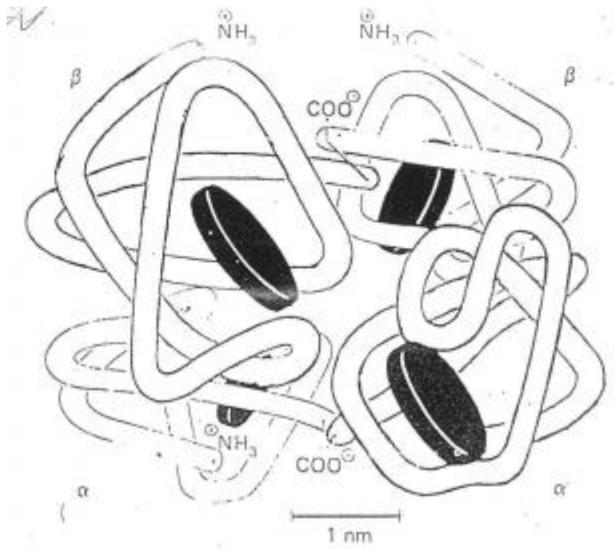
In the previous lecture we talked about erythropoiesis and its regulation by many vitamins like vitamin B12 and folic acid, proteins, iron and trace elements copper and cobalt. Also we talked about pernicious anemia or megaloblastic anemia. Folic acid deficiency causes megaloblastic anemia.

Also the liver has an important role because it is a multifunctional organ that synthesizes proteins, and hormones (erythropoietin, growth hormone, steroids, androgens, and thyroid hormones) which play role in erythropoiesis.

Hemoglobin

It is the oxygen carrying element in the blood.



This is a diagrammatic presentation of a molecule of hemoglobin, showing its 4 subunits. There are two alpha and two beta polypeptide chains, each containing a heme moiety (represented by the disks).

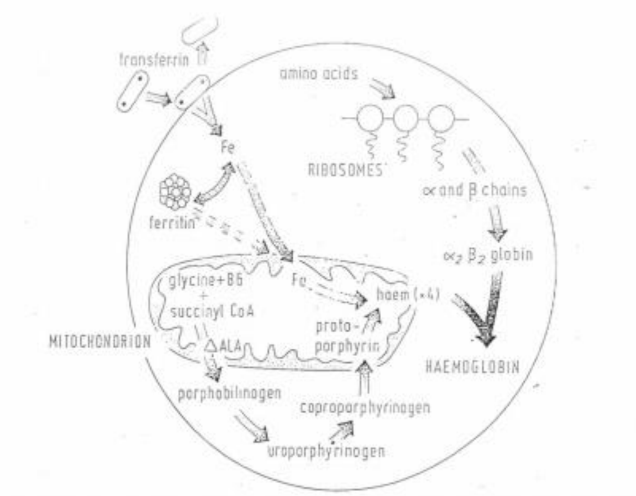
Each alpha subunit has 141 amino acids, and each beta subunit has 146 amino acids.

Hemoglobin has globin part and heme part. Heme part 6%, globin part ~ 94%. We conclude that hemoglobin is considered a protein, its molecular weight is 68,000 Dalton.

Heme part binds oxygen, and globin part binds the other elements like CO2, hydrogen and 2,3-DPG.

Hemoglobin concentration in males is about 16g/100ml blood. In females it is 14g/100ml blood, but sometimes we use one figure for both considering it is 15 g/100ml for both.

Hemoglobin synthesis:



Hemoglobin synthesis occurs in all developing RBCs, heme part synthesis occurs in the mitochondria and globin part on the ribosomes.

Heme part begins by the combination of glycine and succinyl Co-A under the effect of an enzyme called aminolevulinic acid synthase (ALAS) producing delta aminolevulinic acid (ALA) –an intermediate in the synthesis. So this enzyme is essential for this reaction.

For this reaction also we need vitamin B6, which is stimulated by erythropoietin and inhibited by the heme.

Then finally, protoporphyrin is formed and binds with ferrous forming heme which then binds to the globin part (the 4 subunits) forming hemoglobin.

