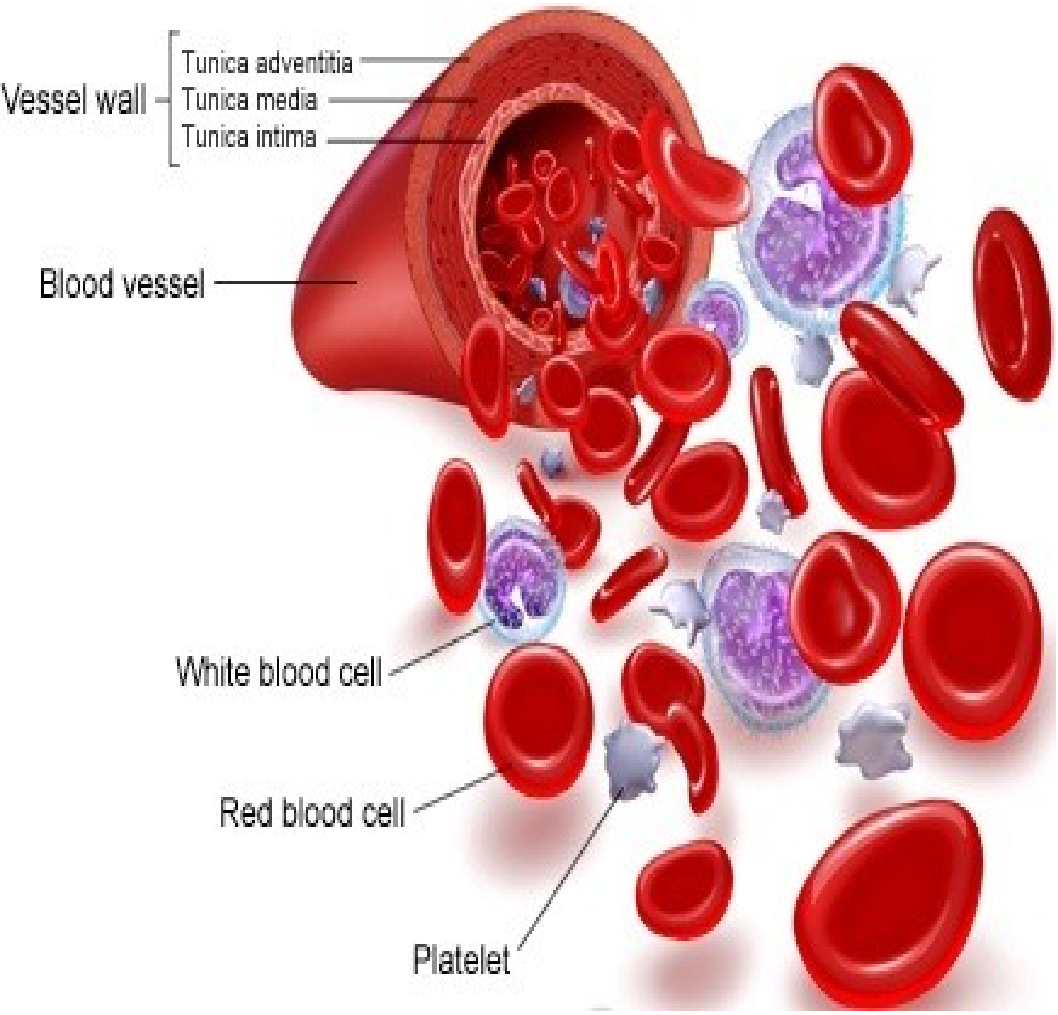
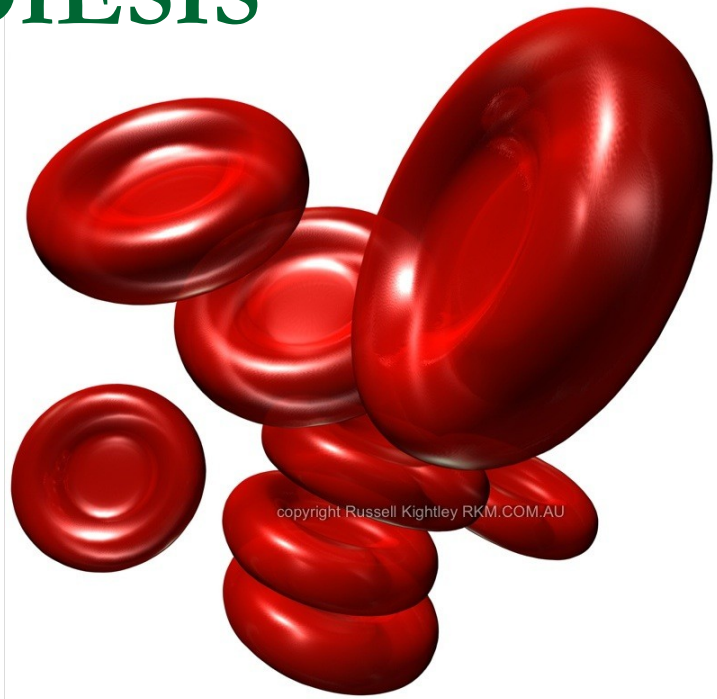
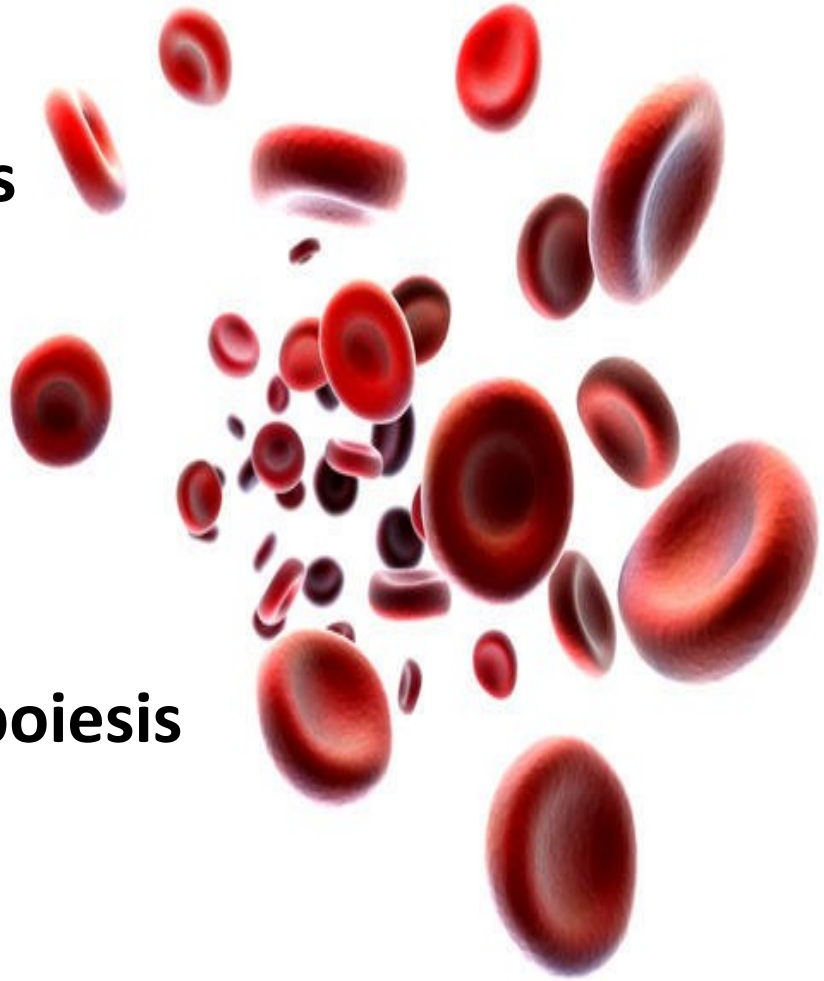
ERYTHROPOIESIS





