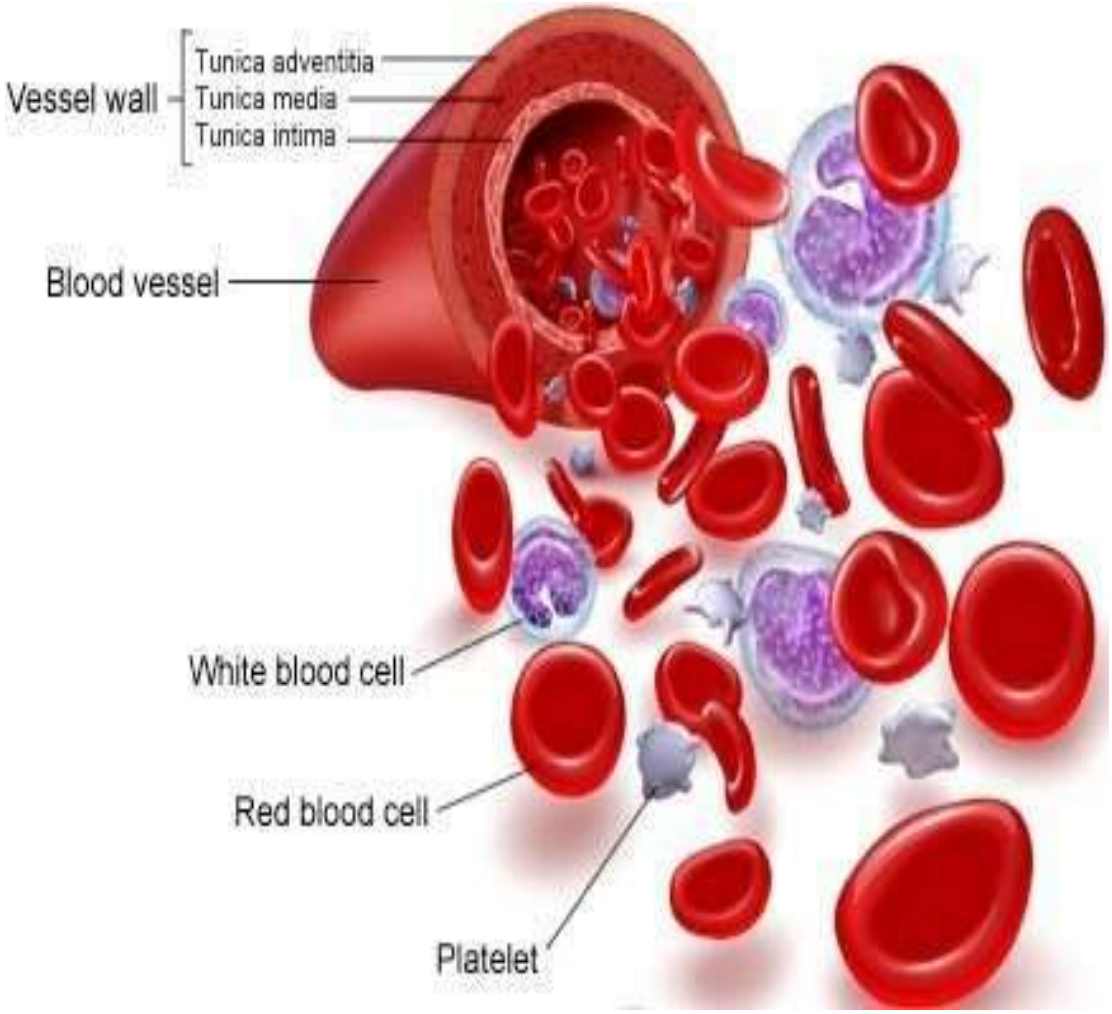
ERYTHROPOIESIS

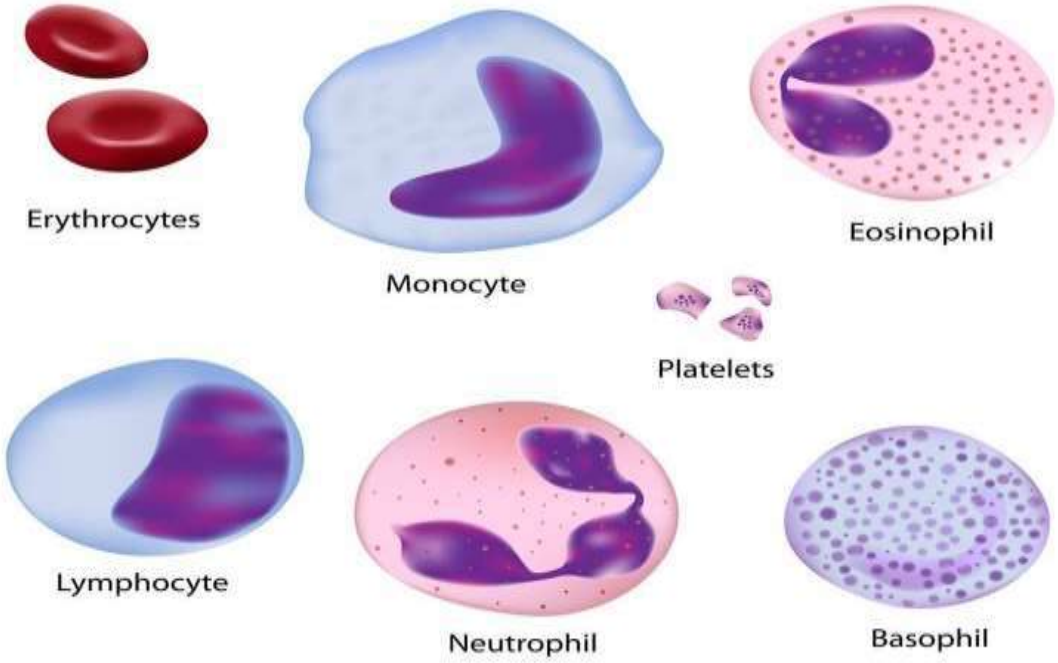


Scheme

1. Definition
2. Theories of erythropoiesis
3. Sites of erythropoiesis
4. Stages of erythropoiesis
5. Reticulocyte
6. Mature Red Cell
7. Factors affecting Erythropoiesis
8. Erythropoietin
9. Vitamin B_{12}
10. Iron

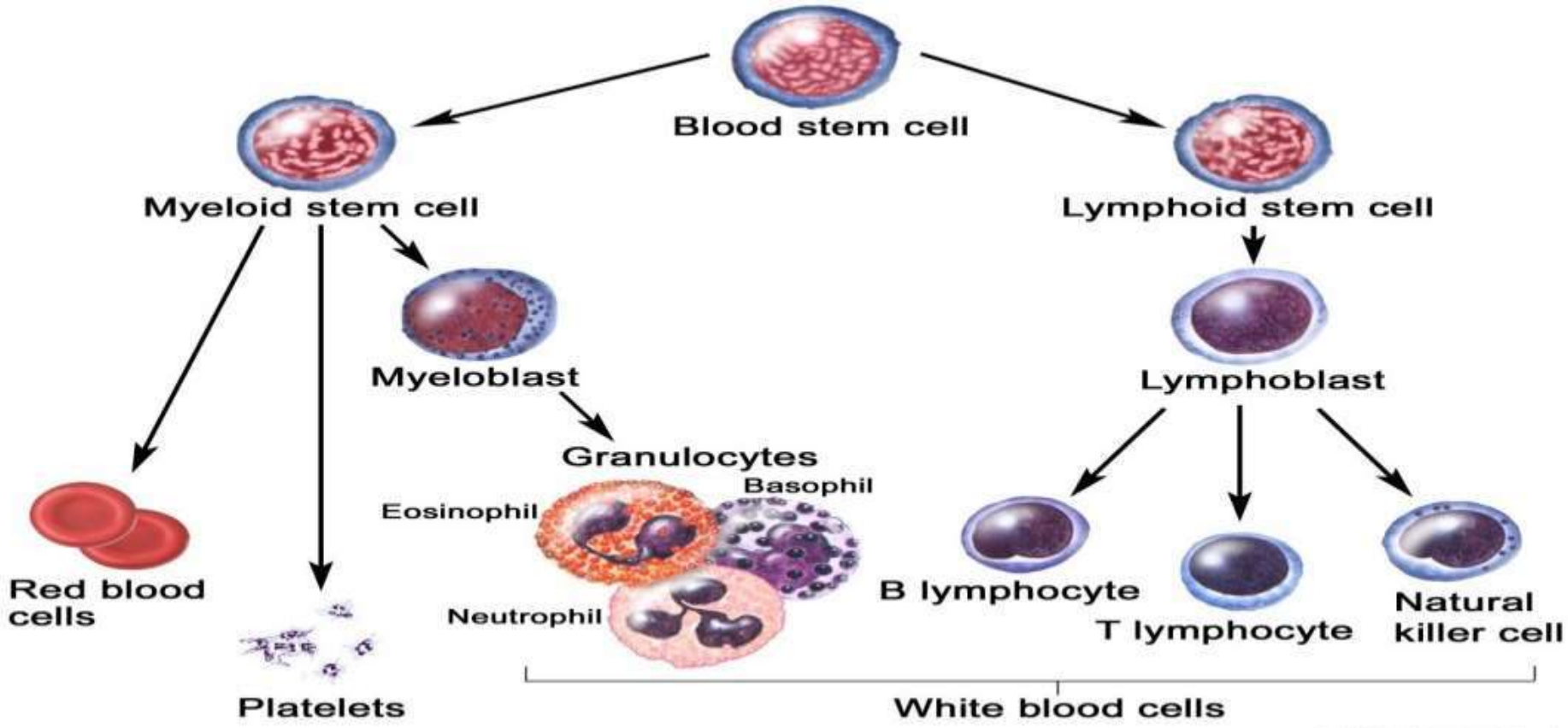
Hemopoiesis

- Hemo: Referring to blood cells
- Poiesis: “The development or production of”
- The word Hemopoiesis refers to the production & development of all the blood cells:
  - Erythrocytes: **Erythropoiesis**
  - Leucocytes: Leucopoiesis
  - Thrombocytes: Thrombopoiesis.



