PHYSIOLOGY Team 433

Lecture 8:
Erythropoiesis & Regulation

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Color Index

Blue = Main Topic
Violet = sup topic
Red = important
Orange = Explanation

White &Black = Addition

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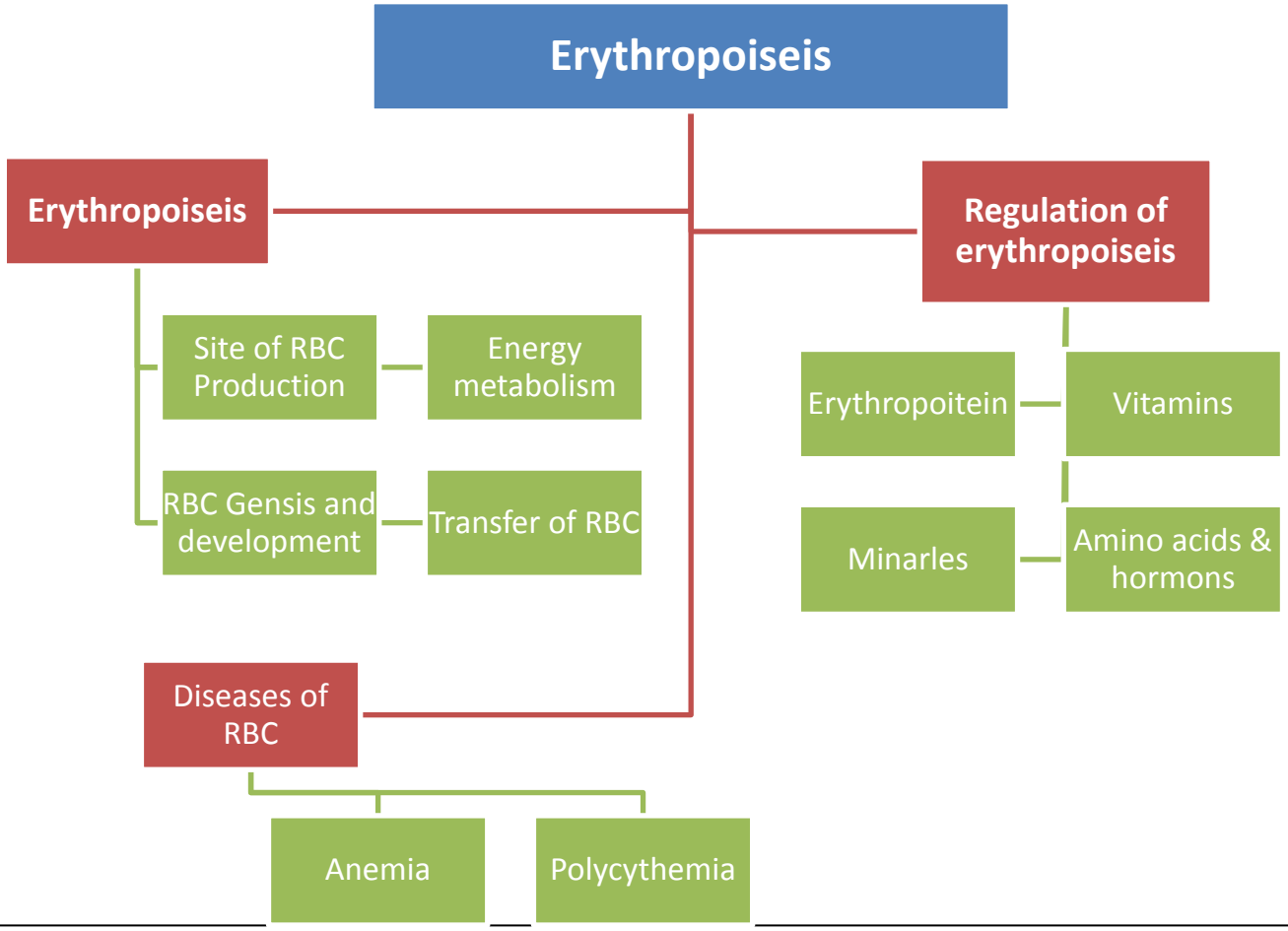
Objectives:

- Sites of Erythropoiesis
- Main features of different stages of Erythropoiesis
- Features of mature RBCs
- The regulation of RBC production and erythropoietin
- hormone secretion in response to hypoxia
- Describe essential elements needed for RBC formation .
- Describe the process of Vit B12 absorption and its malabsorption .
- Recognize the structure and the function of hemoglobin.
- Understand the metabolism of iron (absorption , storage and transport) .
- Recognize the causes of anemia and polycythemia.