**65% of hemoglobin synthesis occurs in the erythroblast stage (cells with nuclei), and 35% in reticulocyte stage. (remember that many reticulocytes are found in bone marrow, sometimes equal to those with nuclei, they remain in the bone marrow for 2 to 3 days then they are released to circulation), the percentage of reticulocytes in the circulation is about 1% which indicates normal erythropoiesis. No hemoglobin synthesis occurs in mature RBCs (erythrocytes).

The 2 alpha 2 beta structure of hemoglobin is called adult hemoglobin, there are other hemoglobin types, some of them are not seen in the newborn nor in the adult, which are: Gower 1, Gower 2 and Portland.

Table 4-4. Normal Human Hemoglobins—Genetic Variants

Name	Designation	Molecular Structure	Proportion in Adults	Proportion in Newborns
Adult hemoglobin	A	$\alpha_2\beta_2$	97%	20%
Hemoglobin A_2	A_2	$\alpha_2\delta_2$	2.5%	0.5%
Fetal hemoglobin	F	$\alpha_2\gamma_2$	<1%	80%
Portland		$\zeta_2\gamma_2$	0	0
Gower I		$\zeta_2\epsilon_2$	0	0
Gower II		$\alpha_2\epsilon_2$	0	0

We see in the table the molecular structure of each hemoglobin type:

Adult hemoglobin : alpha, beta.
Hemoglobin A2: alpha, delta.
Fetal hemoglobin: alpha, gamma.
Portland: zeta, gamma.
Gower 1: zeta, epsilon.
Gower 2: alpha, epsilon.
So of these 6 types found in human being, the last three are only found in fetus and not found in newborns or adults.
**See please in the table the proportions of each type of hemoglobin in adults and newborns.

This graph shows the proportions of hemoglobin in newborn, adult, and fetal hemoglobin:

The fetal hemoglobin is gradually replaced by adult hemoglobin. 6 months after birth, it is totally replaced by adult hemoglobin. We see in the diagram how gamma chain is decreasing and beta chain is increasing.

Myoglobin also is a protein that contains a heme moiety carrying oxygen in the muscles, and the affinity of this myoglobin for oxygen is very high. And also lately they found another heme protein called neuroglobin in the nervous system.

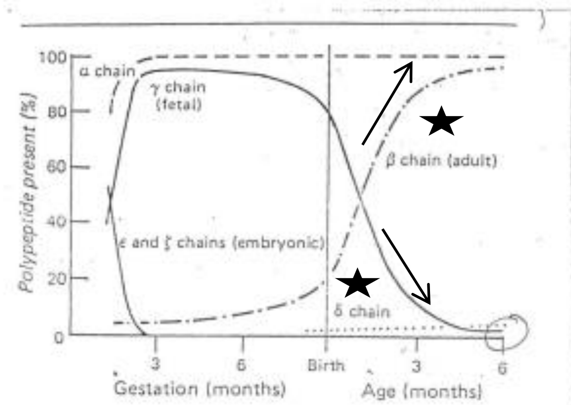
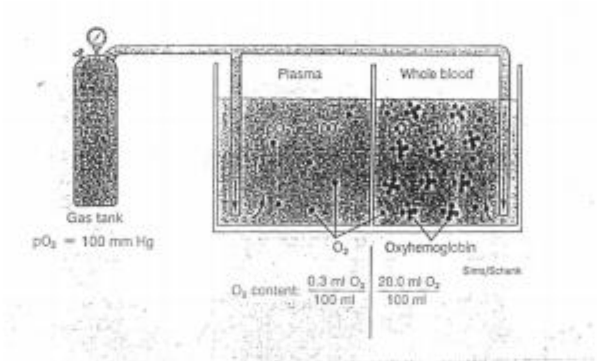


Figure 27–14. Development of human hemoglobin chains.



1g of hemoglobin carries 1.34 ml oxygen. We have 20 ml oxygen/100 ml of the whole blood, and 0.3 ml oxygen/100 ml plasma. So the capacity of hemoglobin in the blood to carry oxygen is higher than the capacity of plasma (mostly water) which almost doesn't carry any oxygen.