DEFINITION

It is the process of **development**, **differentiation** and **maturation** of RBCs from primitive stem cells



Theories of erythropoiesis

Monophyletic theory

Also known as **unitary theory.**

There is a **common parent cell** of all formed elements of blood.

Alexander A. Maximow

Diphyletic Theory

lymphocytes and monocytes derived from one stem cell (lymphoblast), granular leukocytes and RBCs from another stem cell (myeloblast)

L Aschoff

Polyphyletic theory

Also known as trialistic theory

Suggests **different group of stem cells** gives rise to different blood cells.

Site of Erythropoiesis

Intravascular erythropoiesis

Extravascular erythropoiesis

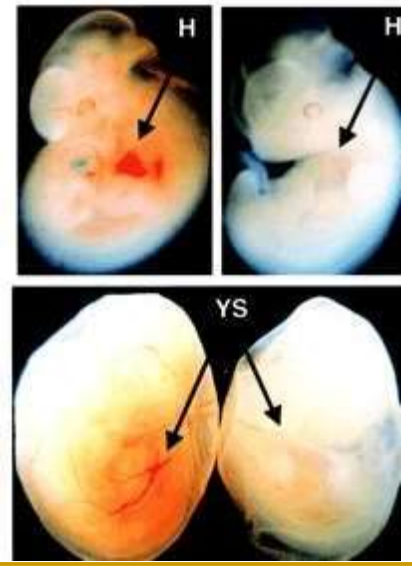
Nucleated RBCs

During intrauterine life

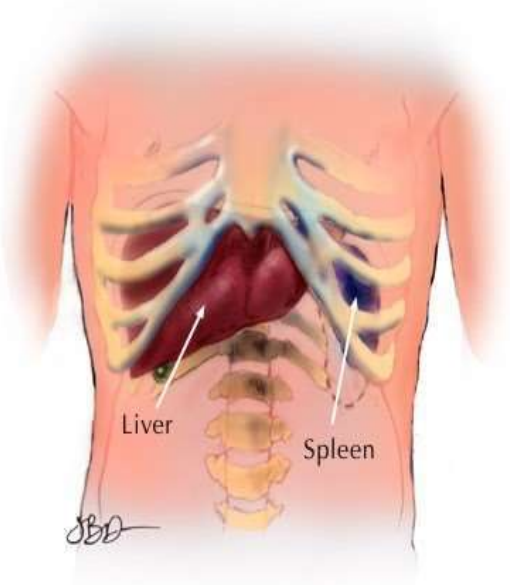
Mesoblastic stage (3 rd week to 3 months)

Hepatic stage (after 3 months)

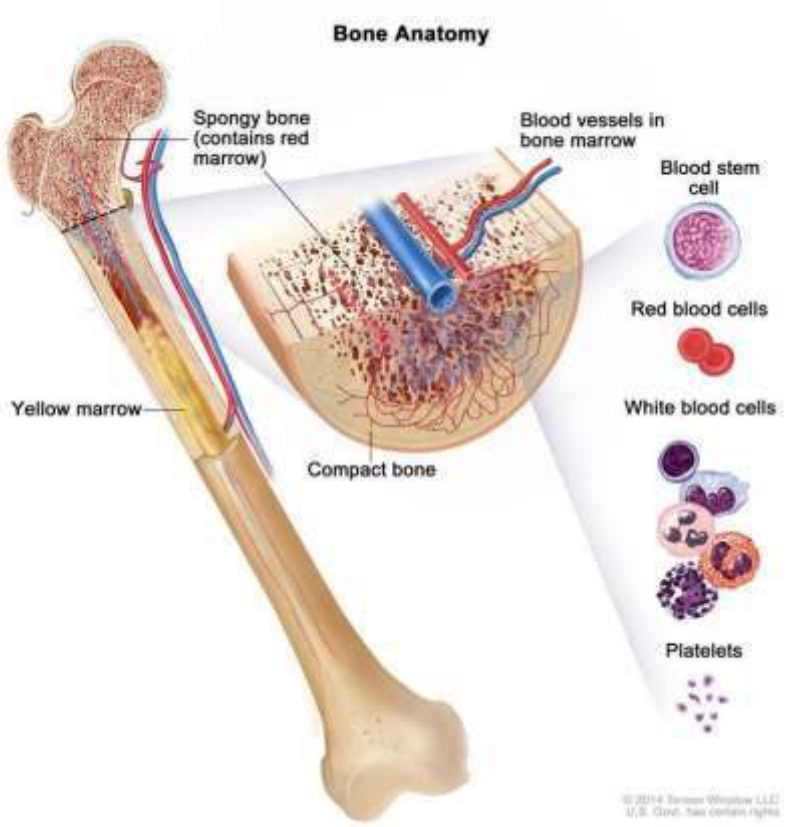
Myeloid stage (3rd trimester)



Yolk sac



Liver & spleen



Bone marrow

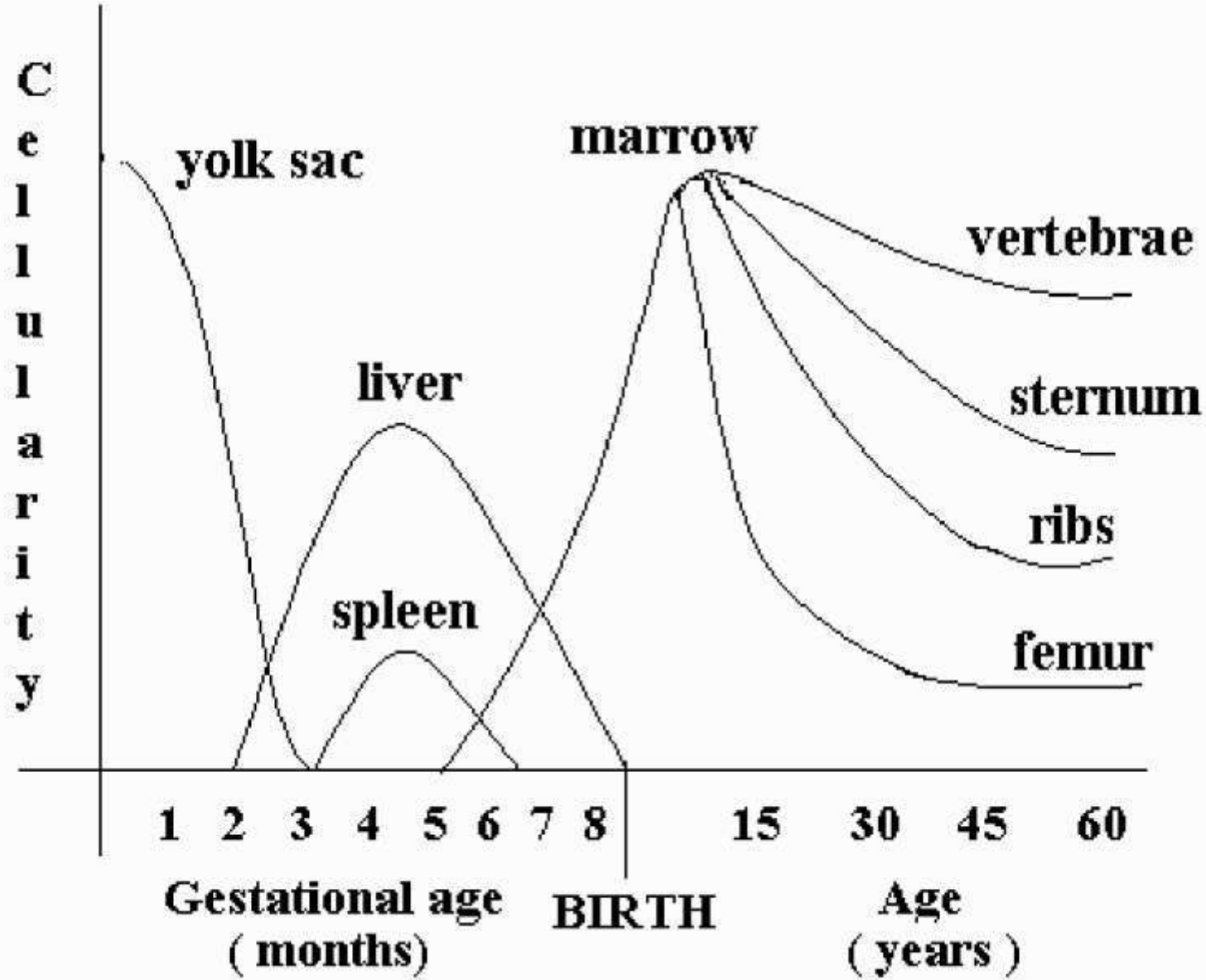
In children

- All bones with red bone marrow
- Liver & spleen

In adults (after 20yrs)

- Ends of long bones like femur, humerus
- Skull
- Vertbrae
- Ribs
- Sternum
- pelvis

SITES OF ERYTHROPOIESIS



ERYTHROPOIESIS

PHSC Pluripotent Hemopoietic stem cell

IL-1,IL-6,IL-3 → ← GM CSF erythro

BFU-E (Burst Forming Unit Erythrocyte)

CFU-E (Colony Forming Unit Erythrocyte)

← GM CSF erythro

PROERYTHROBLAST

BASOPHILIC ERYTHROBLAST

POLYCHROMATOPHILIC ERYTHROBLAST

ORTHOCHROMATIC ERYTHROBLAST

RETICULOCYTE

ERYTHROCYTE

ERYTHROPOIESIS

PHSC Pluripotent Hemopoietic stem cell

IL-1,IL-6,IL-3 → ← GM CSF erythro

BFU-E (Burst Forming Unit Erythrocyte)

↓

CFU-E (Colony Forming Unit Erythrocyte)