Mind map

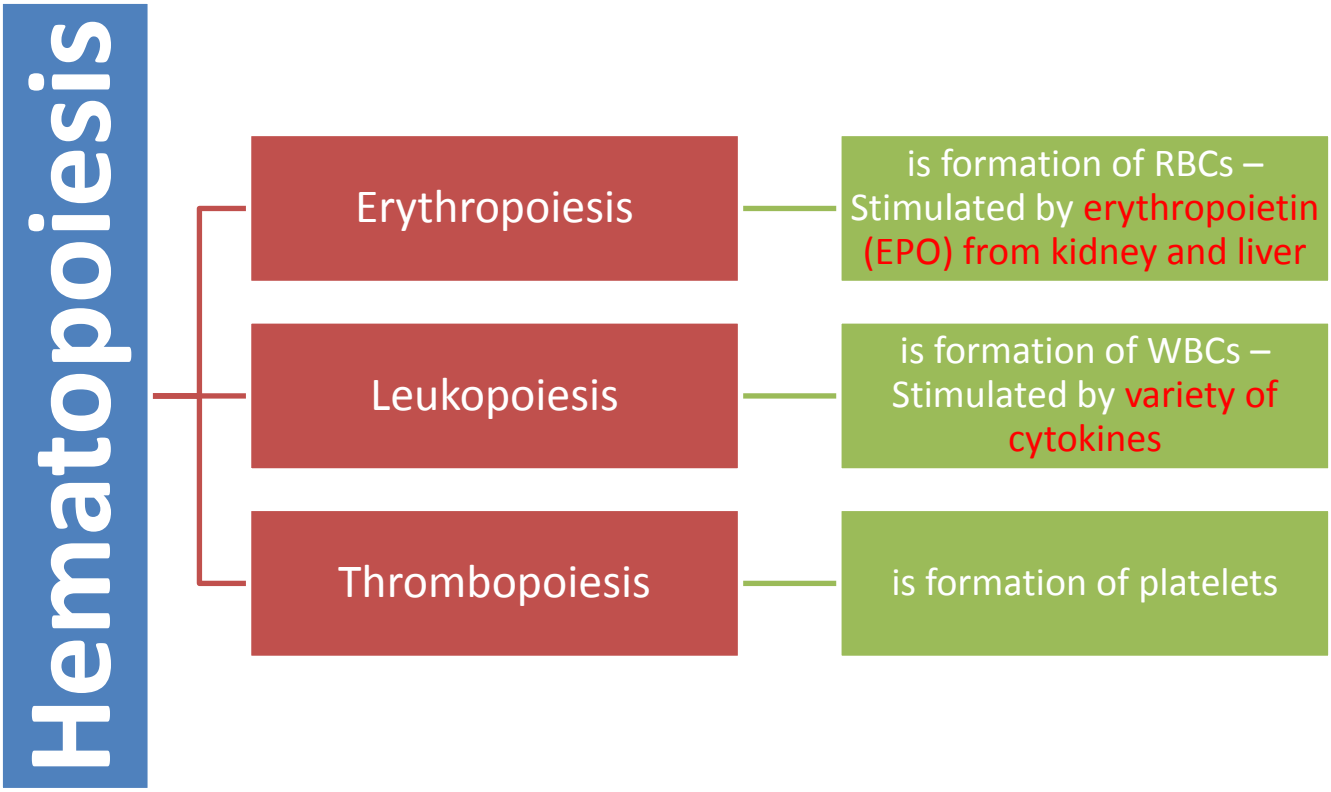


Hematopoiesis

Is a formation of blood cells from stem cells in:

1- **The red bone marrow (myeloid stem cell)**

2- **Lymphatic tissue (lymphoid stem cell)**



❖ Erythropoiesis :

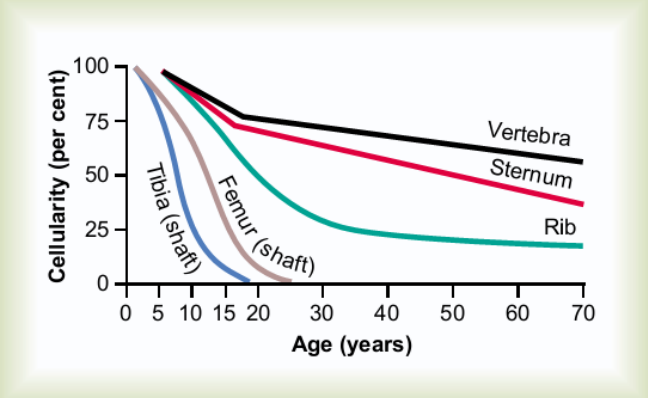
Site of RBC Production

- **Early weeks of embryonic life** → Nucleated RBCs - Yolk sac
- **Middle trimester of gestation** → Liver form blood cells **(Mainly)**; Spleen + lymph nodes form blood cells
- **Last month of gestation and after birth** → Red bone marrow **(exclusively)**