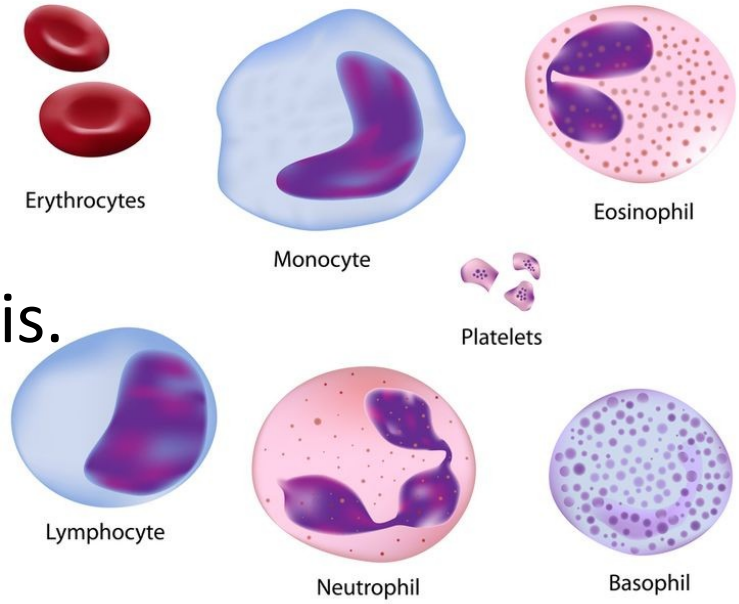
Scheme

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



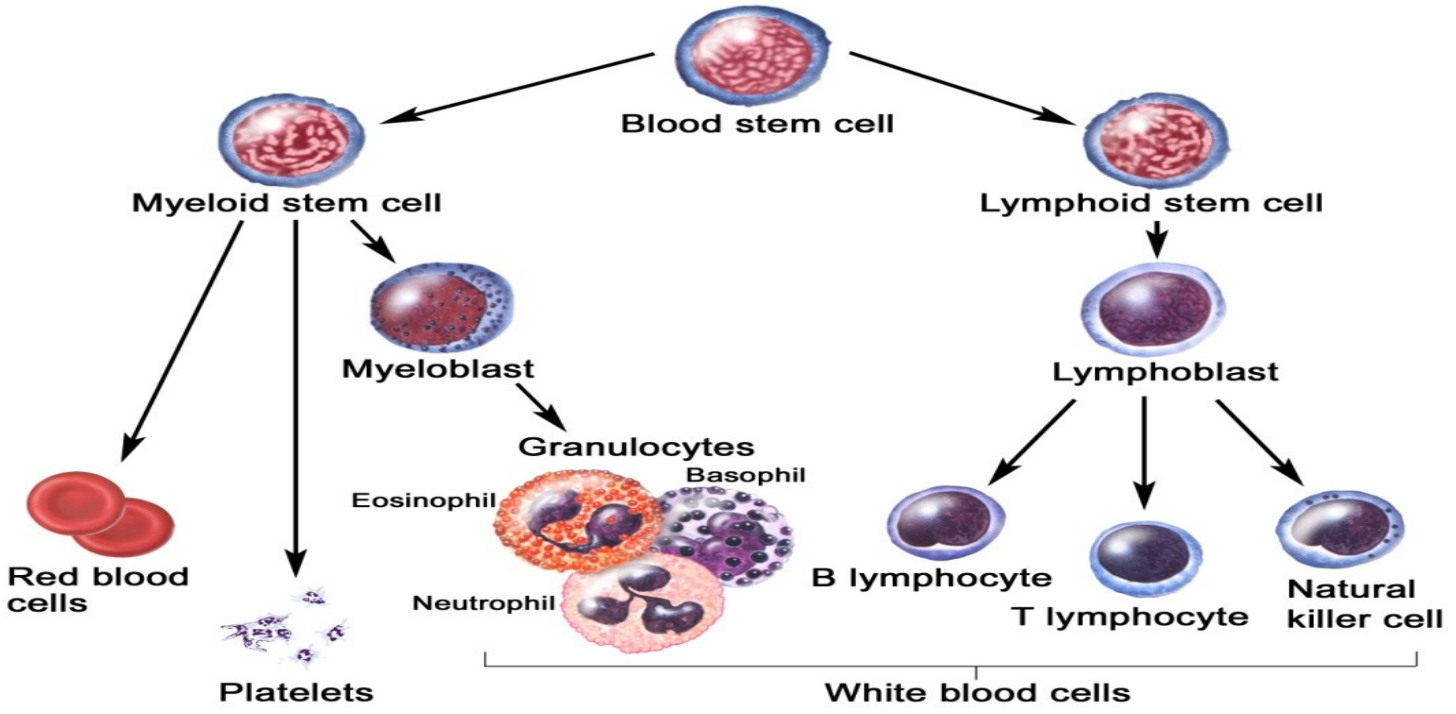
Hemopoiesis

- 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

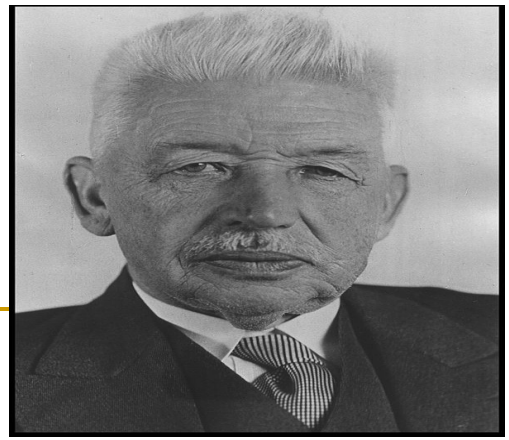
- **Monophyletic theory**

  - Also known as **unitary theory.**
  - There is a common parent cell of all formed elements of blood.

Alexander A. Maximow

- **Polyphyletic theory**

  - Also known as trialistic theory
  - Suggests different group of stem cells gives rise to different blood cells.



L. Aschoff

Site of Erythropoiesis

Intravascular erythropoiesis

Extravascular erythropoiesis

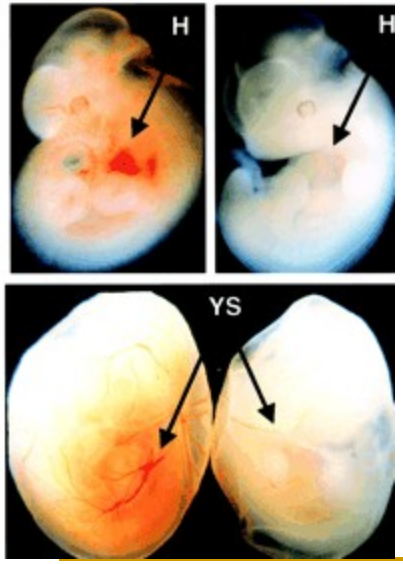
- **During intrauterine life**

  Mesoblastic stage (3rd week to 3 months)