↓ ← GM CSF erythro

PROERYTHROBLAST

↓

EARLY NORMOBLAST

↓

INTERMEDIATE NORMOBLAST

↓

LATE NORMOBLAST

↓

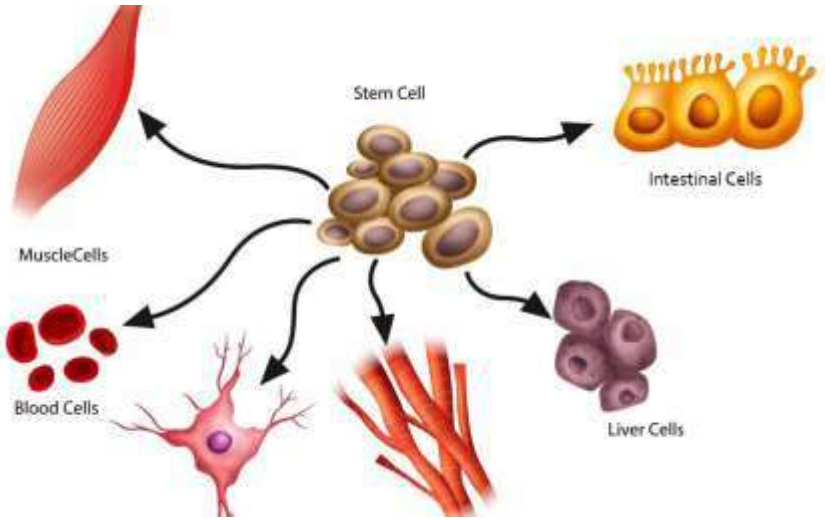
RETICULOCYTE

↓

ERYTHROCYTE

1. STEM CELLS

- These cells have extensive proliferative capacity and also the:
  - Ability to give rise to new stem cells (**Self Renewal)**
  - Ability to differentiate into any blood cells lines **(Pluripotency)**
- Hematopoietic stem cells (HSCs) are bone marrow cells that are capable of producing all types of blood cells.
- They differentiate into one or another type of committed stem cells (progenitor cells).



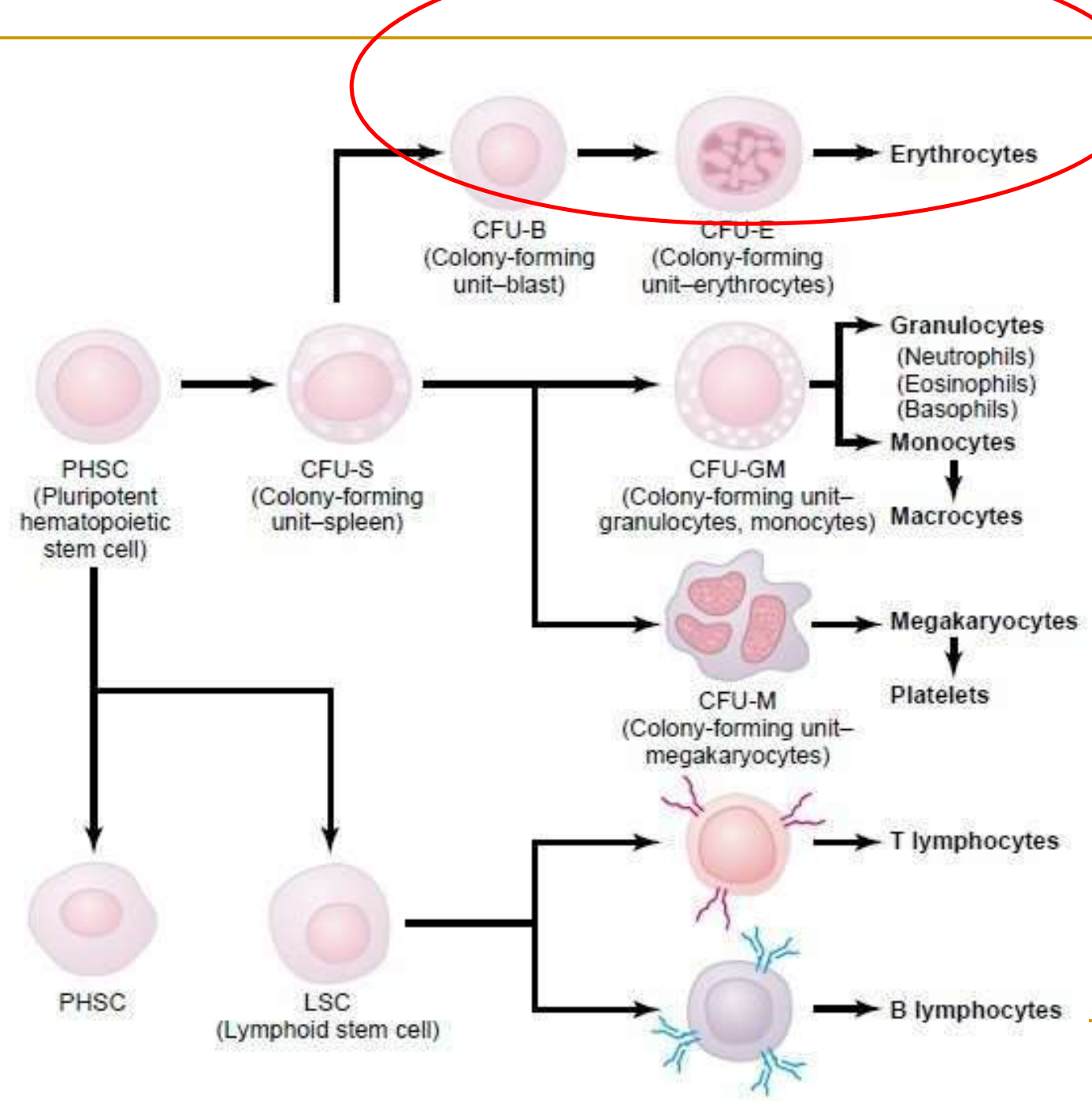


Figure 32–2

Formation of the multiple different blood cells from the original *pluripotent hematopoietic stem cell* (PHSC) in the bone marrow.

2. Progenitor cells

- Committed stem cells lose their capacity for self-renewal.
- They become irreversibly committed.

BFU-E & CFU-E

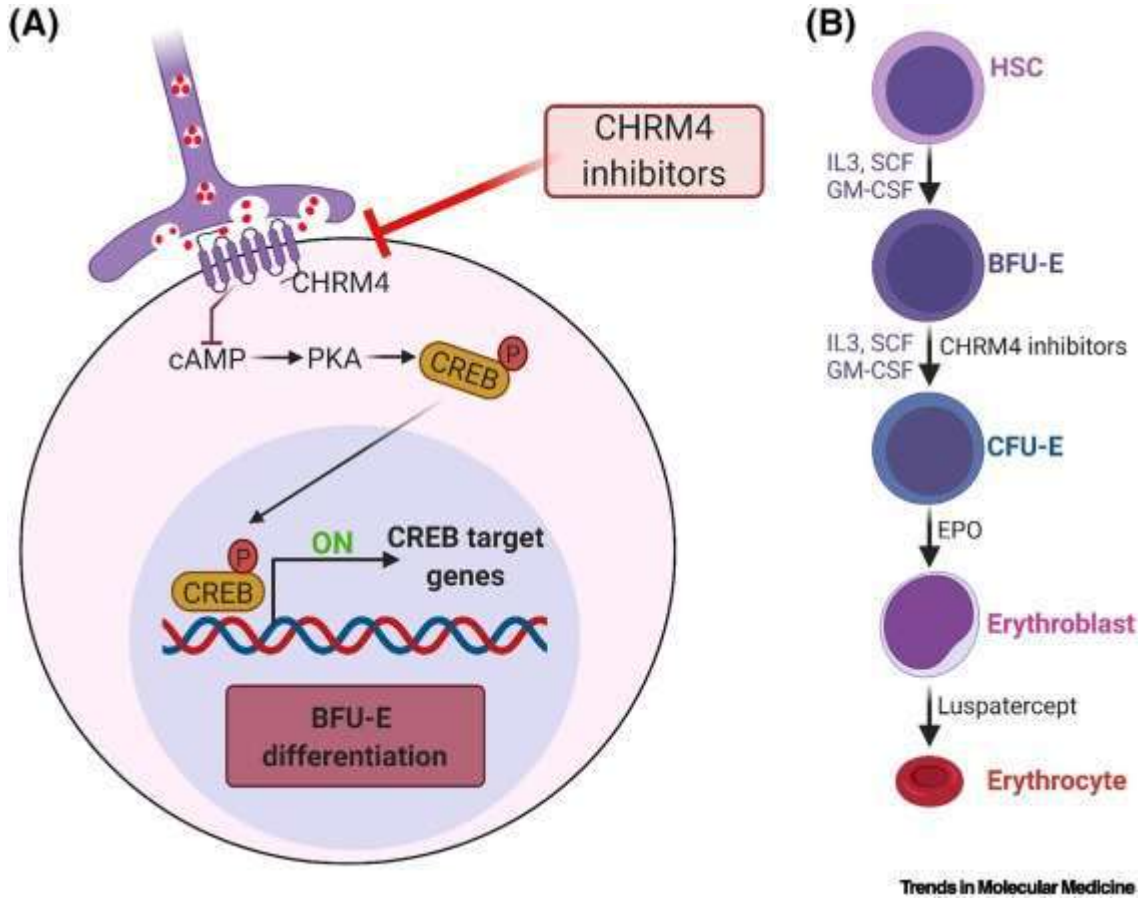
- BFU-E Give rise each to thousands of nucleated erythroid precursor cells.
- Undergo some changes to become the Colony Forming Units-Erythrocyte (CFU-E)
- Regulator: Burst Promoting Activity (BPA)