RBC Production after birth

After birth until 5 years: The bone marrow of all bones **(except for the proximal humerus and tibia of the long bones)**

After the age of 20 years: No more red blood cells are produced except the marrow of **the membranous bones, such as:**
– Vertebrae, Sternum, Ribs, and Ilia

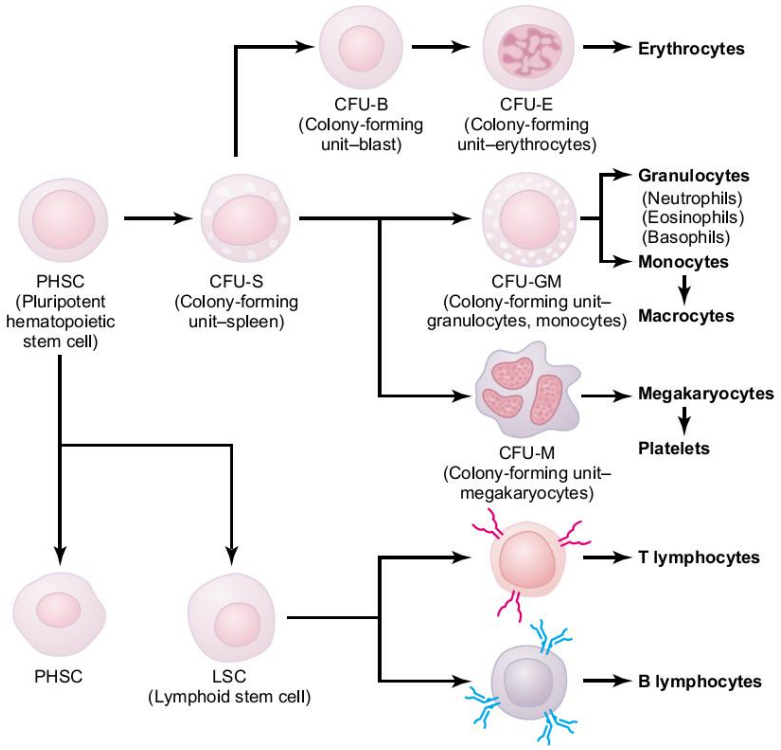


❖ Genesis (Production) of RBC :

1- The blood cells begin their lives in the bone marrow from a single type of cells called: **The pluripotential hematopoietic stem cell**

2- the pluripotential stem cells, become committed to a particular line of cells called: **committed stem cells**

3- A committed stem cell that produces **erythrocytes** is called a **colony-forming unit–erythrocyte**, the abbreviation **CFU-E** is used to designate this type of stem cell.



There are some essential factors for RBC Production such as

Growth inducers (interleukin-3) and **differentiation inducers**

❖ RBC development is characterized by:

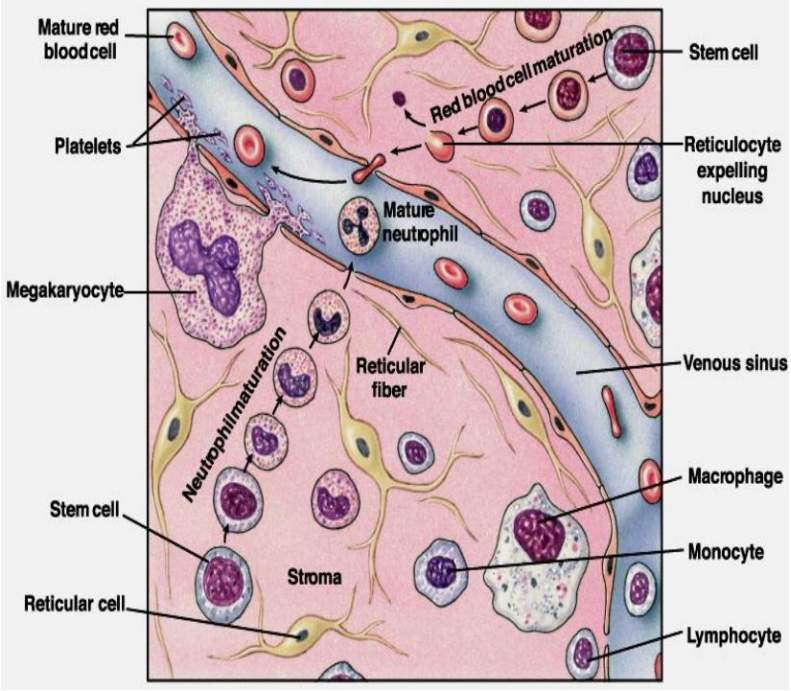
– A decrease in cell size
– A disappearance of nucleus
– An appearance of hemoglobin