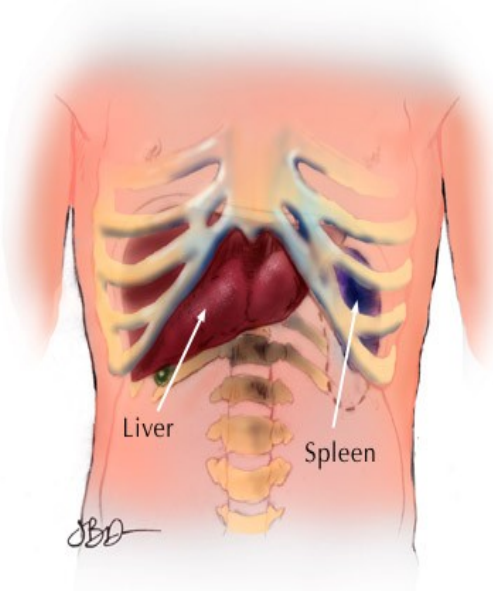
  Hepatic stage (after 3 months)

  Myeloid stage (3rd trimester)

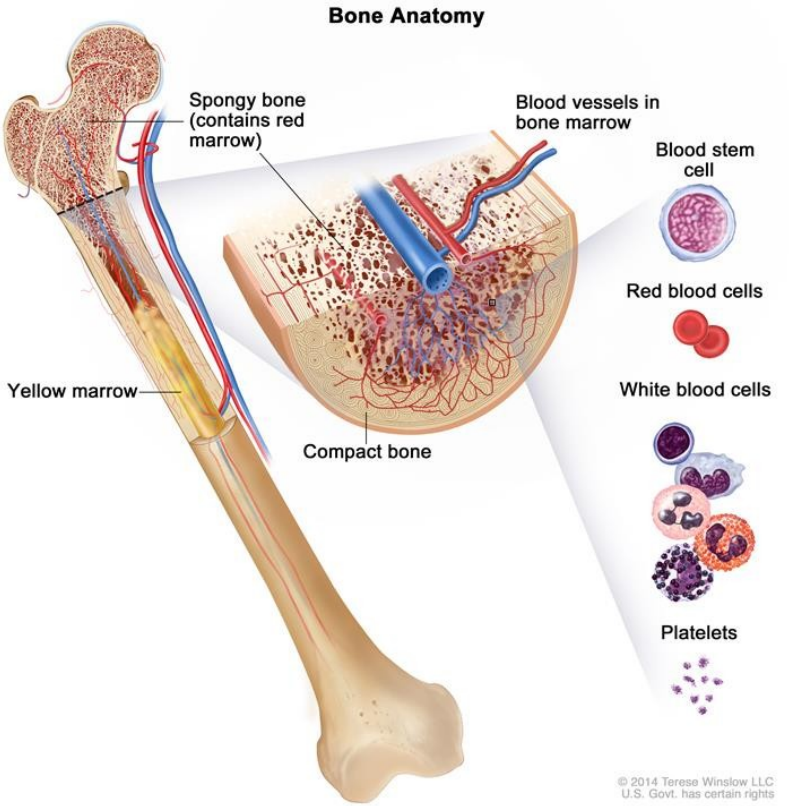
Nucleated RBCs



Yolk sac

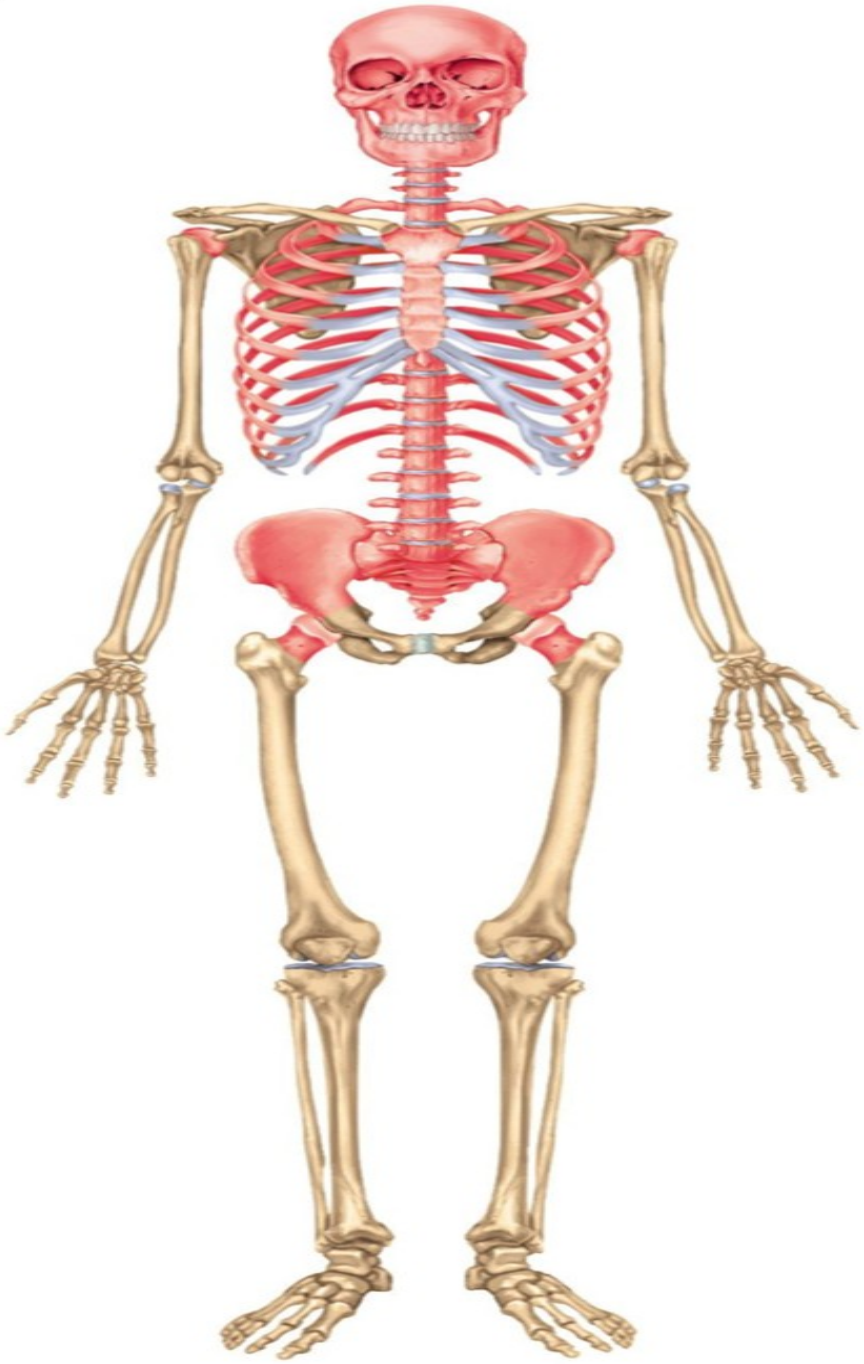


Liver & spleen

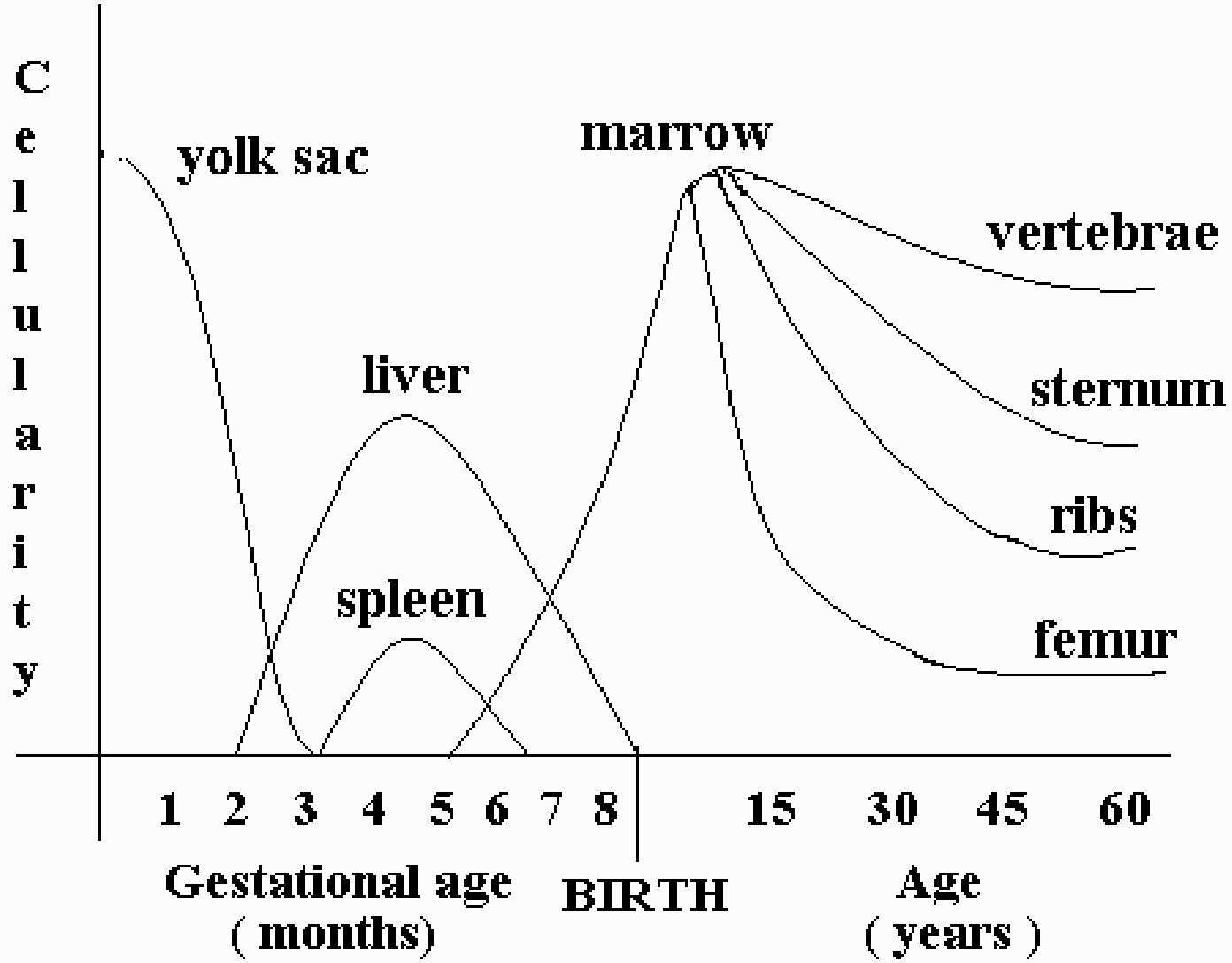


Bone marrow

