HEMATOLOGY
& LYMPH SYSTEM

physiology sheet

Number	2
Done BY	Zahraa Muneer
Correction	Enas Ajarma
Doctor	Saleem

Blood parameters:

1. RBCs count
2. Haematocrit
3. Haemoglobin content

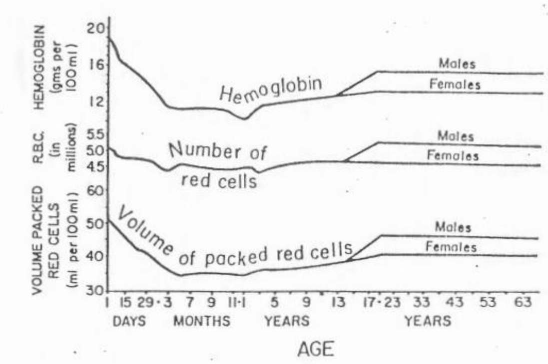


Figure 4–1. Relationship of age and sex to the hemoglobin content, red blood cell count, and hematocrit of the blood.

In new-born babies all three parameters of blood are higher than in normal adults. This happens because of:

a. Placental or foetal oxygenation which will later shift into pulmonary oxygenation.
b. Foetal haemoglobin which will later turn into adult haemoglobin.

These three parameters are normalized in the 7th month after birth, when foetal oxygenation and foetal haemoglobin turn into pulmonary oxygenation and adult haemoglobin respectively.

- **Haematopoiesis**: production of <u>all</u> blood cells.
- **Erythropoiesis**: production of blood cells <u>mainly</u> RBCs.

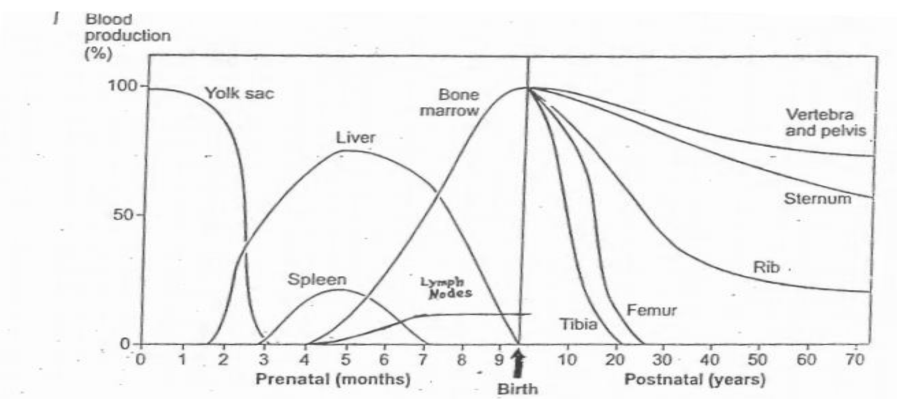


Fig. 1 Sites of blood production in the fetus and after birth. (Erythropoiesis)

This figure shows the production of blood during foetal life and after birth.

a. In foetal life (prenatal) you will notice that erythropoiesis during the first 2 months occurs mainly in the yolk sac, then in the liver (and to a lesser extent, in the spleen)
   At the beginning of the 5th month the bone marrow and the lymph nodes take the responsibility.
b. After birth the bone marrow is the only site for production of blood cells.

