Hematology

- Histology
- Biochemistry
- Pathology
- Pharmacology
- Physiology
- Microbiology

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lecture number : 2

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Handout | Sheet | Slide

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BODY FLUIDS 2.0

Note: some sentences weren't very clear so I referred back to last year's sheet and used them here.

-Vitamin B12

Vitamin B12, we said all the vitamins play a role in erythropoiesis but vitamin b12 and folate are **essentials** in erythropoiesis, how?

Firstly, vitamin b12 is essential for DNA formation, i.e without it, no DNA, having low vitamin b12 is impossible but there still could be deficiency, and when there is a deficiency, the count of RBCs would drop. So the first function of vitamin b12 is: DNA formation

Secondly, Vitamin b12 it is needed for the normal function of myelin sheath in the nervous system (CNS).

Vitamin b12 pathway is also called extrinsic pathway, maturation pathway or cyanocobalamin pathway.

In the stomach, vitamin b12 binds to the intrinsic factor that is produced by the gastric mucosa cells, then this complex goes down to the lower ileum where it is absorbed into circulation, and goes either into bone marrow (where erythropoiesis takes place) or liver in order to be stored.

In vitamin b12 deficiency, the number of RBCs produced is low, (low count) but these cells are larger than normal, they contain a lot of haemoglobin, mcv is high sometimes reaching 160micro cubules? The cells would be oval in shape with a short half-life.

Deficiency of vitamin b12 due to diet is very rare, because 2-3mg of vitamin b12 is sufficient for normal body function for 2-4years, so the main deficiency would be due to a problem in the production of the intrinsic pathway.

Anemia due to deficiency of vitamin b12 is called pernicious anemia, or megaloblastic anemia.

The role of folic acid similar to vitamin b12 but does not affect mylination, so just the RBCS count is affected, the cells produced due to vit. b12 are similar to cells produced by folic acid, so we have to know the causes in order to distinguish between the two.

Folic acid is reabsorbed through the jejunum from the upper part of the small intestine.

Causes of vitamin b12 deficiency:

1. Veganism

2. Malabsorption:

a. gastric causes : congenital lack of intrinsic factor, total or partial gastroectomy

b.intestinal causes: Chronic tropical sprue (diarrhea), illeal resection

Causes of folic acid deficiency

1. Inadequate dietary intake

2. malabsorption: coeliac disease, jejunal resection, tropical sprue (diarrhea)

3. Increased requirement: pregnancy, premature infants, chronic haemolytic anemia

Iron requirements

Iron is the forth factor, after oxygen, vitamin b12 and folate, we have 5-6 grams of it in our body.

What is the role of iron in the body?

Production of HAEMOGLOBIN and certain enzymes

Daily intake: 15-20mg, however, we only benefit from 4% (less than 1 mg)

Iron is found in ferrous state (Fe2+) and ferric state (Fe3+), the body can utilise only the ferrous iron.

In the digestive system, mainly the stomach, the iron is converted into ferrous state as an effect from the acidic conditions, iron is bound to heme (part of HAEMOGLOBIN), in the epithelial cells there are enzyme that split iron from heme, then it (iron) is absorbed into circulation and binds to transferrin which carries 2 ferrous iron molecules at a time, the transferrin carries the iron to the apical membrane of epithelial cells then it enters the cells while transferrin remains out, inside the epithelial cells there is ferritin which also transports the iron.

Excess Iron stays in epithelial cells, its fate is determined according to the half-life of the epithelial cell, it can be either absorbed or lost.

Absorption of iron occurs in small intestine almost always, highest in duodenum, less in the jejunum, lesser in the lieum, and least in colon (very little).

Estimated daily iron requirements

IRON REQUIREMENTS

The amount of iron required each day to compensate for losses from the body and growth varies with age and sex; it is highest in pregnancy and in adolescent and menstruating females (Table 2.3). These groups, therefore, are particularly likely to develop iron deficiency if there is additional iron loss or prolonged reduced intake.

Table 2.3 Estimated daily iron requirements. Units are mg/day.

	Urine, sweat, faeces	Menses	Pregnancy	Growth	Total
Adult male	0.5–1				0.5–1
Post-menopausal female	0.5–1	0.5–1			1–2
Menstruating female*	0.5–1		1–2	0.6	1.5–3.0
Pregnant female*	0.5			0.6	1
Children (average)	0.5–1	0.5–1			1–2.5
Female (age 12–15)*					

*The doctor mentioned (the first and the last Colum) in this table so you have to memorize it.

Menstruating female: the requirement is 1milligram, however the loss is almost the same, so they have to take more iron as in=out

Pregnant women are similar to menstruating ladies; their daily requirment in total is 1.5-3milligrams per day

Menstruating females, female age group (12-15yrs) and pregnant ladies are most likely to develop iron deficiency if iron supplements weren't taken.

Distribution of iron in body

iron is mainly distributed in Haemoglobin (65%), it can also be found in ferritin and haemosiderin (30%), myoglobin (3.5%), heme enzyme (0.5%) and transferrin (0.1%)

Factors affecting absorption

Table 2.2 Iron absorption.