- **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).

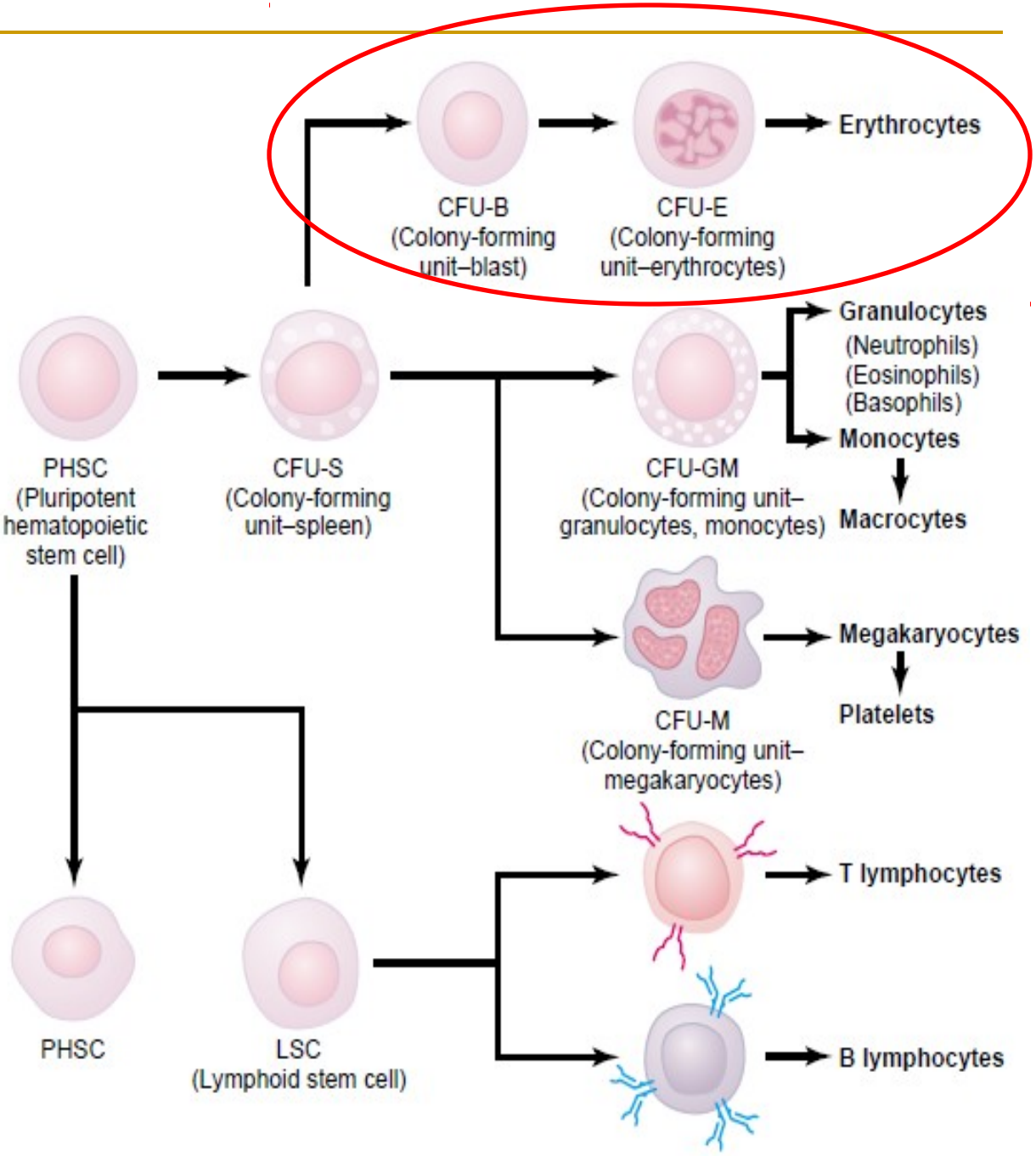


Figure 32–2

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

2. Progenitor cells BFU-E & CFU-E

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

- 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)