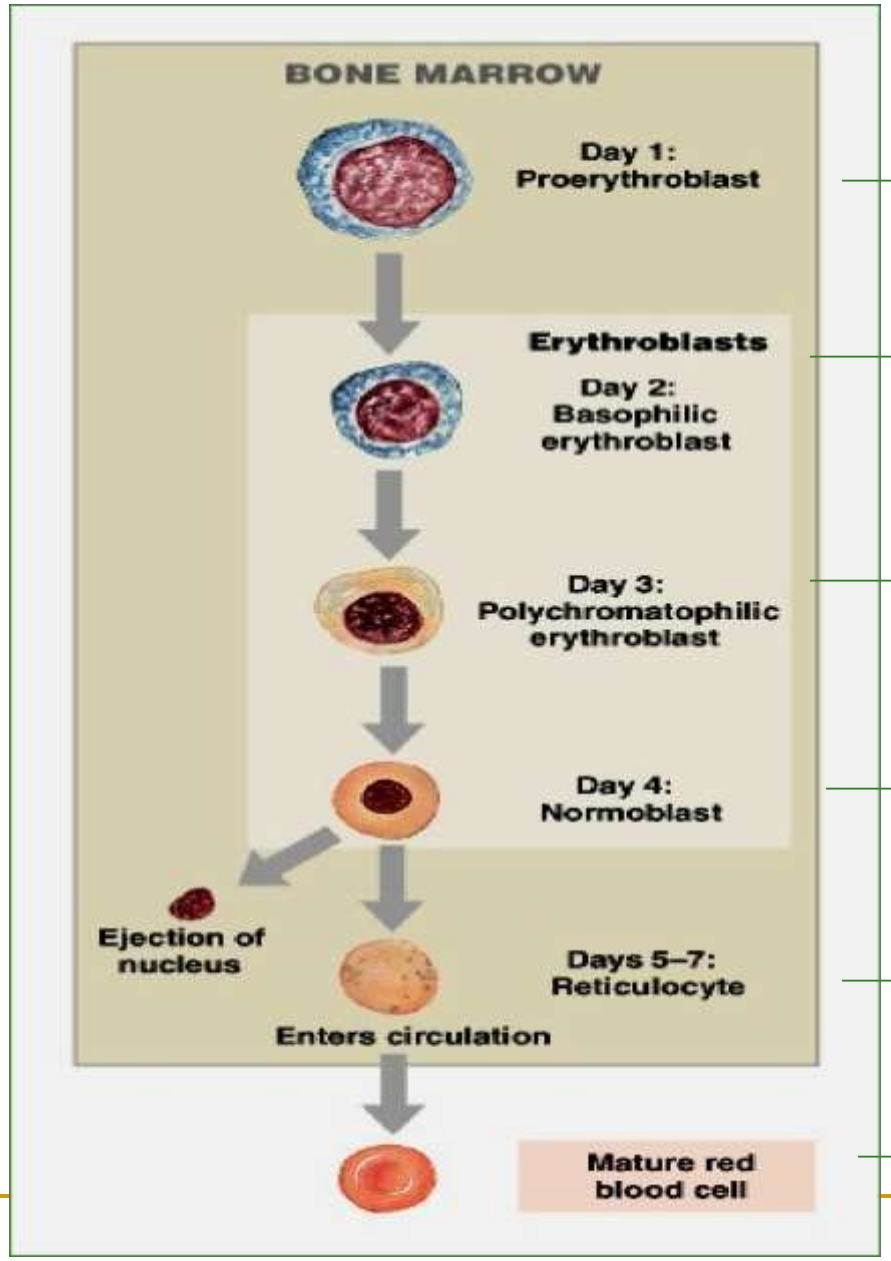
Burst forming unit BFU(E)

- Unipotent progenitor cell
- Less sensitive to erythropoietin
- Responds to other stimulus forms

Colony forming unit CFU (e)

- Highly sensitive and dependent on erythropoietin





ERYTHROPOIESIS

15-20µm- basophilic cytoplasm, nucleus with nucleoli.

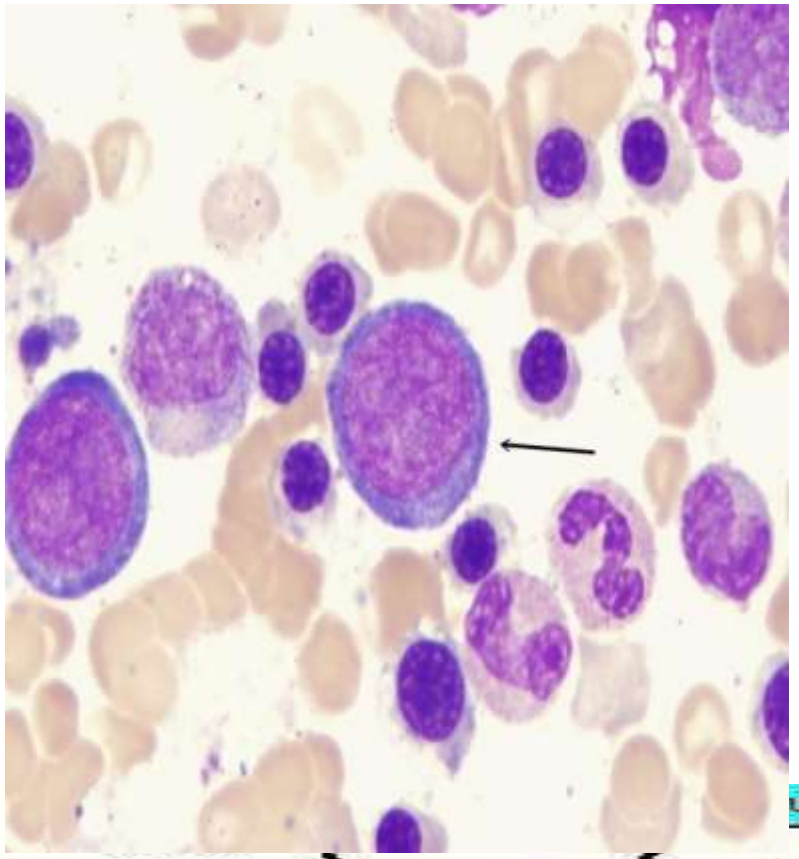
14-17µm-mitosis, basophilic cytoplasm, nucleoli disappears.

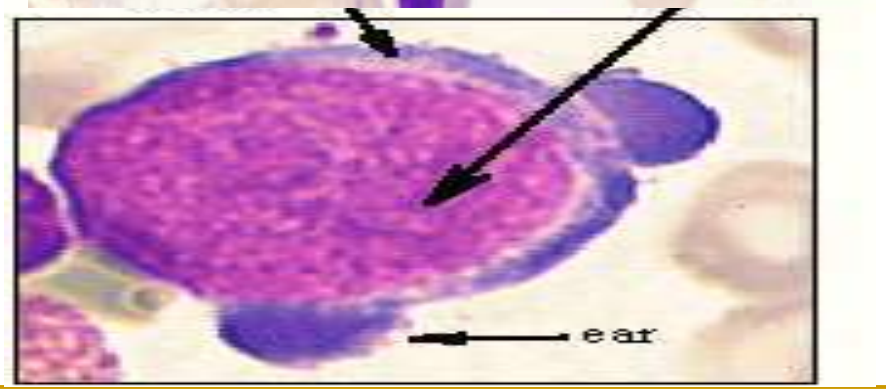
10-15µm- ’POLYCHROMASIA’
Hb appears, nucleus condenses.

7-10µm- PYKNOTIC Nucleus.
Extrusion, Hb is maximum.

7.3µm- Reticulum of basophilic material in the cytoplasm.

7.2µm- Mature red cell with Hb.

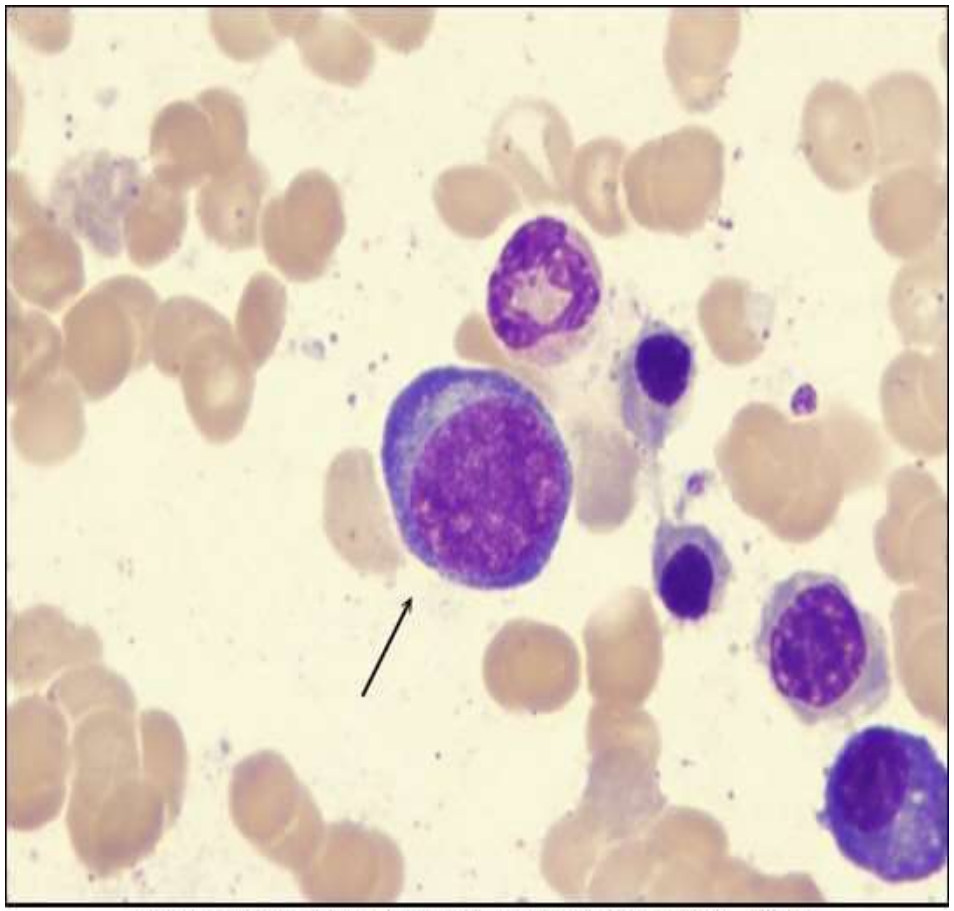




3. Proerythroblast

- 15-20 microns
- Nucleus with multiple nucleoli
- Basophilic cytoplasm with perinuclear halo
- No hemoglobin
- Mitosis present