Factors favouring	Factors reducing
1 Ferrous form	1 Ferric form
2 Inorganic iron	2 Organic iron
3 Acids—HCl, vitamin C	3 Alkalis—antacids, pancreatic secretions
4 Solubilising agents—e.g. sugars, amino acids	4 Precipitating agents—phytates, phosphates
5 Iron deficiency	5 Iron excess
6 Increased erythropoiesis	6 Decreased erythropoiesis
7 Pregnancy	7 Infection
8 Primary haemachromatosis	8 Tea
	9 Desferrioxamine

Eating bread while drinking tea can reduce the absorption of iron and can cause anemia.

Causes of iron deficiency:

Table 2.4 Causes of iron deficiency.

1 BLOOD LOSS
Uterine.
Gastrointestinal. e.g. oesophageal varices, hiatus hernia, peptic ulcer, aspirin ingestion, partial gastrectomy, carcinoma of stomach or caecum, colon or rectum, hookworm, angiodysplasia, colitis, piles, diverticulosis, etc.
Rarely haematuria, haemoglobinuria, pulmonary haemosiderosis, self-inflicted blood loss.

2 INCREASED DEMANDS (see also Table 2.3)
Prematurity.
Growth.
Child-bearing.

3 MALABSORPTION
e.g. gastrectomy, coeliac disease.

4 POOR DIET
A contributory factor in many countries but rarely the sole cause.

If you remember with vit. B12 cells produced are larger than normal but with iron, cells are small with little HAEMOGLOBIN, Hypochromic = less than normal, microcytic = less than normal

Causes of hypochromic microcytic anemia; these include lack of iron, or of iron release from macrophages to serum (anemia of chronic inflammation or malignancy), failure of protoporphyrin synthesis (siderblastic anemia) or of globin synthesis (a or b-thalassemia). Lead also inhibits heme and globin synthesis.

Fun facts about Iron deficiency (the doctor read them off a slide)

1. Iron deficiency is estimated to affect about 30% of the world population
2. Iron deficiency Anemia is still the most important deficiency related to malnutrition.
3. Iron deficiency anemia (IDA) and thalassemia trait (TT) are the most common forms of microcytic anemia.
4. Some discrimination indices calculated from red blood cell indices are defined and used for rapid discrimination between TT and IDA.
5. Iron-deficiency anemia (IDA) is a common clinical problem throughout the world and an enormous public health risk in developing and even in industrialized countries.
6. Traditionally, several methods other than serum ferritin were used to assess IDA.

*TT: thalassemia / IDA: iron deficiency anemia

Hemoglobin is the red pigment in RBCs, formed from a heme part and a globin part, considered a protein as 96% of it is a protein (globin) and 4% is heme.

The adult hemoglobin is composed of 4 subunits: 2 alpha, 2 beta

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

Haemoglobin estimated concentration in males is about 16g/100ml blood. In females it is 14g/100ml blood.

As we said 65% of haemoglobin synthesis occurs in the erythroblastic last stage (cells with nuclei), and 35% in reticulocyte stage.