RBC development

TYPE	DAY	NUCLEUS	NUCLEOLI	HEMOGLOBIN	MITOSIS	NORMOBLAST
Proerythroblast 	1	12 um	Contain nucleoli	No hemoglobin	-	-
Erythroblast						
Basophil 	2	Contain Nucleus	disappear	Hemoglobin starts	Show mitosis	Early
Polychromatophil 	3	smaller	-	Hemoglobin increases	-	Late
Orthochromatic 	4	small dense nucleus- Nuclear lysis and extrusion	-	Hemoglobin increases	-	Normoblast
Nuclear extrusion						
Reticulocyte 	5-7	-	-	80%	-	-
Erythrocytes 	-	-	-	100%	-	-

❖ Transfer of RBC to Circulation :

RBC pass from the bone marrow into the blood capillaries
By
Diapedesis
(Squeezing through the pores of the capillary membrane)



❖ Energy metabolism:

- Less energy required
- Utilize Glucose for energy by:

- Anaerobic glycolysis
- Pentose phosphate pathway

Regulation of Erythropoiesis

Factors affecting Erythropoiesis:

–Tissue Oxygenation

- Anemia, High Altitudes, heart and lung problems.
- ERYTHROPOITEN

–Vitamins

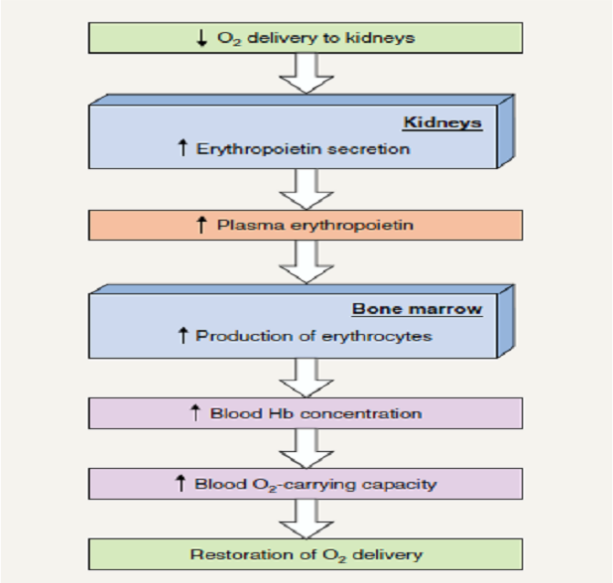
–Metals

–Proteins

–Hormones

–Other factors/Conditions

The regulation of RBC production and erythropoietin hormone secretion in response to hypoxia



❖ Erythropoietin (EPO) :

Glycoprotein, 90% of EPO is produced from peritubular fibroblasts in the renal cortex and 10% from the liver.

Renal failure or Chemotherapy? Low levels of EPO

If someone has Renal failure or he needs Chemotherapy, that mean the EPO level is low.

What is Renal failure?

Stimulate the growth of early stem cells, Can be measured in plasma & urine.

High levels of erythropoietin may cause:

- **Anemia, hemorrhage**
- **High altitude**
- **Heart failure**
- **Lung Disease**

(Result in polycythemia)

Role of EPO

- **EPO stimulates increased cell division rates in erythroblasts and stem cells that produce erythroblasts.**
- **EPO speeds up the maturation of RBCs by accelerating the rate of Hb synthesis.**
- **Under maximum EPO stimulation, bone marrow can increase the rate of RBC production tenfold.**

Blood doping?

is the practice of boosting the number of red blood cells in the bloodstream in order to enhance athletic performance

❖ Vitamins :

Vitamin B12 & Folic acid

The function of Vitamin B12 & Folic acid	The Dietary source of Vitamin B12 & Folic acid	The Deficiency of Vitamin B12 & Folic acid
1- DNA synthesis. 2- Final maturation of RBC.	MEAT-MILK-LIVER - FAT-GREEN VEGTABLES.	1- failure of nuclear maturation & divison. 2- abonormally large & oval shape RBC. 3- short life span . 4- reduce RBC count & HB. 5- macrocytic anemia.