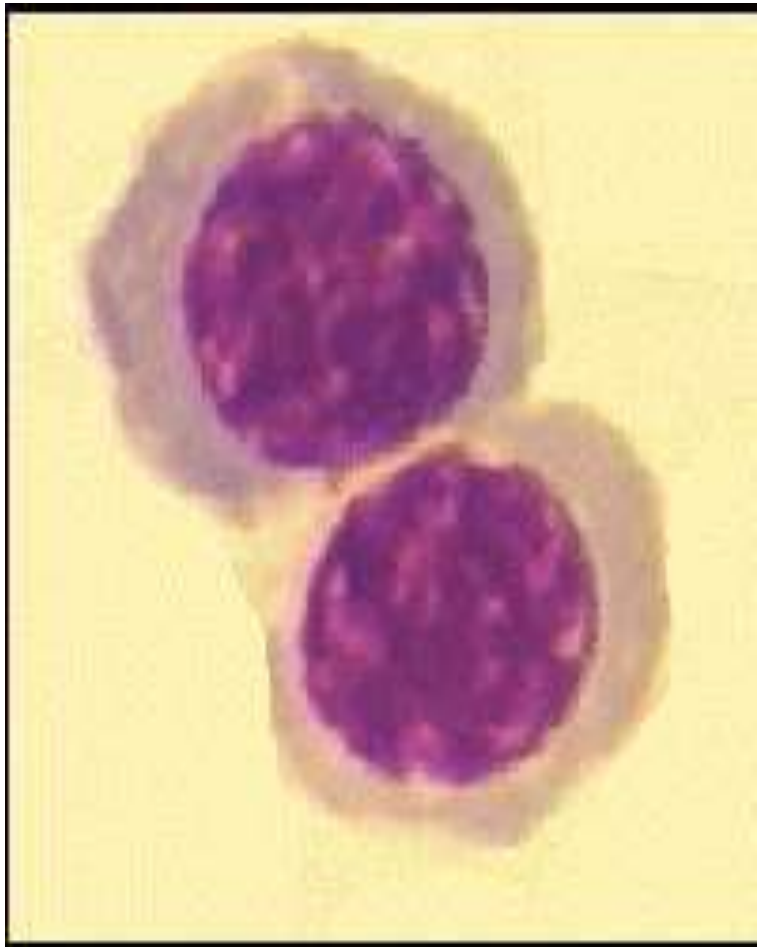
4. Basophilic/ early normoblast



Bone marrow aspirate smear, Wright-Giemsa stain, 1000x

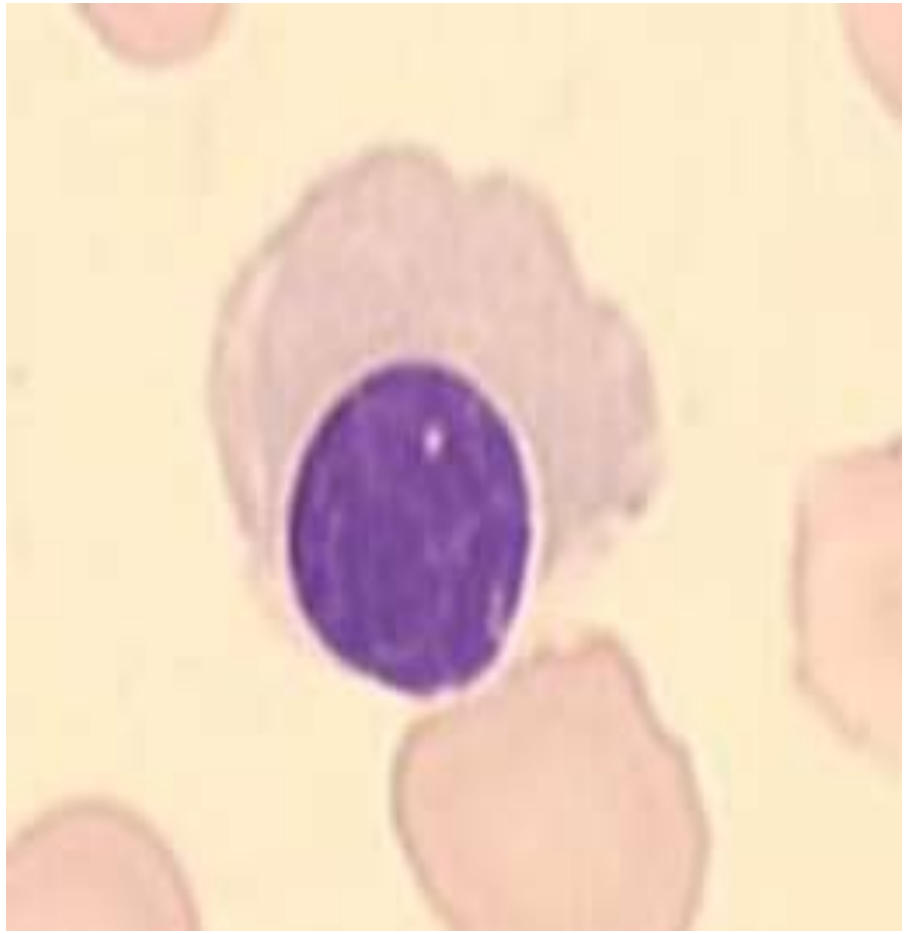
- Slight reduction in size 14-17µm
- Large nucleus, **nucleoli reduce in number**
- Basophilic cytoplasm
- Active mitosis

5. Polychromatophilic/ intermediate normoblast



- 10-15 µm size
- ’POLYCHROMASIA’
- nucleus condenses Chromatin lumps
- Hb starts appearing
- Reduced mitoses

6. Orthochromatic normoblast



- 7-10µm

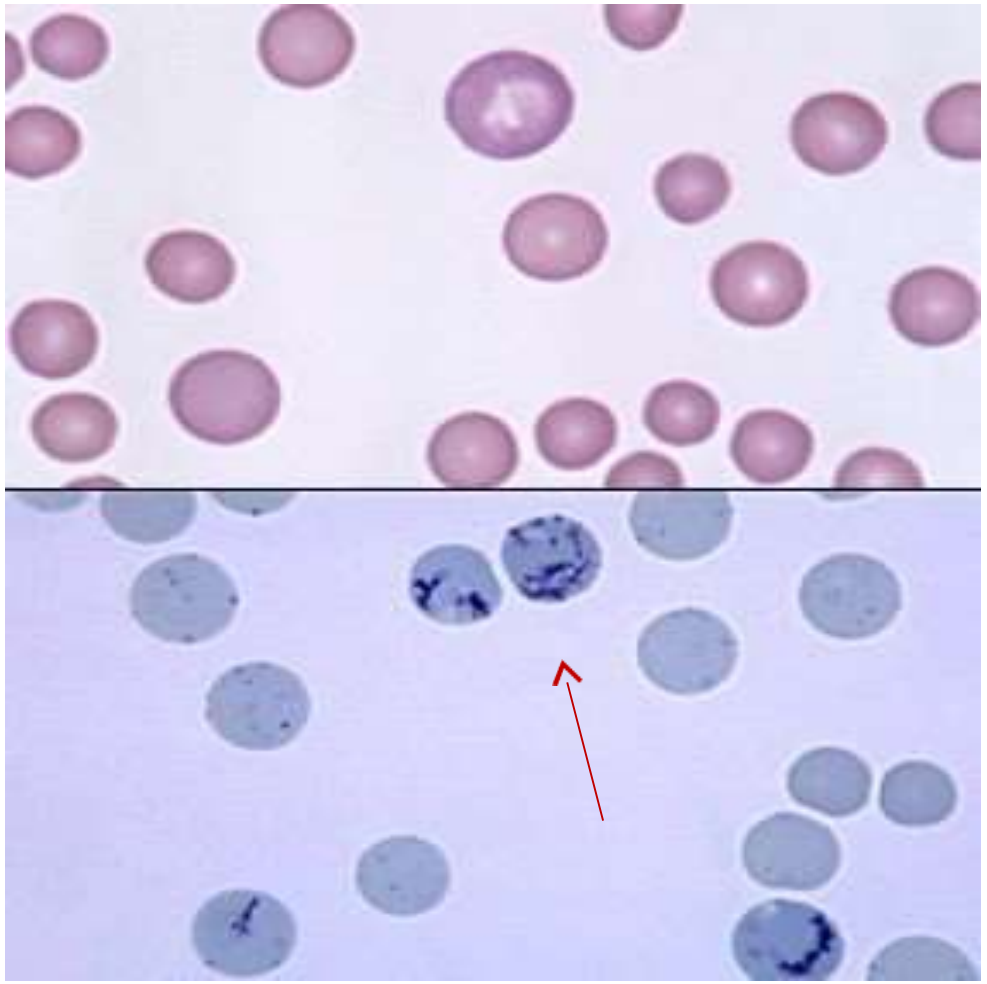
•Acidophilic erythroblast which is the last precursor with a nucleus.

•Nucleus is compact & situated near the membrane pyknotic nucleus is extruded

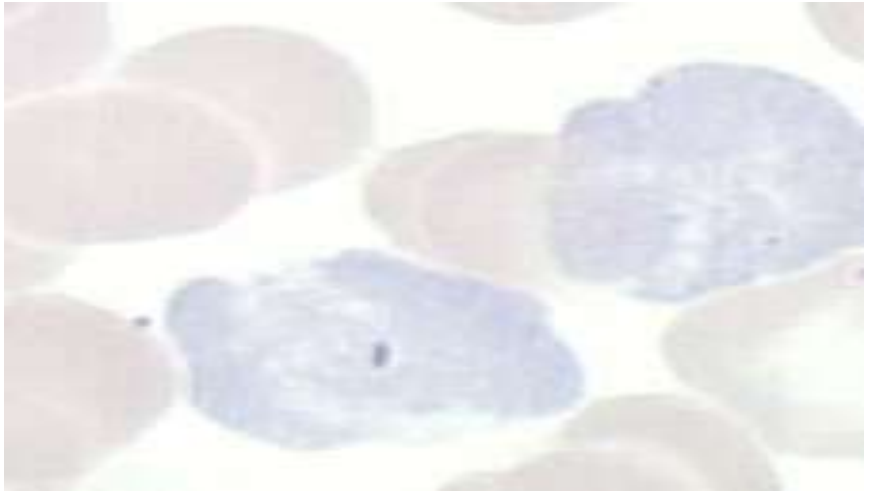
•Cytoplasm is like mature red cell, reflecting a high Hb content.