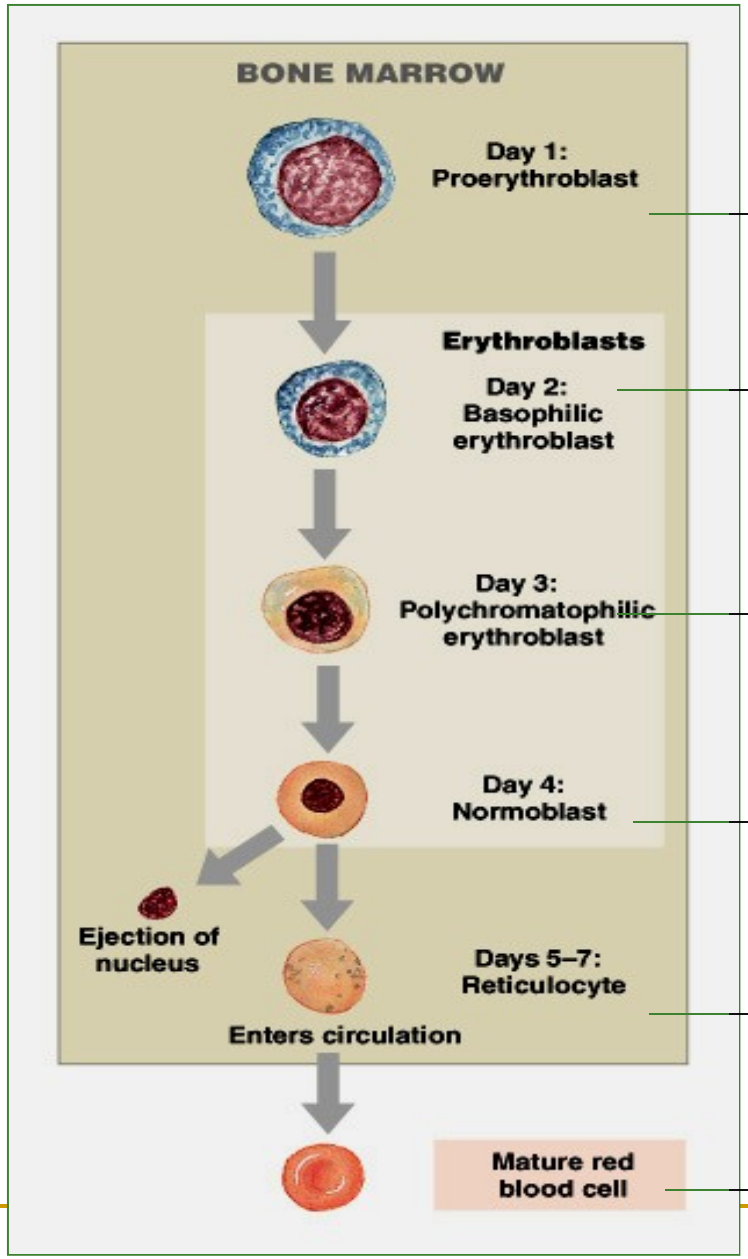
Burst forming unit BFU(E)

- 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’

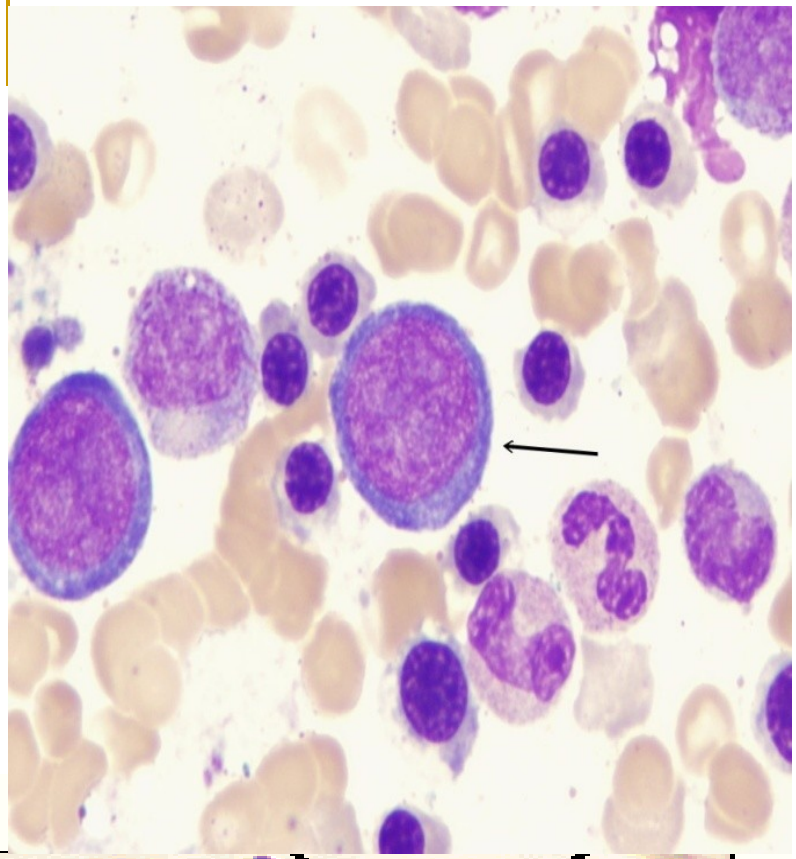
Hb appears, nucleus condenses.

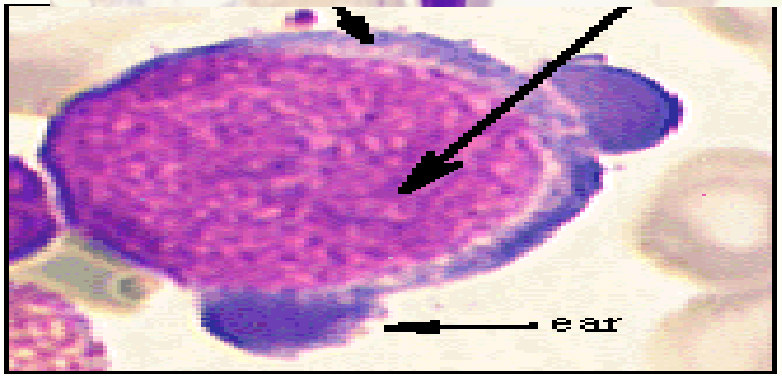
7-10µm- PYKNOTIC Nucleus.

Extrusion, Hb is maximum.

7.3µm- Reticulum of basophilic material in the cytoplasm.

7.2µm- Mature red cell with Hb.