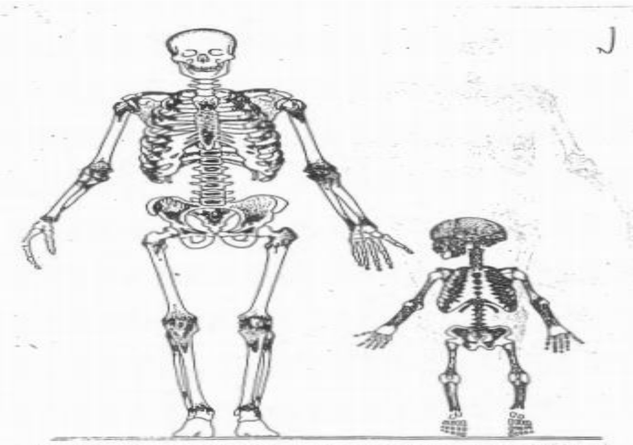


Fig. 8.4 Sites of active haematopoietic marrow (red marrow) in children and adults. There is a similar amount of red marrow (1000 to 1500 g) in each despite the differences in body weight. (*From* Bierman, H. R. (1961) In *Functions of the Blood*, ed. MacFarlane, R. G. & Robb-Smith, A. H. T., p. 357. Oxford: Blackwell.)

During childhood bone marrow of all bones produce blood cells.

At the age of 18 in females and 20 in males blood cell production is confined to some bone marrow found in the vertebrae, pelvis, sternum, ribs, and especially the ends of long bones like the femur, tibia, ulna, and radius, as well as the scapula and the clavicle.

Successive appearance of different forms of blood cells:

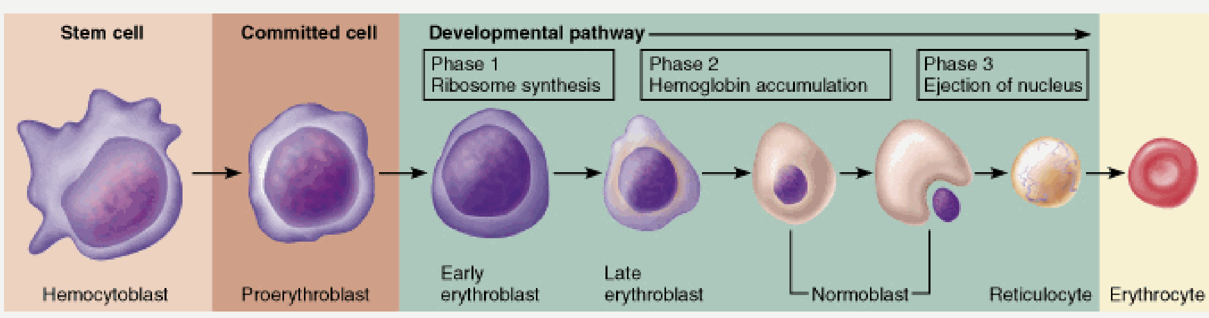
1. Primitive Erythrocytes (RBCs): in the first month
2. Megakaryocytes: responsible for the production of blood thrombocytes (platelets)

Defence:

3. Granulocytes (Neutrophils)
4. Lymphocytes
5. Monocytes

You can find all these cells in the 5th month

Erythropoiesis:



- The last stage of erythropoiesis is **reticulocytes**. These cells contain fragments of their nuclei (mature RBCs don't have nuclei) and synthesize the haemoglobin.

They are present in the bone marrow and remain there for 2-3 days before they are released into the circulation.

- Reticulocytes don't contain a proper nucleus but they can synthesize the remaining haemoglobin as reticulocytes, which are immature erythrocytes. Once they complete the synthesis of haemoglobin they will become mature RBCs.
- Haemoglobin synthesis does not occur in mature RBCs
- If Reticulocytes make up 1-2% of RBCs then erythropoiesis is normal, below that→ erythropoiesis is low, above that →erythropoiesis is high.
- In the bone marrow: the number of reticulocytes = the number of nucleated cells (erythroblast cells)
- The number of reticulocytes in the circulation is less than their number in the bone marrow.

In haemolytic anaemia, the reticulocyte percentage is high, low RBC count (abnormal condition)

Regulation of erythropoiesis:

Factors that regulate RBCs and keep their number relatively constant:

1. ***Oxygen supply***: when the amount of oxygen decreases (hypoxia) the number of RBCs increases to compensate for this reduction, and vice versa with hyperoxia such as in people who live around the sea level (RBC count is lower among them).