- The RBCs don't have nucleus (mature RBCs) but RBCs need it before maturation to carry information.

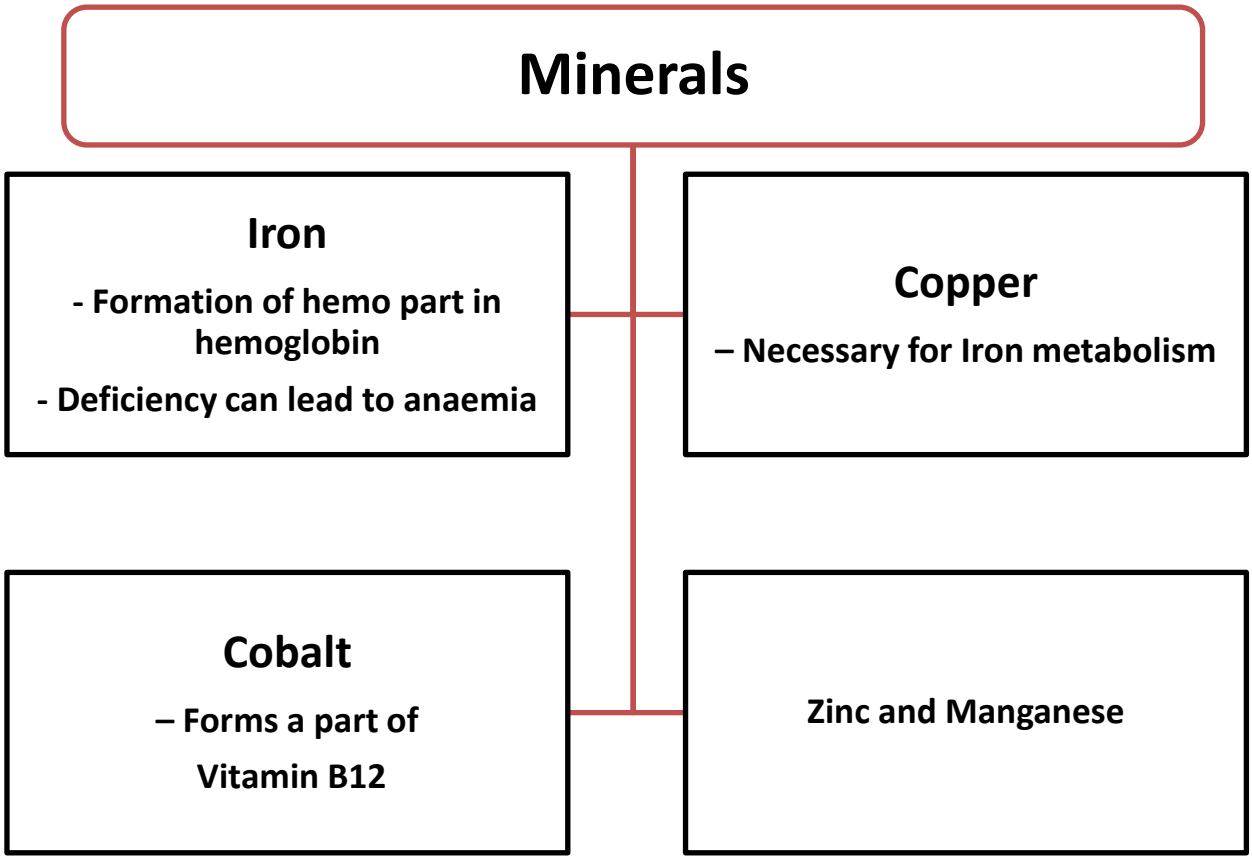
Pernicious Anemia

1- VB12 absorption needs intrinsic factor secreted by parietal cells of stomach .
2- VB12 + intrinsic factor are absorbed in the terminal Ileum.

Causes of deficiencies :
- Inadequate intake
- Poor absorption due to Intestinal disease

Intrinsic factor: is a glycoprotein produced by the parietal cells of the stomach. It is necessary for the absorption of vitamin B_{12} later on in the small intestine.