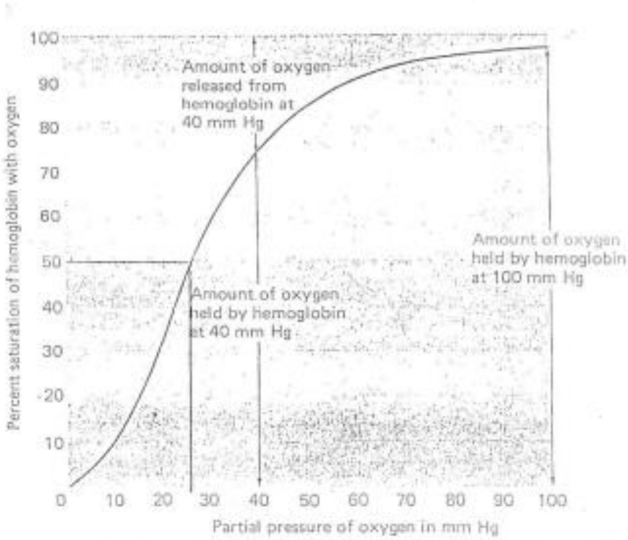


Figure 17.15 Hemoglobin Dissociation Curve for Oxygen in an Adult

When we draw the saturation of hemoglobin against the partial pressure of oxygen (PO_2) we get this figure, which is the hemoglobin dissociation curve in an adult human.

From this figure we understand three points:

1- Normally, when the partial pressure of oxygen in the lungs is about 100%; not all hemoglobin becomes saturated with oxygen but only 97%. More or less than that is pathological.
2- At tissue level, when partial pressure of oxygen is 40 mmHg; just 25% of oxygen is released, and the remaining is still held by the hemoglobin.
3- We can determine the partial pressure of oxygen when 50% of hemoglobin is saturated, we call it P50. In the figure we see that the P50=26 mmHg.

This curve is always the same for any person, despite the difference in Hb concentration.

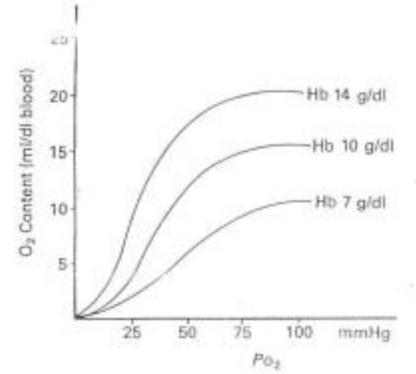


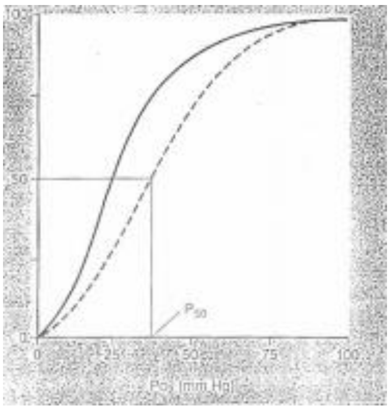
Fig. 6.12 Effect of anaemia on oxygen content of the blood at different Po_2 values.

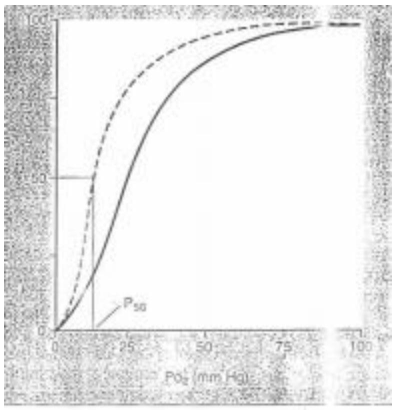
This figure shows the relation between oxygen content and PO_2. In this relation we get different curves depending on hemoglobin concentration. So here we have different curves whether hemoglobin concentration is 7, 10 or 14 g/dl.

*We have 4 subunits in hemoglobin molecules, these subunits do not bind at the same time with oxygen molecules, they bind one by one. Binding of the first heme with the first oxygen molecule facilitates the binding of the second one and so on.

**In one RBC there are more than 500 million hemoglobin molecules.

We said that the hemoglobin dissociation curve in an adult human is always the same and does not change, but sometimes in the same individual in some conditions this curve changes:





The curve shifts to the right

*P50 is increased.