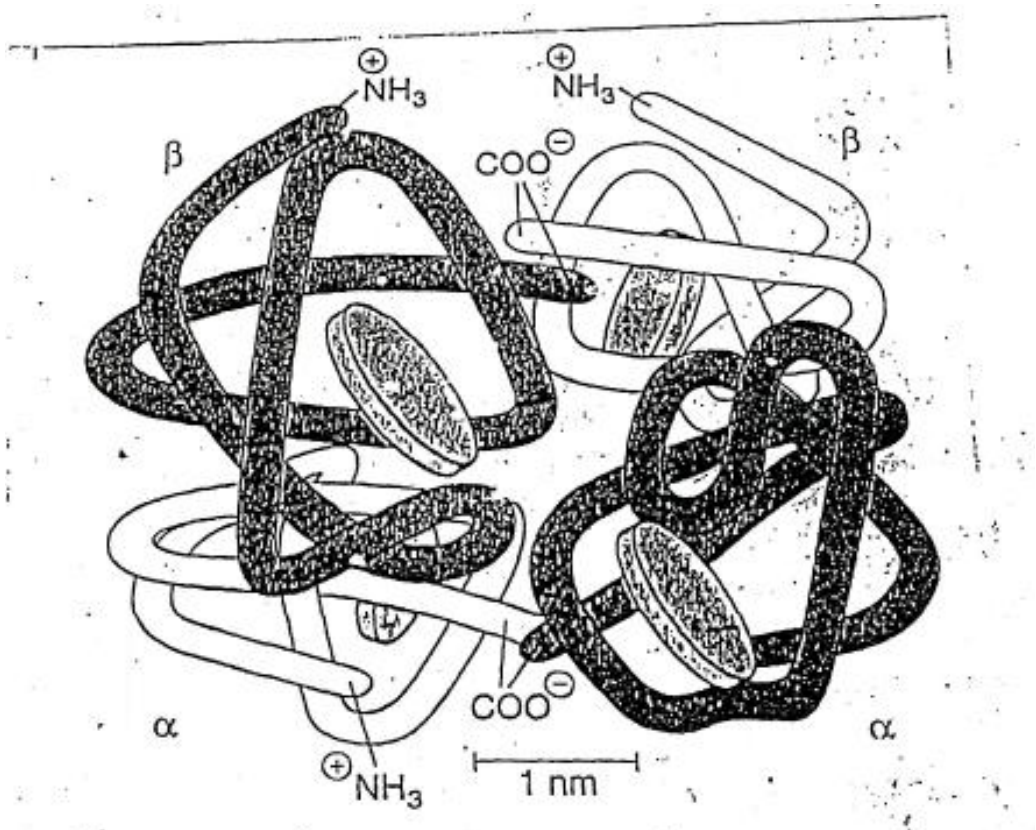

Figure 27–12. Diagrammatic representation of a molecule of hemoglobin A, showing the 4 subunits. There are 2 α and 2 β polypeptide chains, each containing a heme moiety. These moieties are represented by the disks. (Reproduced, with permission, from Harper HA et al: *Physiologische Chemie*. Springer-Verlag, 1975.)

Haemoglobin synthesis:

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

Production of heme begins by the combining glycine and succinyl Co-A using an enzyme called aminolevulinic acid synthase (ALAS) which produces delta aminolevulinic acid (ALA)

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

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

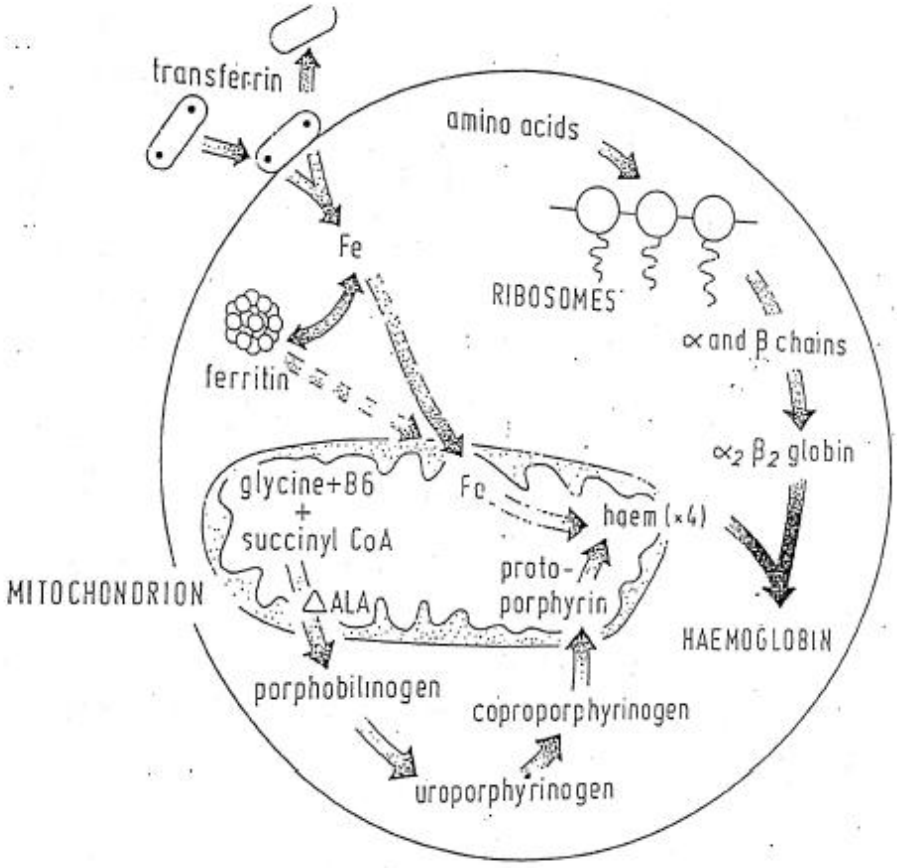

Fig. 1.7 Haemoglobin synthesis in the developing red cell. The mitochondria are the main site of protoporphyrin synthesis, iron is supplied from circulating transferrin and globin chains are synthesised on ribosomes. △ALA = delta-amino laevolinic acid.

inner

In 1 red blood cell, we have 640 or 500 million hemoglobin *molecules.*

Heme part binds oxygen; globin binds carbon dioxide, hydrogen and 23DPG (2, 3-Bisphosphoglyceric acid).

We have 6 genetic hemoglobin variants in the body, each of their 4 chains contain heme moiety (protoprophyrin and iron)

3 of them are found only in the fetus (portland, gower I and gower II)

Adult hemoglobin, hemoglobin A2 and Fetalhemogloin are present in all stages of life, however the concentration is different from time to time, for example; Hemoglobin A, in adults, the proportion is 97% while in newborns it is 20%

the doctor read this slide

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

In the adult, fetal hemoglobin almost disappears after 6 month of birth (<1%)

Myoglobin also is a protein that contains 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.

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.

Binding of hemoglobin with oxygen is reversible.

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