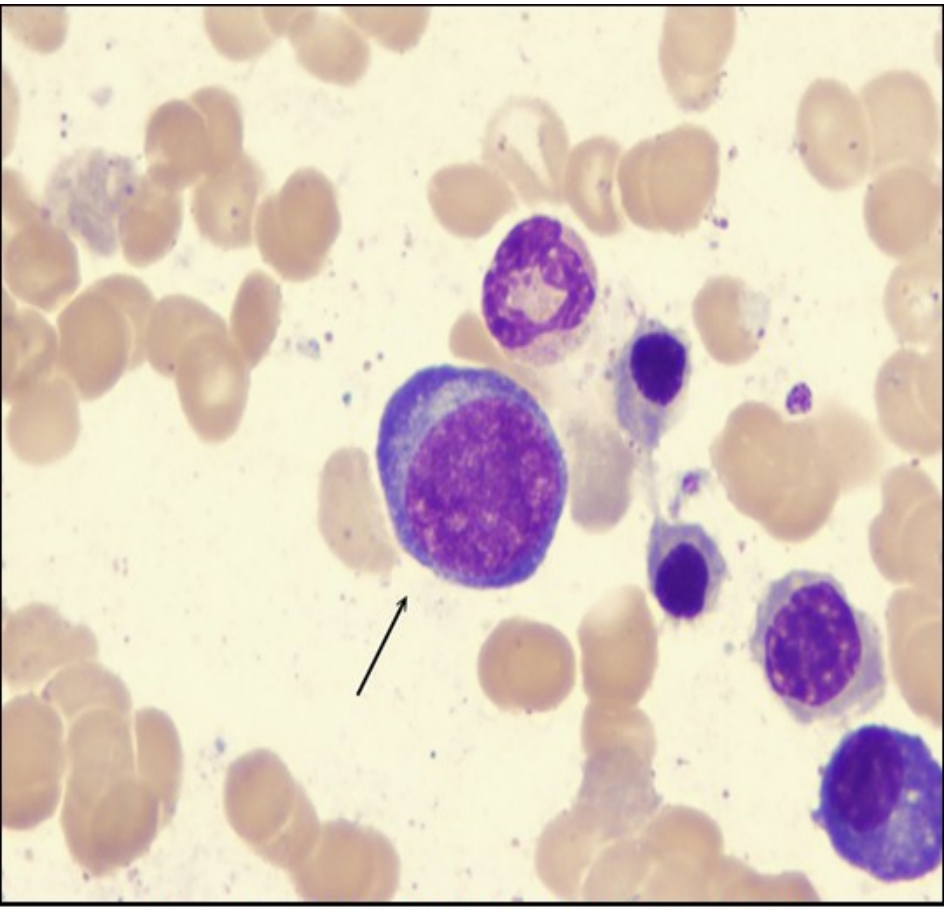




3. Proerythroblast

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

4. Basophilic/ early normoblast



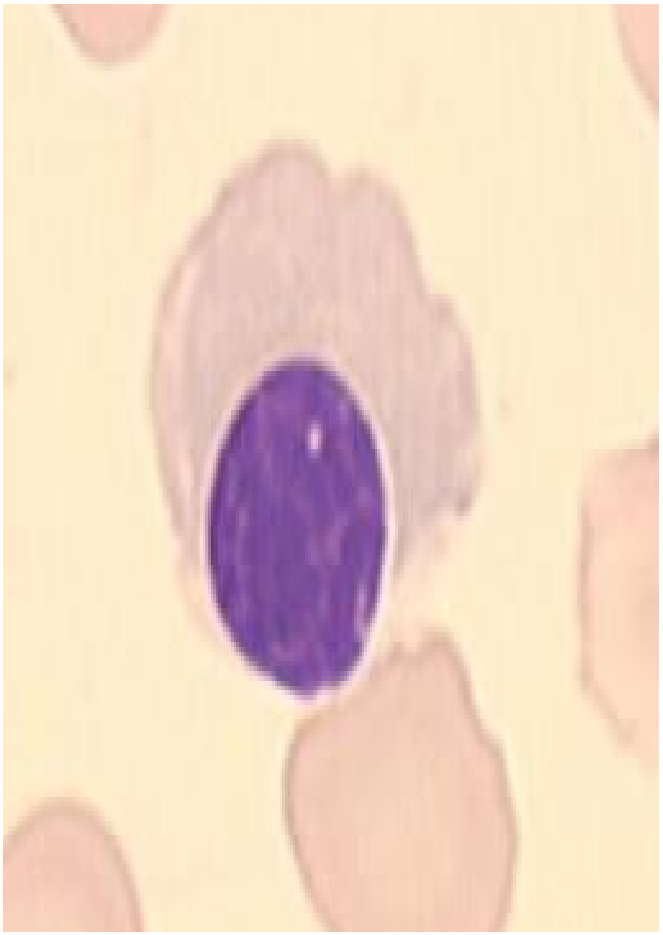
Bone marrow aspirate smear, Wright-Giemsa stain, 1000x

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

5. Polychromatophilic/ intermediate normoblast

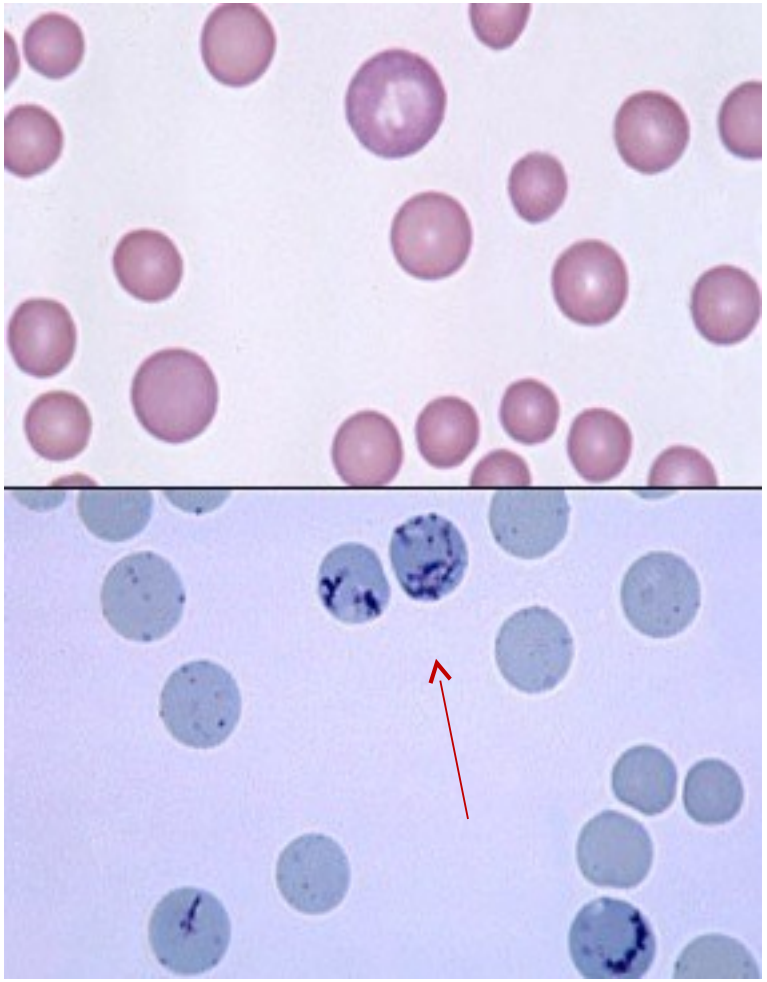
- 10-15µm size
- 'POLYCHROMASIA'
- nucleus condenses Chromatin lumps
- Hb starts appearing
- Reduced mitoses

6. Orthochromatic normoblast

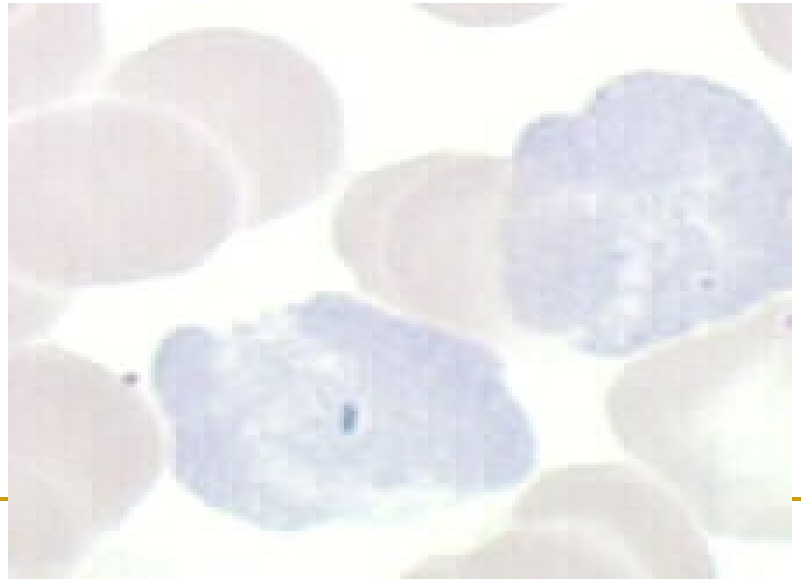


- 7-10µm
- Acidophilic erythroblast which is the last precursor with a nucleus.
- Nucleus is compact & situated near the membrane pyknotic nucleus is extruded
- Cytoplasm is like mature red cell, reflecting a high Hb content.
- Mitosis absent