*Affinity of hemoglobin for O_2 is decreased, which means there is demand for oxygen.

*Factors that shift the curve to the right:

↑ Partial pressure for CO_2

↑ 2,3-DPG

↑ Temperature

↓ PH

The curve shifts to the left

*P50 is decreased.

*Affinity of hemoglobin for O_2 is increased, which means either a pathological condition or that there isn't much need for oxygen.

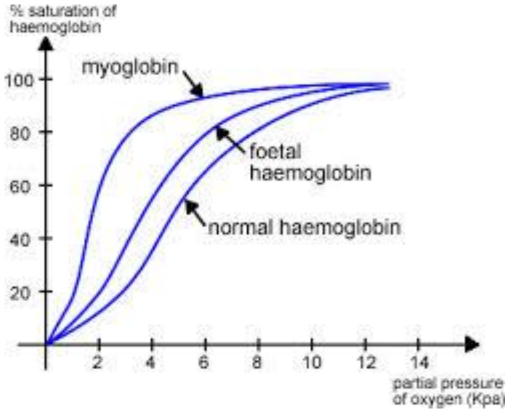
*Factors that shift the curve to the left:

↓ Partial pressure for CO_2

↓ 2,3-DPG

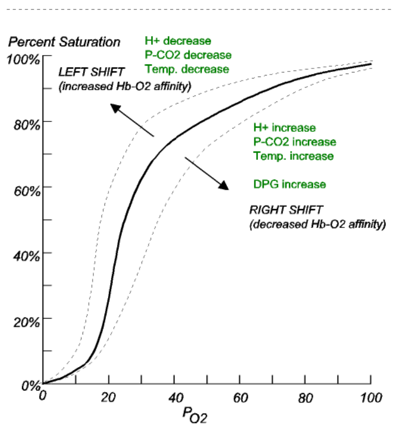
↓ Temperature

↑ PH

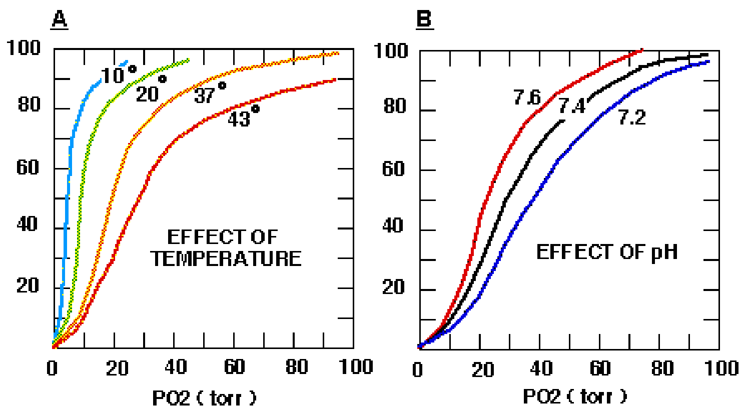


Here we see the differences in dissociation of oxygen from adult hemoglobin and fetal hemoglobin. In fetal hemoglobin the curve is shifted to the left, P50 is low and the affinity is high.

And we see myoglobin and hemoglobin, the myoglobin curve is too much shifted to the left, which means that myoglobin in the muscles does not release oxygen unless the partial pressure for oxygen is very low and there is s o much need.



With 2,3-DPG, the curve is shifted to the right, which means there is need for oxygen. In hypoxia 2,3-DPG is high.



Here we see the effect of pH and temperature. When the temperature is high the curve shifts to the right.

When the PH is high the curve shifts to the left, and when it is low it shifts to the right.