❖Minerals :



Iron metabolism (Fe)

Iron is needed for the synthesis of hemoglobin, myoglobin, cytochrome oxidase , peroxidase & catalase

Total Iron in the body = 4-5g

65% - Hemoglobin
4% - In the form of myoglobin
1% - other heme-containg proteins
0.1% - Is combined with transferrin in the bood plasma
15-30% - stored iron in the form of ferritin in the liver, spleen and bone marrow.

Iron absorption

- Iron in food mostly in **oxidized form (Ferric ,F+3)**
- Better absorbed in **reduced form (Ferrous, F+2)**
- Iron in stomach is **reduced** **by gastric acid & Vitamin C**
- Rate of iron absorption depend on the amount of iron stored

Transport and storage of iron

Iron is transported in the plasma in the form of Transferrin (apotransferrin + iron)

Iron is stored in two forms :

1- Ferritin (apoferritin + iron)

2- Hemosiderin (insoluble complex molecule, in liver, spleen, bone marrow)

Daily loss of iron is 0.6 mg in male & 1.3mg /day in females.

❖ Amino acids and hormones :

- **Proteins & Amino acids:** formation of globin in hemoglobin

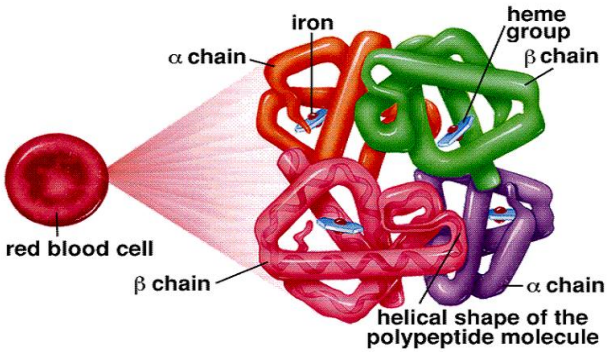
–sever protein deficiency results in anaemia

- **Hormones:**

- Testosterone
- Growth hormone
- Thyroid hormone
- Cortisol
- Adrenocorticotrophic hormone (ACTH)

Hemoglobin (Hb)

- Each RBC contains 280 million Hb molecules.
- Hb molecules consist 4 chains each formed of heme & polypeptide chain (globin).
- Heme consist of porphyrin ring + iron (F2+).



Types of normal Hb

- Hb A (2 alpha and 2 beta chains) (adult Hb) (98%).
- Hb A2 (2 alpha and 2 delta chains) (2%)
- Hb F (2 alpha and 2 gamma chains) (Hb of intrauterine life).

-Abnormality in the polypeptide chain → abnormal Hb (hemoglobinopathies)
e.g thalassemias, sickle cell (HbS).

Functions of Hemoglobin

1- Carriage of O2
- Hb reversibly binds O2 to form Oxyhemoglobin, affect by pH, temperatre, H+

2- Carriage of CO2
- Hb binds CO2 = Carboxyhemaglobin

3- Buffer "Resistant changing in pH"

Destruction of RBC

❑ RBC life span in circulation = 120 days.

❑ Metabolic active cells.

❑ Old cell has a fragile cell membrane, cell will rupture as it passes in narrow capillaries (and spleen).

❑ Released Hb is taken up by macrophages in liver, spleen & bone marrow:

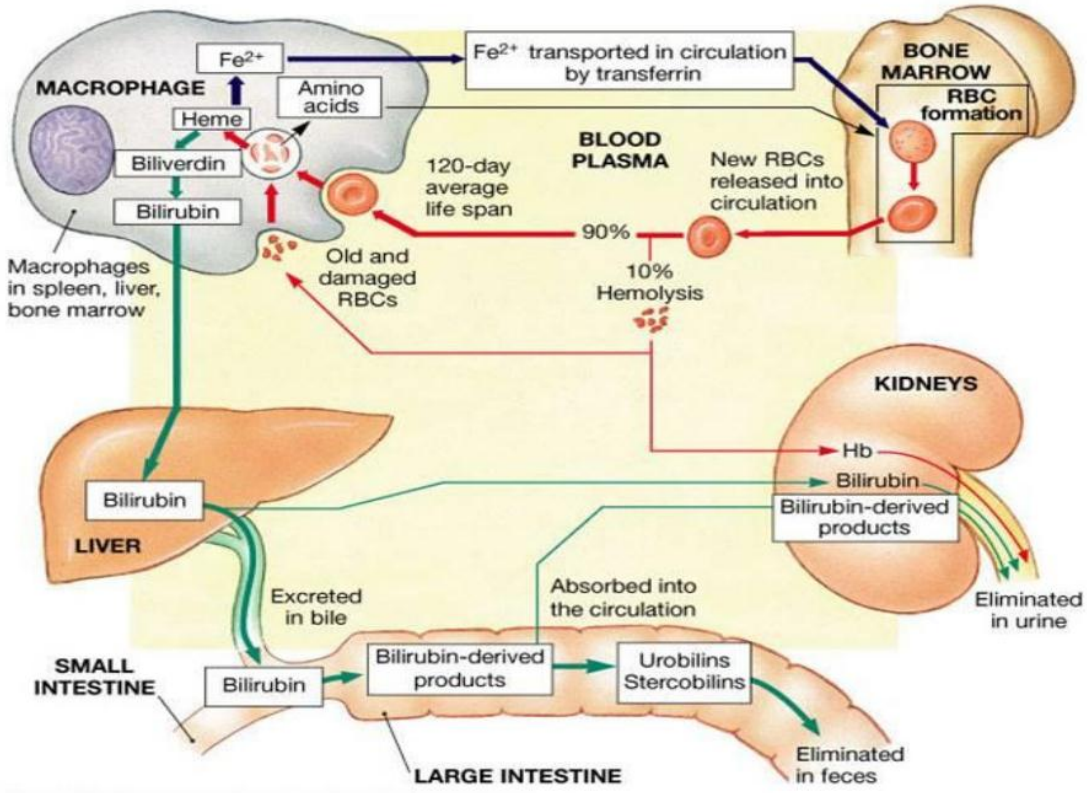
- Hb is broken into its component:

○ Polypeptide—amino acids (protein pool = storage)
○ Iron ---- stored in liver and bone marrow as ferrtin
○ Heme (Porphyrin)>>—bilirubin>>—secreted by the liver into bile. [excess destruction of RBC ---Jaundice]