Hypoxia can be caused by low blood volume, anaemia, low haemoglobin, poor blood flow, and pulmonary diseases.

Hypoxia	Insufficient O_2 at the cellular level
Anemic hypoxia	Reduced O_2-carrying capacity of the blood
Circulatory hypoxia	Too little oxygenated blood delivered to the tissues; also known as stagnant hypoxia
Histotoxic hypoxia	Cells unable to utilize O_2 available to them
Hypoxic hypoxia	Low arterial blood P_{O_2} accompanied by inadequate hemoglobin saturation

Hypoxia does not directly affect the blood marrow; it affects the cells in the kidneys which sense oxygen in the body, and when oxygen is low it produces **erythropoietin** and stimulates erythropoiesis by this pathway: haematopoietic stem cells→proerythroblasts→ RBCs→ tissue oxygenation → decreased erythropoiesis.

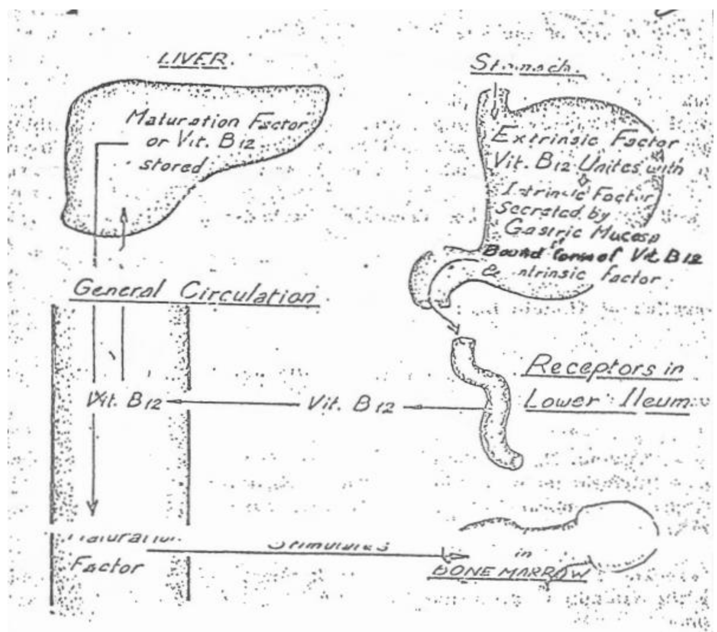
What's **erythropoietin**?

- It is <u>a glycoprotein hormone</u> that enhances the production of RBCs by affecting erythrocyte stem cells until hypoxia is relieved.
- Promotes the formation of red blood cells by the bone marrow.
- Half-life: 10 hours.
- 90% is produced by the kidney and 10% by the liver and a very little amount is produced by the spleen <u>if the spleen does produce it</u>. (The kidney cells that make erythropoietin are sensitive to low oxygen levels in the blood that travels through the kidney)
- The duration of erythropoietin activity is 3-7 days.

2. ***<u>Vitamins</u> (from the diet):*** all vitamins play a role in erythropoiesis. Mainly B12 (essential), Folate (essential), Vitamin C (involved in every process in the body).

<u>Vitamin B12</u> (aka: extrinsic factor, cyanocobalamin, maturation factor) from the diet.

- In the stomach it combines with the intrinsic factor produced by the stomach cells. This complex moves toward the lower ileum where it is absorbed into the circulation and either participates in the erythropoiesis (bone marrow) or is stored in the liver.



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  B12 is essential for many functions:
  a. DNA formation
  b. Normal function of myelin sheathes in CNS
  c. Maturation of RBCs

Deficiency of Vitamin B12

- Neutrophils are affected by deficiencies of vitamin B12.