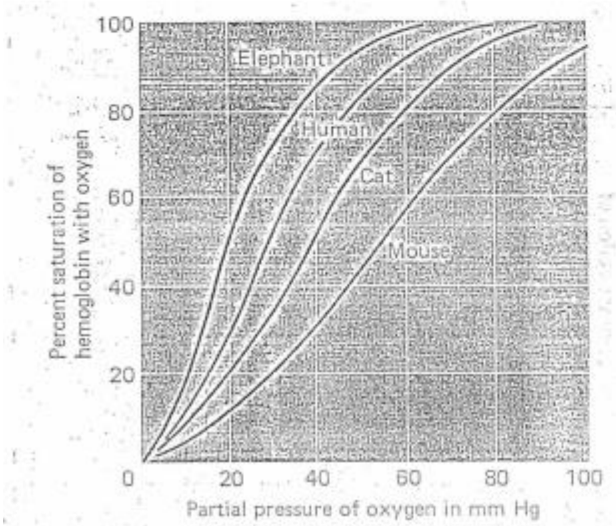


Figure 17.18 Effects of Mammalian Size on Oxygen Dissociation from Hemoglobin.

Here we apply the oxygen dissociation from hemoglobin curve to other mammals.

The elephant is too much to the left, because it is lazy. The cat and mouse are on the right, they move a lot. The human is in between.

Blood parameters

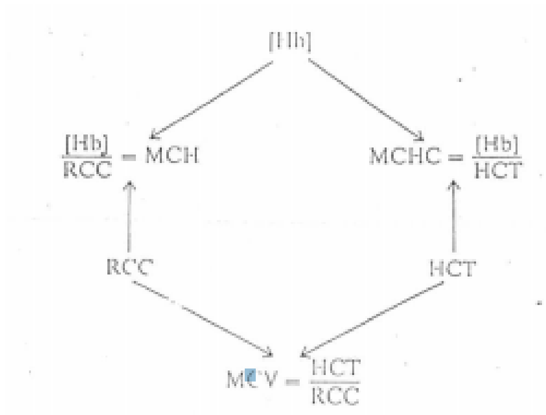
We know three parameters:

- Red blood Cell Count (RCC): normally: 4.5 million to 6 million cell/mcL in males, and 3.8 million to 5 million cell/mcL in females.

- Hematocrit (HCT).

-Hemoglobin concentration of the blood [Hb]: in males 16 g/ml, in females 14 g/ml.

We use these three parameters to calculate other parameters as the following diagram shows:



Mean Cell Hemoglobin (MCH): Indicates the amount of hemoglobin in the red blood cell, and should always correlate with the MCV and MCHC (this point will be discussed more in a while).

MCH = (Hemoglobin * 10) / RBCs count in millions

Normal value= 28-32 Picograms/cell, It is almost fixed within this range.

If it was below 28 pg/cell then the cell is hypochromic. If it was above 32 pg/cell, the cell is hyperchromic.

*The MCH actually does not give us the right knowledge, it indicates the amount of hemoglobin in one RBC in Picograms, it does not indicate if it is normal or not. You have to relate this MCH to MCV (Mean Cell Volume) and MCHC (Mean Cell Hemoglobin Concentration). If the hemoglobin occupies 32-36% of MCV then the RBC is normal.

So MCH alone is not enough, it should be correlated with MCV and MCHC.

(This is like when you want to know the right measures of a person, you should relate the weight to the height and not only depend on one of these measurements; an 80 kgs person seems fat, but knowing its height is 1.85 meters then his weight seems normal).

For example; in pernicious anemia if we just take MCH it is hyperchromic but when we relate it to MCV it is normochromic.

Mean Cell Hemoglobin Concentration (MCHC): Indicates whether the red blood cells are normochromic, hypochromic, or hyperchromic.

MCHC= (Hemoglobin*100)/hematocrit

Normal value= 32-36%

An MCHC below 32% indicates hypochromia, an MCHC above 36% indicates hyperchromia, and RBCs with normal MCHC are termed normochromic.

Mean Cell Volume (MCV): Indicates whether the red blood cells appear normocytic, microcytic (in anemia or thalassemia), or macrocytic. So it indicates the volume of the cells.

MCV= (Hematocrit * 10)/RBCs count in millions

Normal value= 80-100 fL (femtoliters, or 10^-15 L).

If the MCV is less than 80 fL the RBCs are microcytic. If the MCV is greater than 100 fL the RBCs are macrocytic. If the MCV is within the normal range the RBCs are normocytic.

So all these parameters are used to diagnose different types of anemia.

~If you light a lamp for someone it will also brighten your path~

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Aseel Abbad