•Mitosis absent

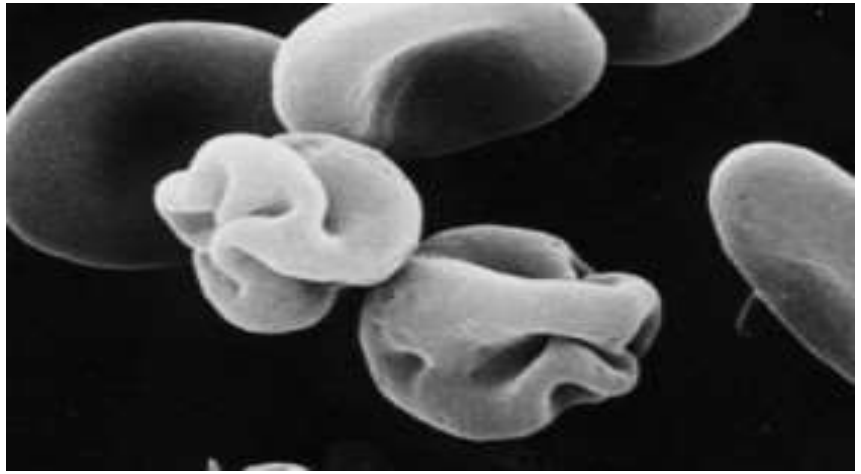
7. Reticulocyte

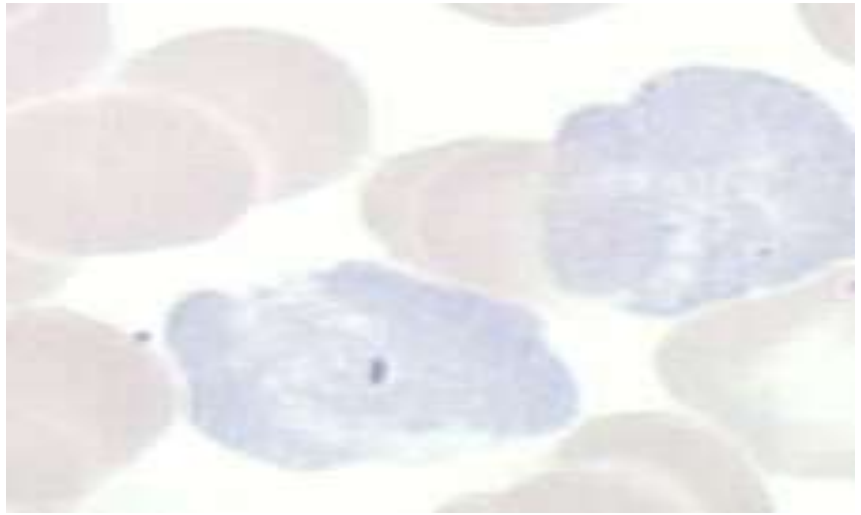


- Reticular nuclear fragments
- Nucleus extruded
- Slightly larger than RBCs



Reticulocyte

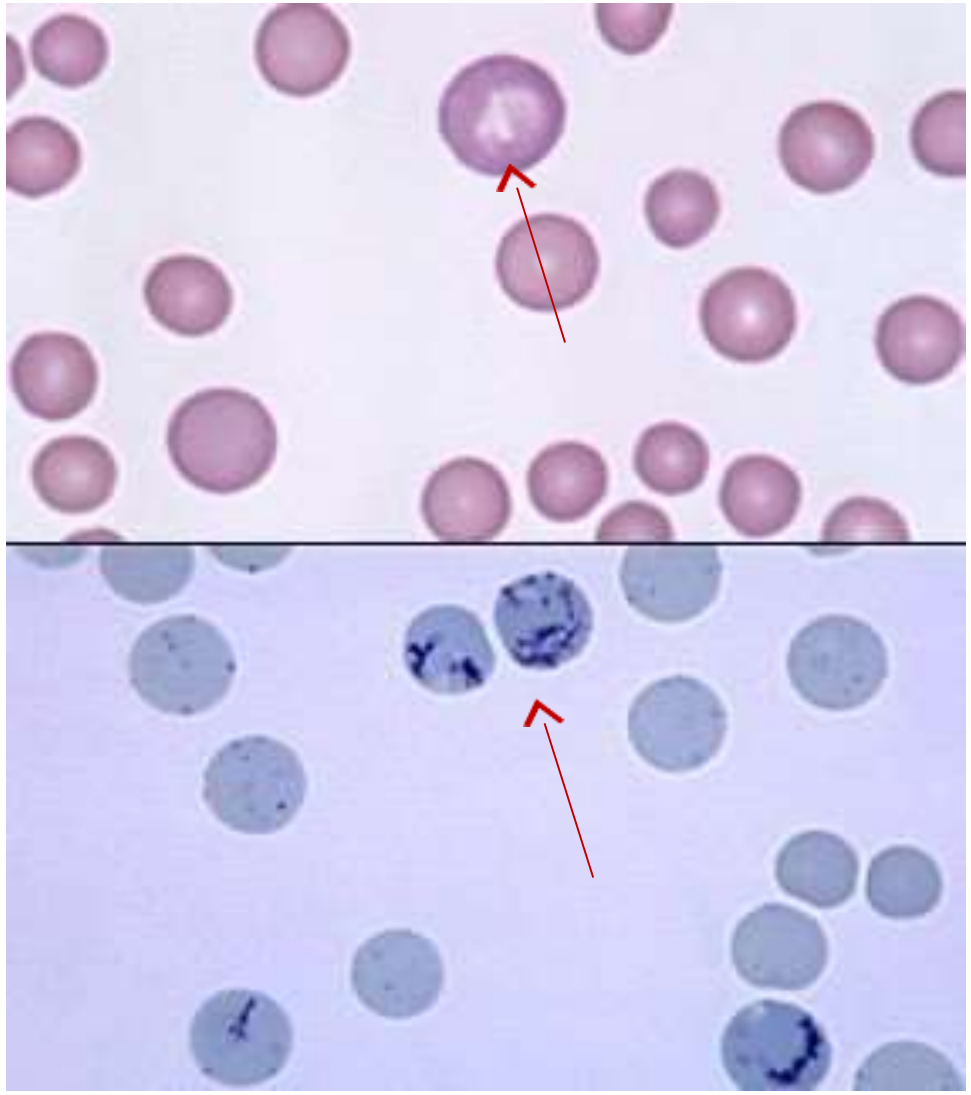




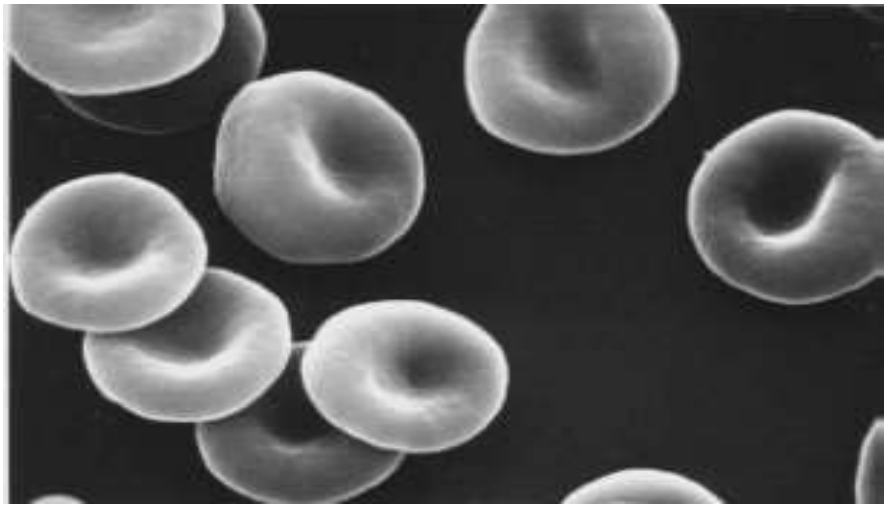
- Young erythrocytes with granular or reticular filamentous structures.
- Makes up 0.5 - 2% of all erythrocytes
- Vital staining required to make this visible.
- Reticulocytosis seen following hemolysis or acute blood loss

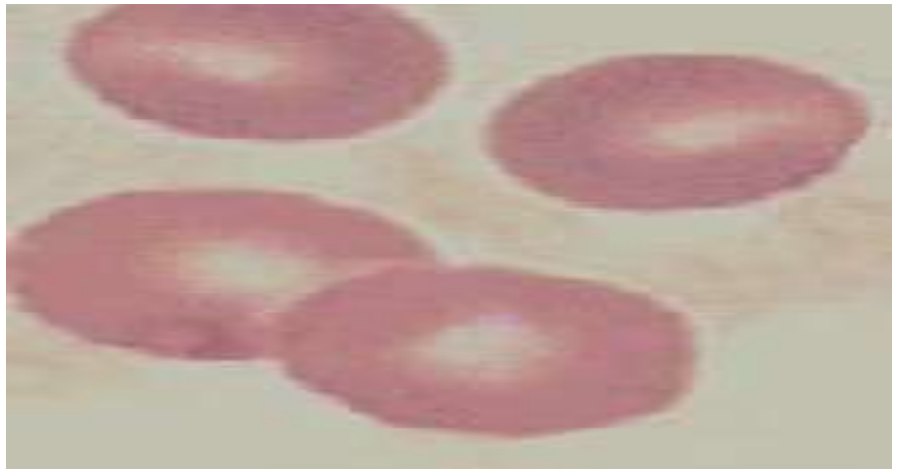
The Reticulocyte

- Has no nucleus
- Has no organelles
- Is larger than the mature RBC
- Is not concave
- Has many polyribosomes
- In severe anemia, many of these are released into the blood prematurely
- Normally 1% of circulating blood are reticulocytes.