- Vitamin b12 deficiency reduces the production of RBCs leading to one type of anaemia called megaloblastic anaemia (pernicious anaemia)

Characteristics of vitamin B12 deficiency:

- The cells produced because of the deficiency of vitamin B12 are larger than normal (MCV relatively high above 110 and might reach 160 μm^3)
- The cell shape is oval, containing more haemoglobin because the maturation time is prolonged (6-7 days 'more than the normal') due to the deficiency of B12 but the haemoglobin synthesis is normal. RBC count is low and the haemoglobin content is relatively high.
- Anaemia means a low amount of haemoglobin. So even though the volume of the cells increases, the number of RBCs decreases, further decreasing the number of cells that retain haemoglobin. This is what causes the anaemia
- 2-3 mg of vitamin b12 is sufficient for normal body function for almost 2-4 years. Therefore; anaemia due to b12 deficiency in the diet is very rare. (Pernicious anaemia may occur due to other causes).

*All vitamins are needed but the most important ones in this process are B12 and folic acid.

- The deficiency of folic acid produces cells similar to the cells produced by the deficiency of vitamin B12.

- Folic acid is also known as maturation factor and the anaemia resulting from its deficiency is called megaloblastic anaemia

Megaloblastic anaemia occurs either from B12 deficiency or folic acid deficiency.

- The jejunum has an enzyme that facilitates the absorption of the folic acid.

Causes of vitamin B12 deficiency:

1. Veganism (people who do not eat meat or other animal products).

2. Malabsorption.

a. Gastric causes:

- Congenital lack of intrinsic factor.
- Partial or total gastrectomy.

b. Intestinal causes:

- Chronic tropical sprue (diarrhoea) “not enough time for absorption ".

-Ileal resection.

Causes of Folate deficiency:

a. Inadequate dietary intake
b. Malabsorption
- celiac disease
- jejunal resection
- tropical sprue

c. Increased requirement
- Pregnancy
- Premature infant
- Chronic haemolytic anaemia

Definite effects of vitamin B12 or folate deficiency

- Megaloblastic anaemia
- Macrocytosis of epithelial cell surface
- Neuropathy(B12 deficiency only)
- Sterility in severe anaemia
- Rarely reversible melanin skin pigmentation

3. ***<u>Iron</u>:*** reduction in iron will cause reduction in haemoglobin
- Iron average in the body 4g in females & 5g in males
- Iron is important for the formation of -not only haemoglobin- but other essential elements in the body such as: myoglobin, cytochromes, cytochrome oxidase, peroxidase, and catalase.
- Daily intake in the US and Europe about 20mg but the amount absorbed is equal to the iron loss in the body. (not the entire iron intake is absorbed)
- Usually the amount of the iron absorbed 3-6% of the iron ingested.
- **Dietary iron takes two major forms** (absorbed by distinctively different mechanisms)
- Dietary→ meat (heme iron), fish (heme iron), liver (heme iron), vegetables (non-heme iron).

a. Heme iron

Heme iron is absorbed more efficiently than non heme iron

b. Non-heme iron

Either ferric (fe3+) or ferrous (fe2+)

Iron movement doesn’t occur passively but requires one or more protein to facilitate its movement in and out of the cell.

The absorption of non-heme iron is restricted to the duodenum due to its high capacity.

The enterocyte takes non-heme iron across the apical membrane through the divalent metal transporter which mediates **iron** transport

Dietary Ferric iron → ferric reductase → reduces ferric to ferrous at the extracellular surface of the apical membrane.

4. ***Proteins:*** reduction in protein will also cause reduction in haemoglobin
5. ***Trace elements:*** copper, cobalt
6. ***Healthy bone marrow:*** when the bone marrow is affected in a pathological condition, the liver and spleen regain the activity to produce blood cells. Usually the liver and spleen stop their activity after birth.
7. ***Liver***: storage, protein synthesis, hormone synthesis
8. ***Hormones*** that play a role in erythropoiesis: erythropoietin, androgen, thyroid hormone, growth hormone, and corticosteroids.

The End