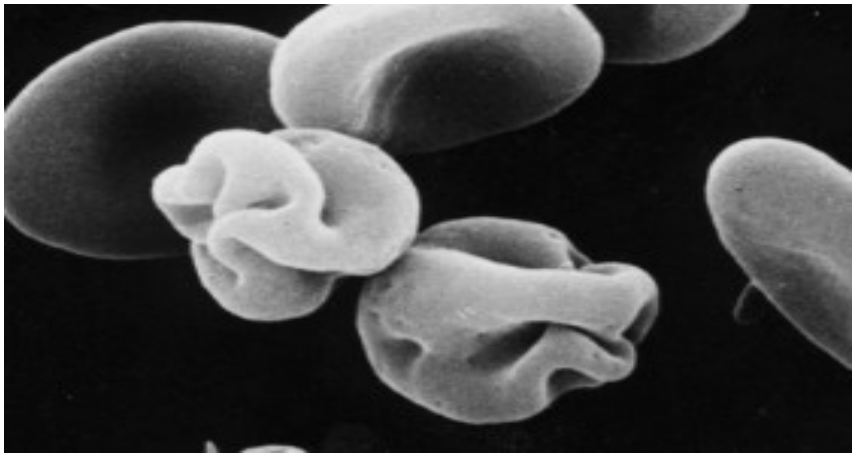
7. Reticulocyte

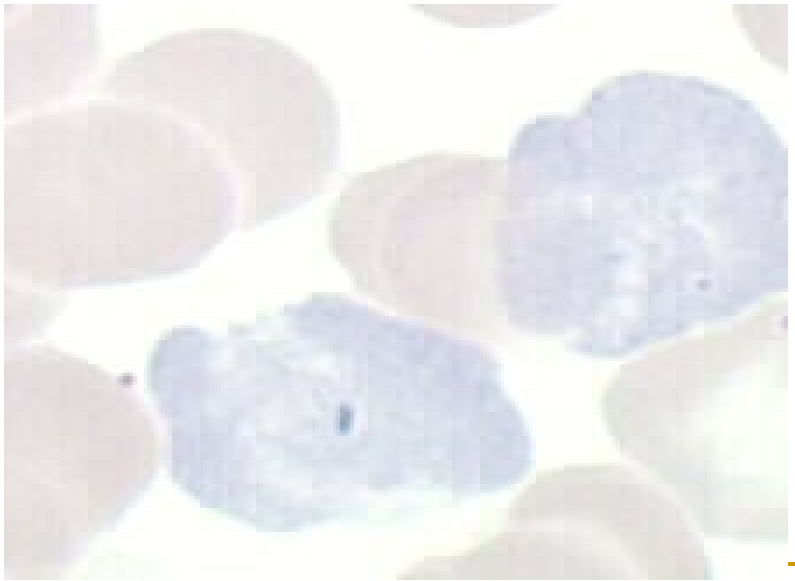


- Reticular nuclear fragments
- Nucleus extruded
- Slightly larger than RBCs



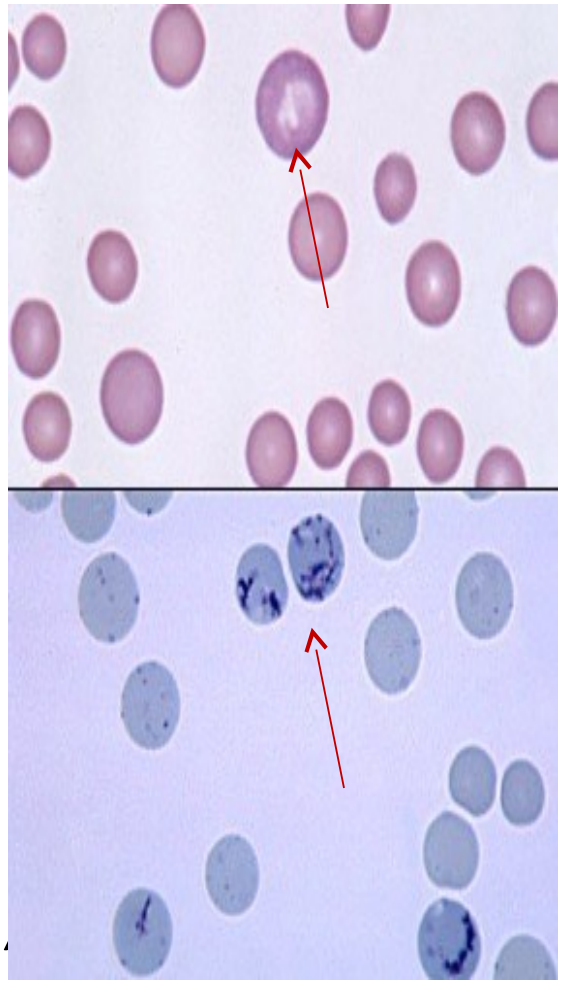
Reticulocyte



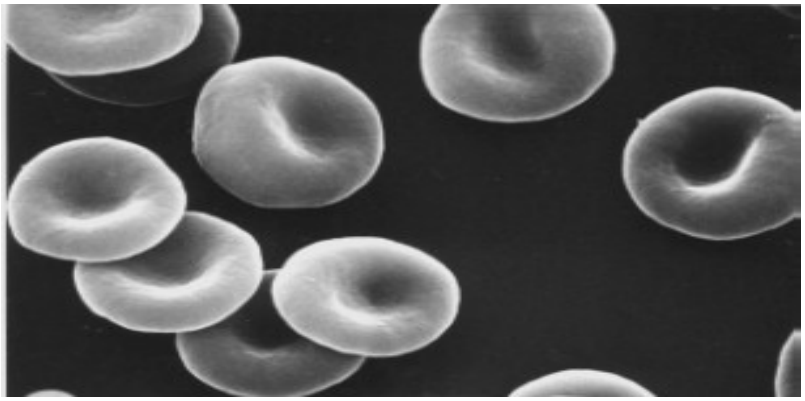


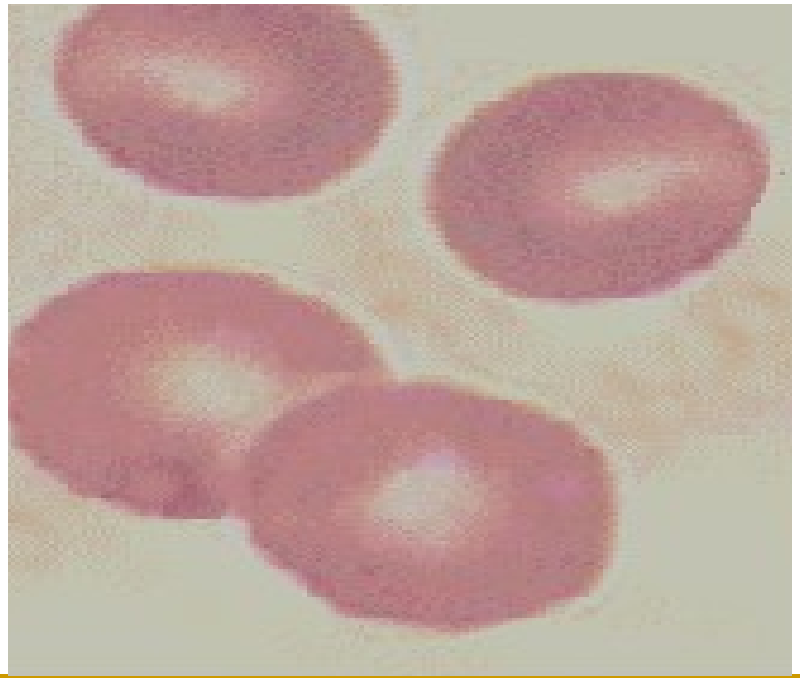
- Young erythrocytes with granular or reticular filamentous structures.
- Makes up 0.5-2% of all erythrocytes
- Vital staining required to make this visible.
- Reticulocytosis seen following hemolysis or acute blood loss

- 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→ Reticulocyte response.
  - Normally 1% of circulating blood are reticulocytes.



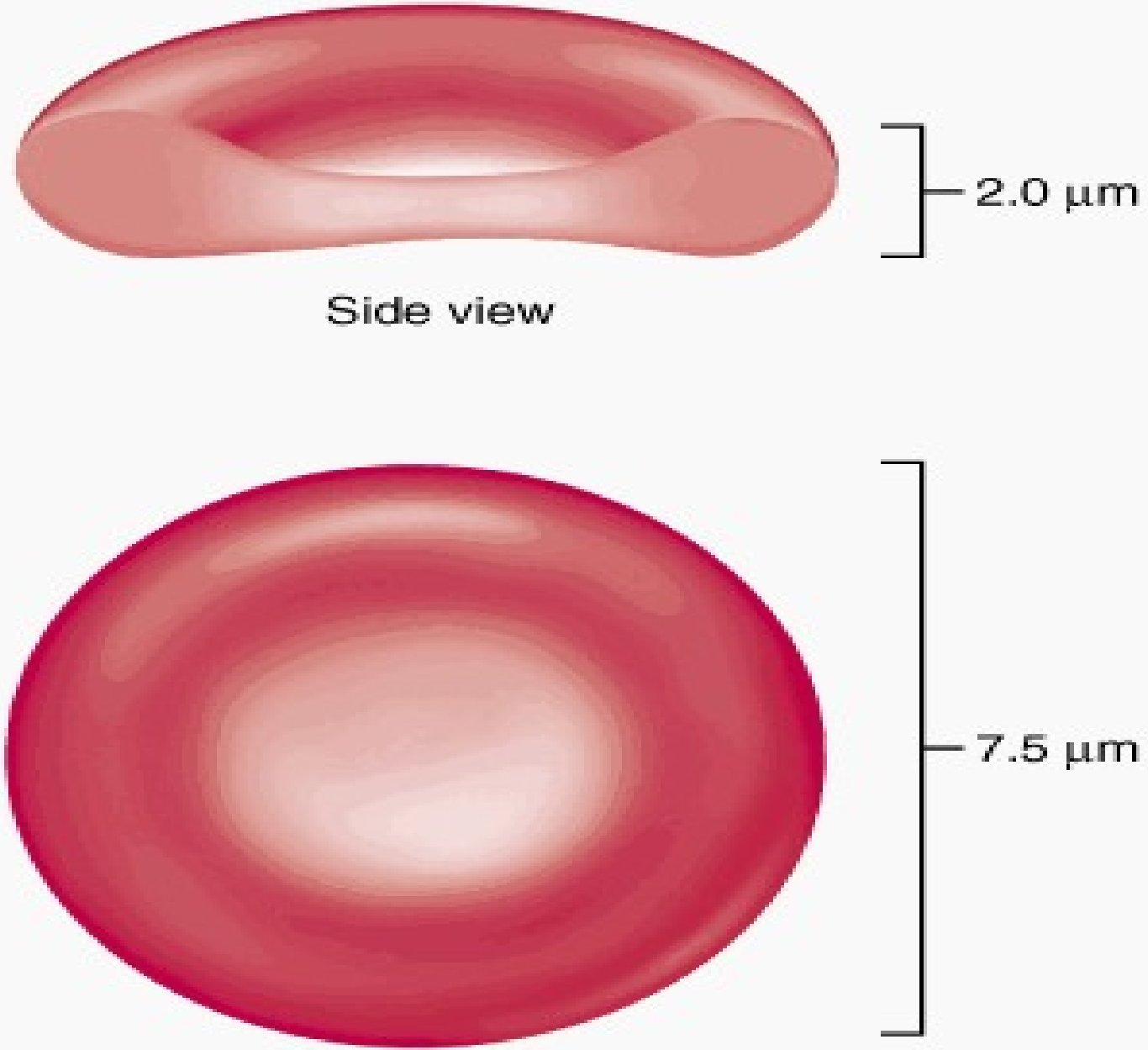
8. Mature erythrocyte