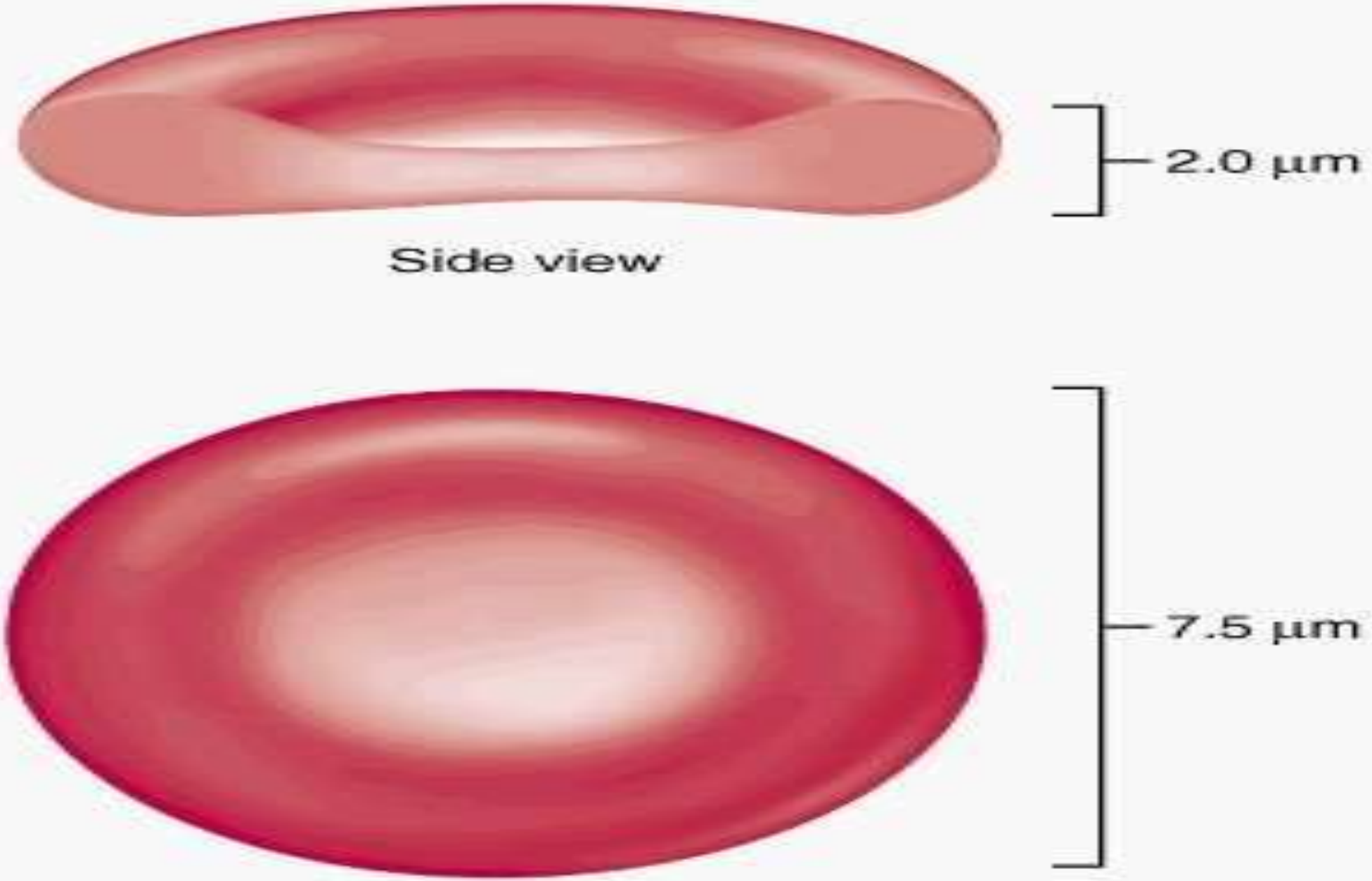


8. Mature erythrocyte



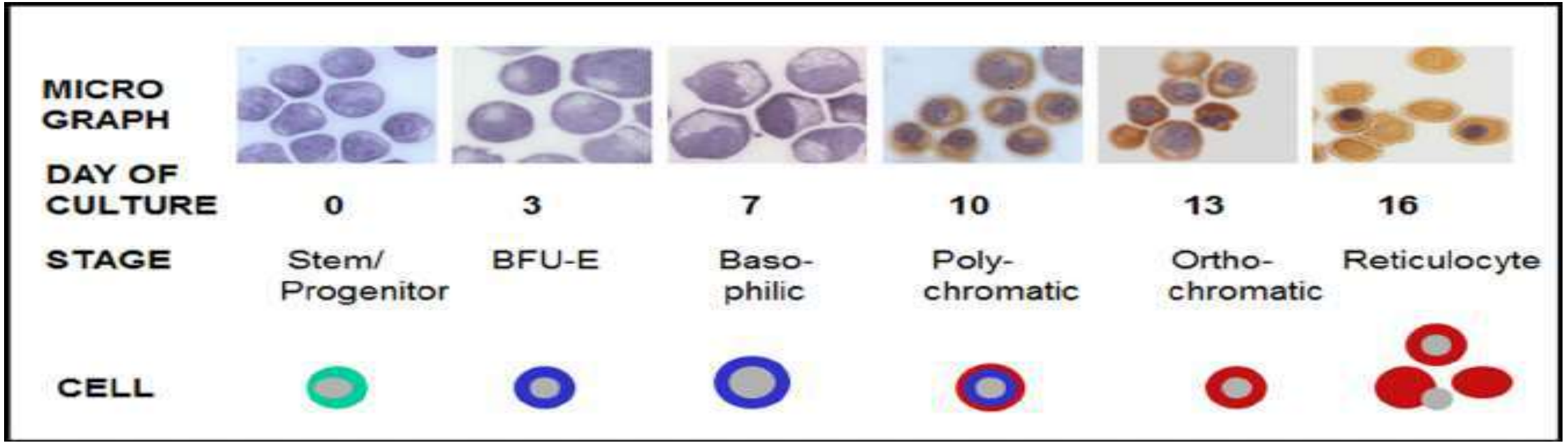


- Reddish, circular, biconcave cells
- 7-8 µ
- No visible internal structure
- High Hb content
- Bright at centre due to biconcave shape



Duration of erythropoiesis

- H S C to R B C- 21 days
- Differentiation phase: from pronormoblast to reticulocyte phase- 5 days
- Maturation phase: from reticulocyte to RBC- 2-4 days



Changes during erythropoiesis

- Decrease in size
- Hemoglobinization (intermediate normoblast)
- Change of cell shape (from globular to biconcave)
- Disappearance of nucleus, mitochondria, RNA, etc
- Change of staining (basophilic – eosinophilic)

Reticulocyte response

- Increase in reticulocyte count after treatment of anemia indicates bone marrow activity.
- A regenerative response that increases RBC production
- A response to blood loss, hemolysis, or replacement therapy for anemia

Regulation of erythropoiesis

- **General factors**

  Hypoxia, erythropoietin, Growth inducers, Vitamins

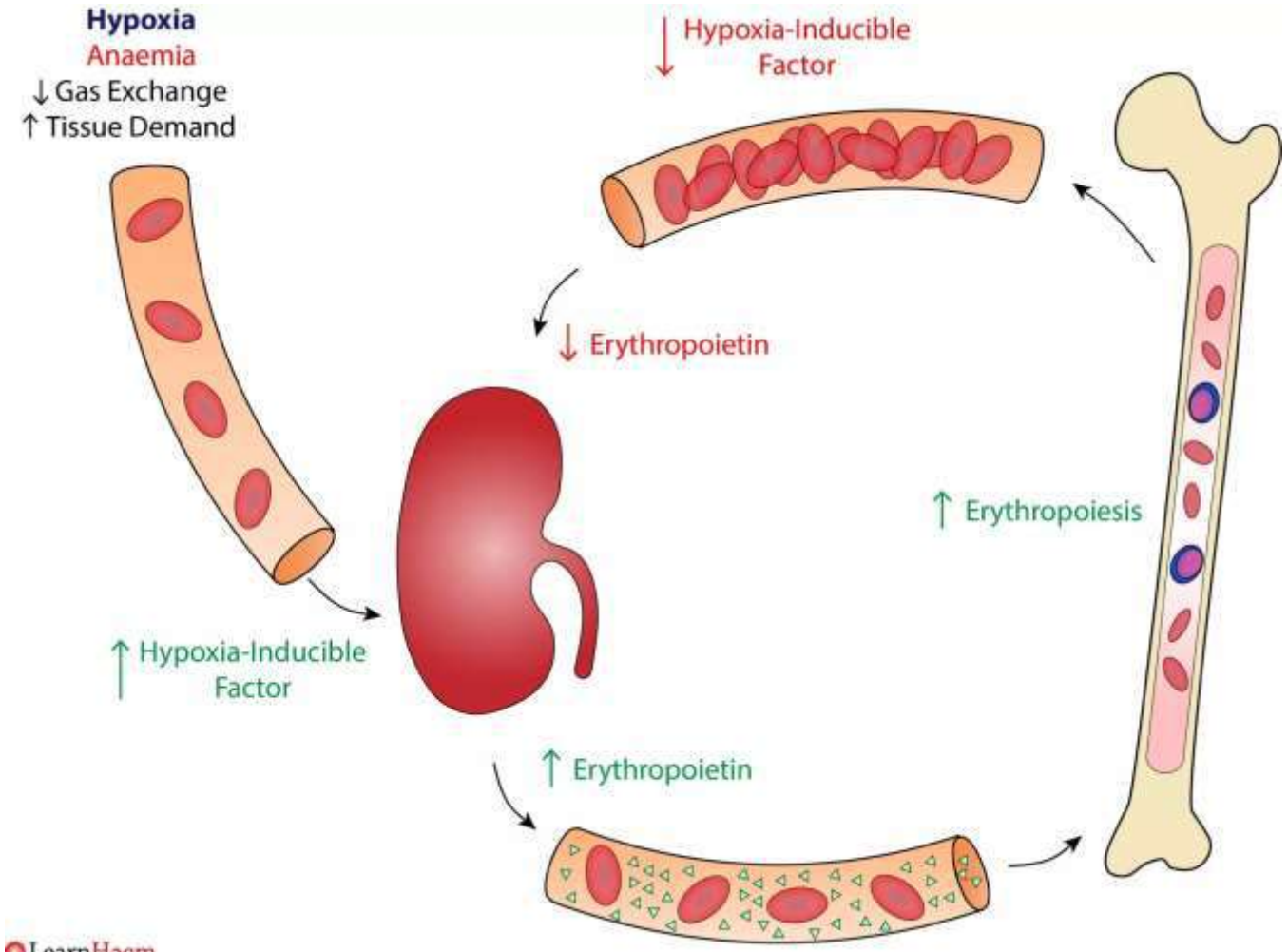
- **Maturation factors**

- Vitamin B 12
- Folic acid

- **Factors necessary for hemoglobin production**

  - Vitamin C: Helps in iron absorption (Fe+++ ,Fe++)
  - Proteins: Amino Acids for globin synthesis
  - Iron & copper: Heme synthesis
  - calcium, bile salts, cobalt & nickel.

