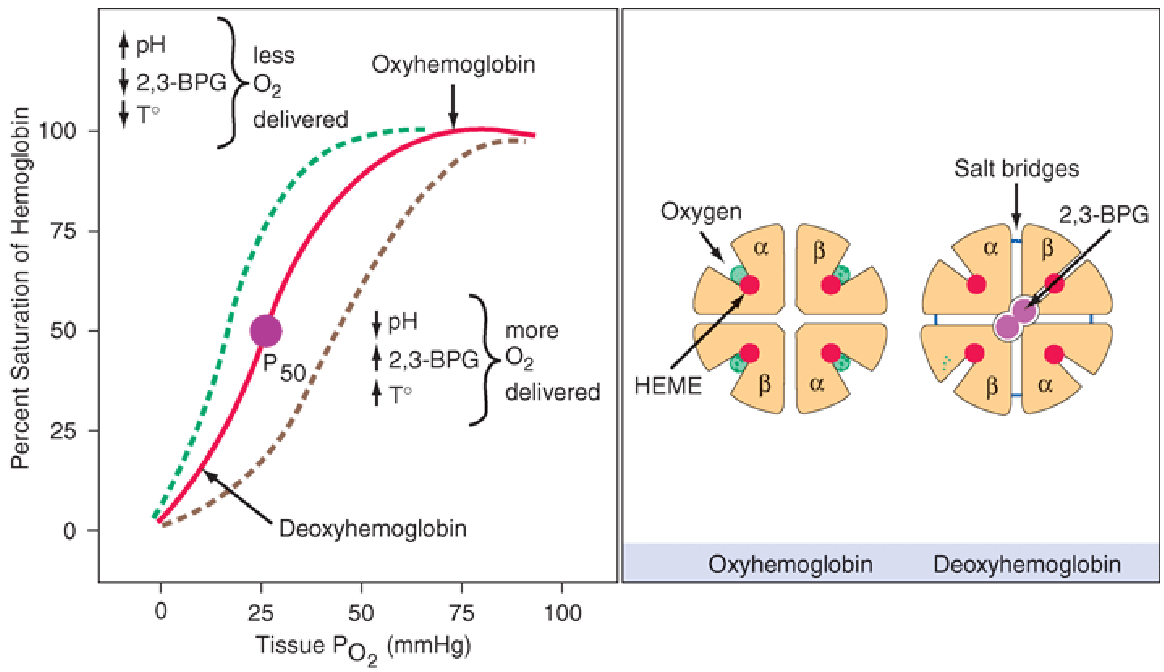


The factors that affect O_2 dissociation curve

1. **Increases in PCO_2 and decreases in pH**, lower affinity of Hb for oxygen. Such as those occurring when there is increased metabolic activity in a tissue (e.g., during exercise called the Bohr Effect).

2. **Increases in temperature**, such as during exercise. Increasing the temperature lower affinity of Hb for oxygen, this increases the amount of oxygen in a tissue. Increasing the temperature denatures the bond between oxygen and haemoglobin, which increases the amount of oxygen and haemoglobin and decreases the concentration of oxyhaemoglobin.

3. **Increases in 2, 3-diphosphoglycerate (2, 3-DPG).** 2, 3 DPG binds to the β chains of deoxyhemoglobin and reduces their affinity for O_2. 2, 3 DPG an intermediate product of glycolysis that is present within the erythrocyte. During hypoxia (such as at high altitude), 2, 3 DPG production in red cells increases, causing a helpful decrease in the affinity of hemoglobin for O_2 (facilitates O_2 unloading in tissues).



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

<u>How does methaemoglobin affect the curve?</u>

- Methaemoglobin is an abnormal form of haemoglobin in which the normal ferrous form is converted to the ferric state. Methaemoglobinaemia causes a left shift in the curve as methaemoglobin does not unload oxygen from haemoglobin.

Fetal haemoglobin

- Fetal haemoglobin (HbF) is the main oxygen transport protein in the human fetus during the last 7 months of development. It persists in the newborn until roughly 6 months of age. HbF has different globin chains to adult haemoglobin (Hb). Whereas adult haemoglobin is composed of two alpha and two beta subunits, fetal haemoglobin is composed of two alpha and two gamma subunits. This change in the globin chain results in a greater affinity for oxygen and allows the fetus to extract blood from the maternal circulation. This increased affinity for oxygen means that the oxygen dissociation curve for fetal haemoglobin is shifted to the left of that of adult haemoglobin.

- Hemoglobin F (HbF).
  The mechanism of the left-shift with HbF relates to 2,3 DPG, which binds weakly to the γ chains of HbF than to the β chains of HbA. With less 2,3 DPG bound to HbF, the O_2 affinity increases, lowering the PO_2 of the fetus and facilitating O_2 diffusion from mother to fetus.

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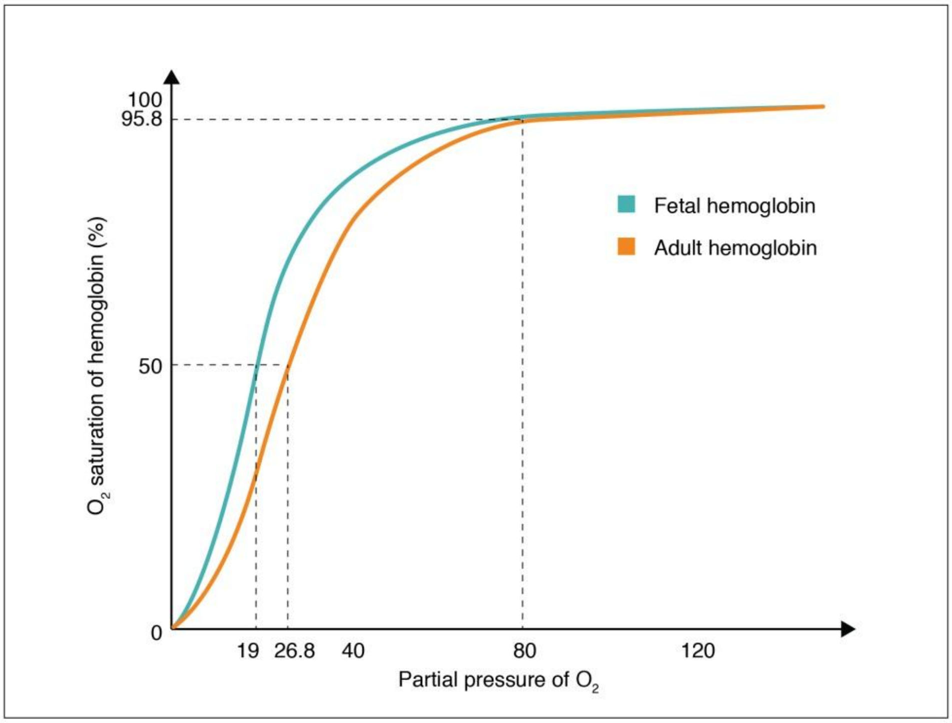

Myoglobin:

- The curve for myoglobin lies even further to the left than that of fetal haemoglobin and have a hyperbolic, not sigmoidal, shape. Myoglobin has a very high affinity for oxygen and acts as an oxygen storage molecule. It only releases oxygen when the partial pressure of oxygen has fallen considerably. The function of myoglobin is to provide additional oxygen to muscles during periods of anaerobic respiration.