-Metabolic Active = young cell

Bilirubin = is the yellow breakdown product of normal heme catabolism

(الصفار أو الصفراء) يأتي الأطفال الحديثي الولادة في الغالب

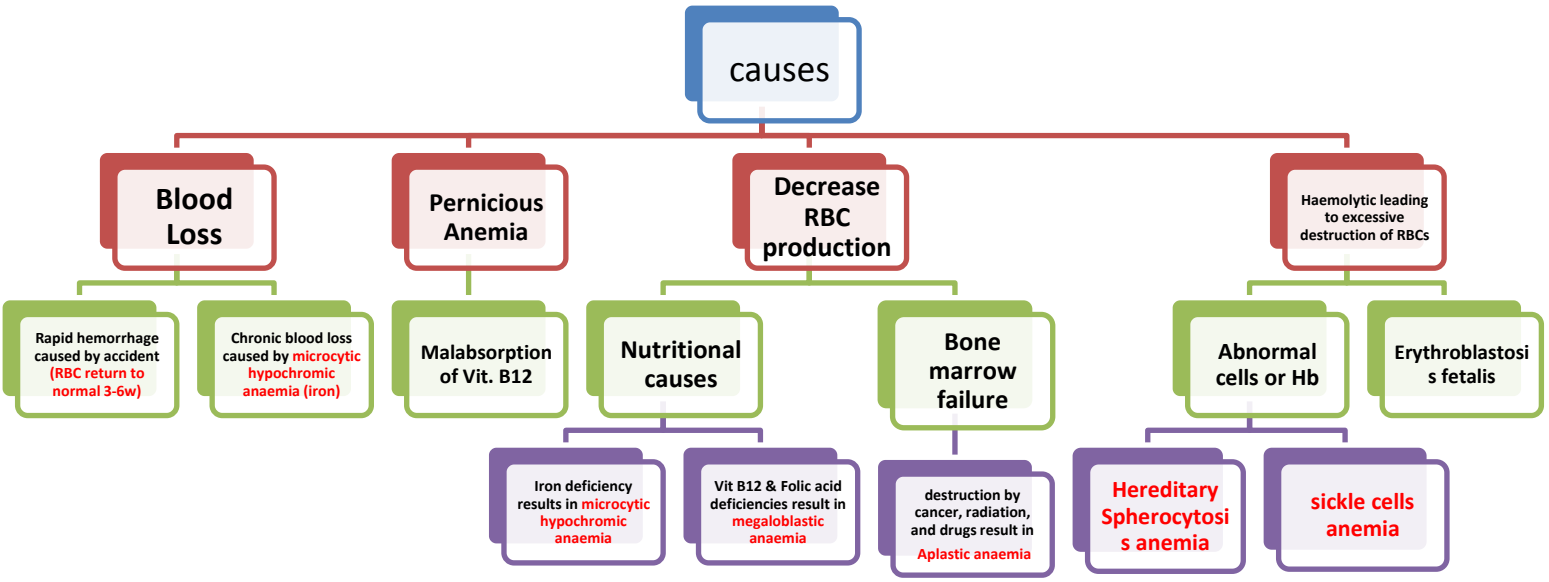


Anemia

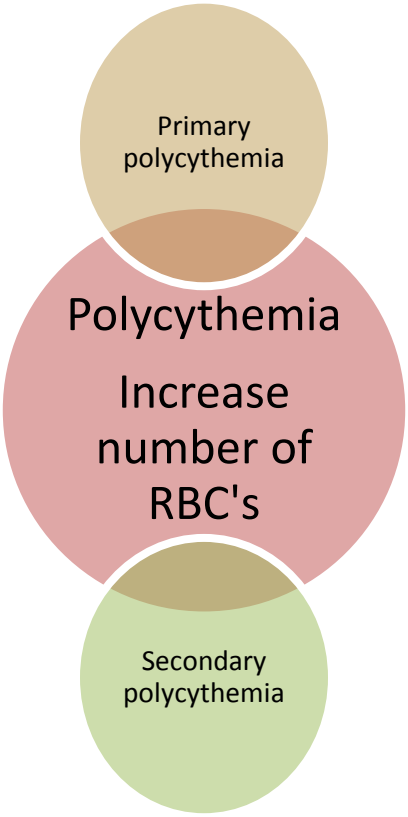
Types
- Decrease number of RBC
- Decrease Hb

Symptoms
- Tired
- Fatigue
- short of breath
- heart failure.

Causes
- Blood Loss
- Decrease RBC production
- Haemolytic leading to excessive destruction of RBCs



Acute: large amount of blood and intermittent
Chronic: small amount of blood and continual
Spherocytosis: the cell transform to a spheral shape



Primary polycythemia **(genetic) (Erythremia)**

- Uncontrolled RBC production (genetic)
- The RBC count can reach 7-8 millions/ mm3 and the hematocrit may be 60 to 70%

Secondary polycythemia

- secondary to hypoxia caused by high altitude (physiological), chronic respiratory or cardiac disease

Summary:

- Erythropoiesis includes five stages to produce erythrocyte.
- Hemoglobin starts appear in Basophilic erythroblast stage.
- Synthesis of RBC's mainly in Liver at Middle trimester of gestation
- Transfer of RBC's from bone marrow into circulating blood through Diapedesis
- There many essential elements for erythropoiesis such as Vitamin and minerals
- Diseases can take place in RBC's such as Anemia and Polycythemia

Erythropoiesis
http://www.youtube.com/watch?v=xpsGsfuffEM

Multiple Choice Questions

Q1: At which of these sites the mainly production of RBC take place in the middle trimester of gestation?

A- Spleen
B- Yolk sac
C- Lymph nodes
D- Liver

Answer is : D

Q2: No more RBC's are produced after the age of

A- 25
B- 20
C- 30
D- 15

Answer is : B

Q3: At which of these stages the ejection of nucleus will take place?

A- Basophilic erythroblast
B- Polychromatophilic erythroblast
C- Reticulocyte
D- Normoblast

Answer is : D

Q4: Which of these stages contain nucleoli?

A- Proerythroblast
B- Basophilic erythroblast
C- Reticulocyte
D- Polychormatophilic erythroblast

Answer is : A

Q5: RBC's can pass from bone marrow into the blood circulating through?

A- Carrier Proteins
B- Help of enzymes
C- Diapedesis
D- Adherence

Answer is : C

Q6: Which of the following responsible of increasing of iron metabolism?

A- Copper
B- Vitamin C
C- Folic acid
D- Cobalt

Answer is : A

Q7: Amino acids will form the heme part of hemoglobin.

A- True

B- False

Answer is : B

Q8: Which of the following statement is true?

A- Iron in food mostly in oxidized form (Ferrous)

B- Iron in food mostly in reduced form (Ferrous)

C- Iron in food mostly in oxidized form (Ferric)

D- Iron in food mostly in reduced form (Ferric)

Answer is : C

Q9: Hemoglobin molecules consist of?

A- 5 Chains

B- 2 Chains

C- 4 Chains

D- 3 Chains

Answer is : C

Q10: Hemoglobin A consist of?

A- 2 alpha 2 beta

B- 2 alpha 2 gamma

C- 2 alpha 2 delta

D- 2 gamma 2 delta

Answer is : A