General factors



Hypoxia, erythropoietin

ERYTHROPOIETIN

- Glycoprotein MW-34000 (165 AA residues)

Formation

- 85% formed in endothelial cells of the peritubular capillaries of the renal tubules.
- 15% formed in liver, hepatic cells & Kupffer cells.

Breakdown

- In liver. Half life is 5hours

Regulation of erythropoietin secretion

- O_2 sensor (heme protein) in kidney & liver
- Deoxy & oxy form of O_2 sensor
- HYPOXIA INDUCIBLE FACTOR-1 (HIF-1)
- Erythropoietin gene
- Erythropoietin mRNA
- Erythropoietin
- 2-3 days to increase RBC count

ERYTHROPOEITIN

Stimuli for production

- **Hypoxia**
- Products of RBC destruction
- High altitude
- Anemia
- Chronic lung or heart diseases
- Catecholamines
- Prostaglandins

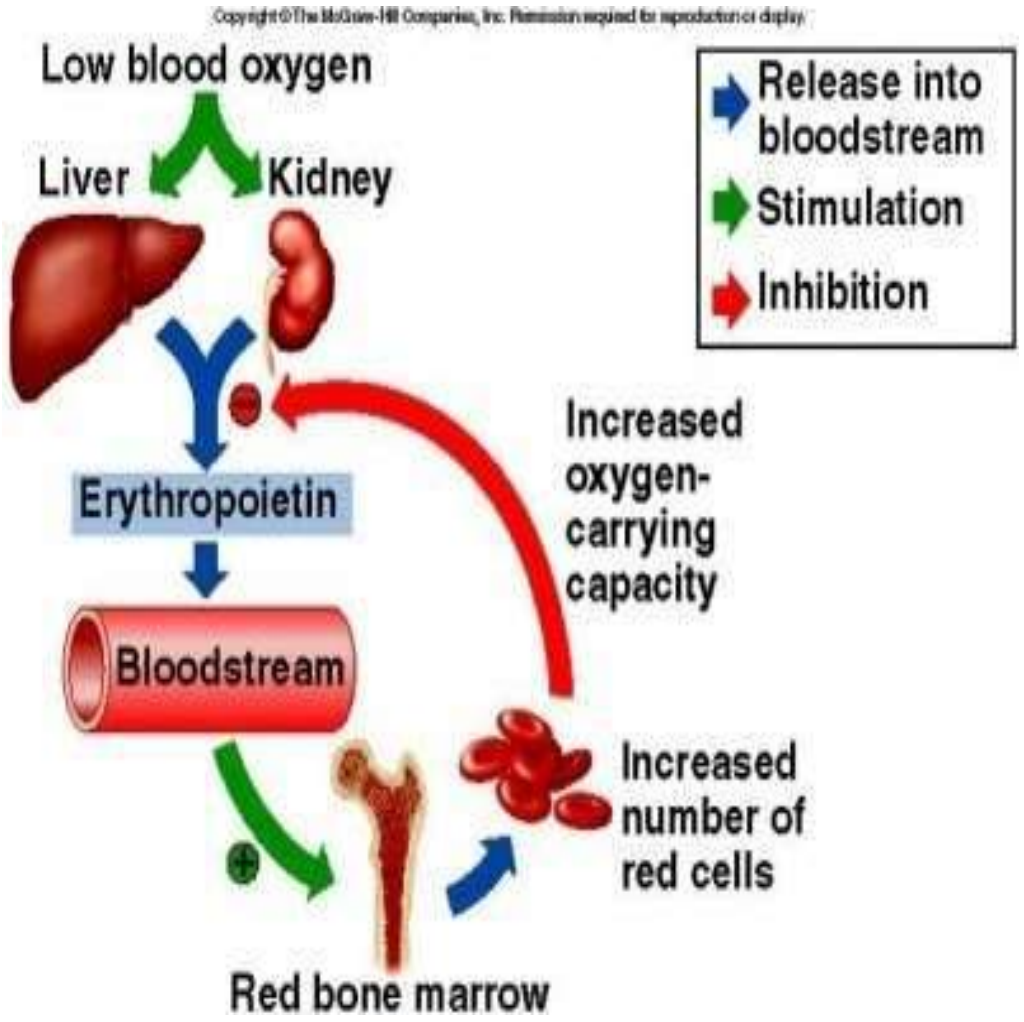
Androgens

Inhibition

- Blood transfusion

Functions of Erythropoietin

- Erythropoietin increases RBC production in 3 ways:
  - Promotes pronormoblast production
  - Shortens the transition time through the normoblast stage
  - Promotes the early release of reticulocytes.



Growth inducers/ Differentiation inducers

- Growth inducers: Molecules that stimulate cell proliferation and division;
- Differentiation inducers: Molecules that promote a cell to specialize into a specific cell type, essentially pushing it towards maturity and halting further division
- Interleukin 1, 3, 6 (IL-3 is a growth inducer for all cell lines)
- CSF- E (colony stimulating factor – erythro)

Maturation factors

Folic acid

- Green leafy vegetables , yeast, liver
- Function : maturation of RBC

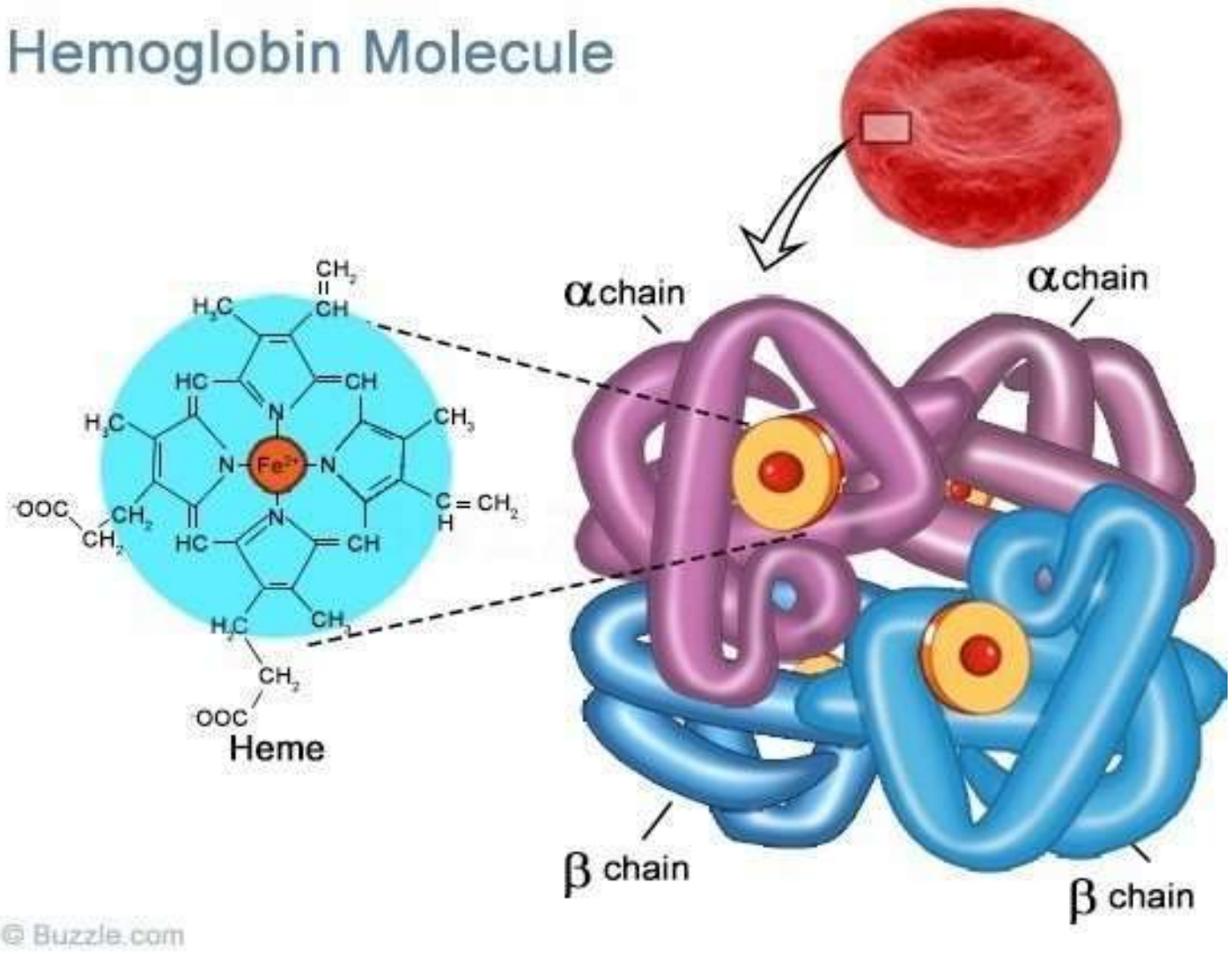
Vitamin B12

- Source : only animal tissues
- Absorption from ileum
- Functions
- Promotes maturation of RBCs (plays an important role in folic acid synthesis of nucleic acid-DNA)

Sources of vitamin B12

Dietary factors

- Iron



Other Factors Regulating erythropoiesis

NUTRITIONAL FACTOR

- Proteins

MINERALS

- Iron – for Hb
- Cu, Zn, Co– Hb synthesis

HORMONES

- Testosterone
- Thyroxine, Adrenal hormones
- Pituitary hormones – stimulate Erythropoietin

VITAMINS

- B12 & folic acid – for synthesis of DNA
- Riboflavin – Normal BM division
- Pyridoxine – Heme synthesis
- Vitamin C – absorption of Fe from gut

NEURAL

Stimulation of Hypothalamus
↑ RBC production

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