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

7.2 µm

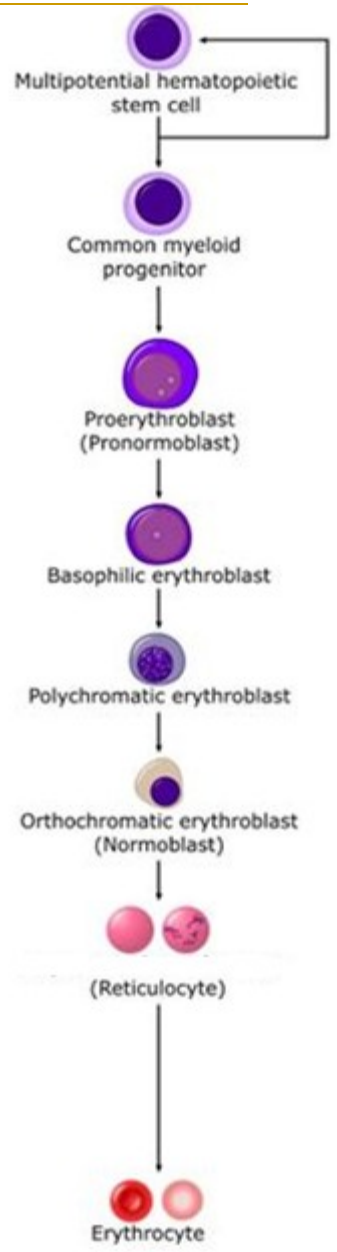


Duration of erythropoiesis

HSC to RBC- 21 days

Differentiation phase: from pronormoblast to reticulocyte phase- 5 days

Maturation phase: from reticulocyte to RBC- 2 days



Changes during erythropoiesis

- Decrease in size
- Loss of mitotic activity (later part of intermediate.normo)
- 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

1. Definition
2. Theories of erythropoiesis
3. Sites of erythropoiesis
4. Stages of erythropoiesis
5. Reticulocyte
6. Mature Red Cell

Part – II
ERYTHROPOIESIS

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

© Can Stock Photo - csp12168501

Hypoxia → erythropoietin

ERYTHROPOIETIN

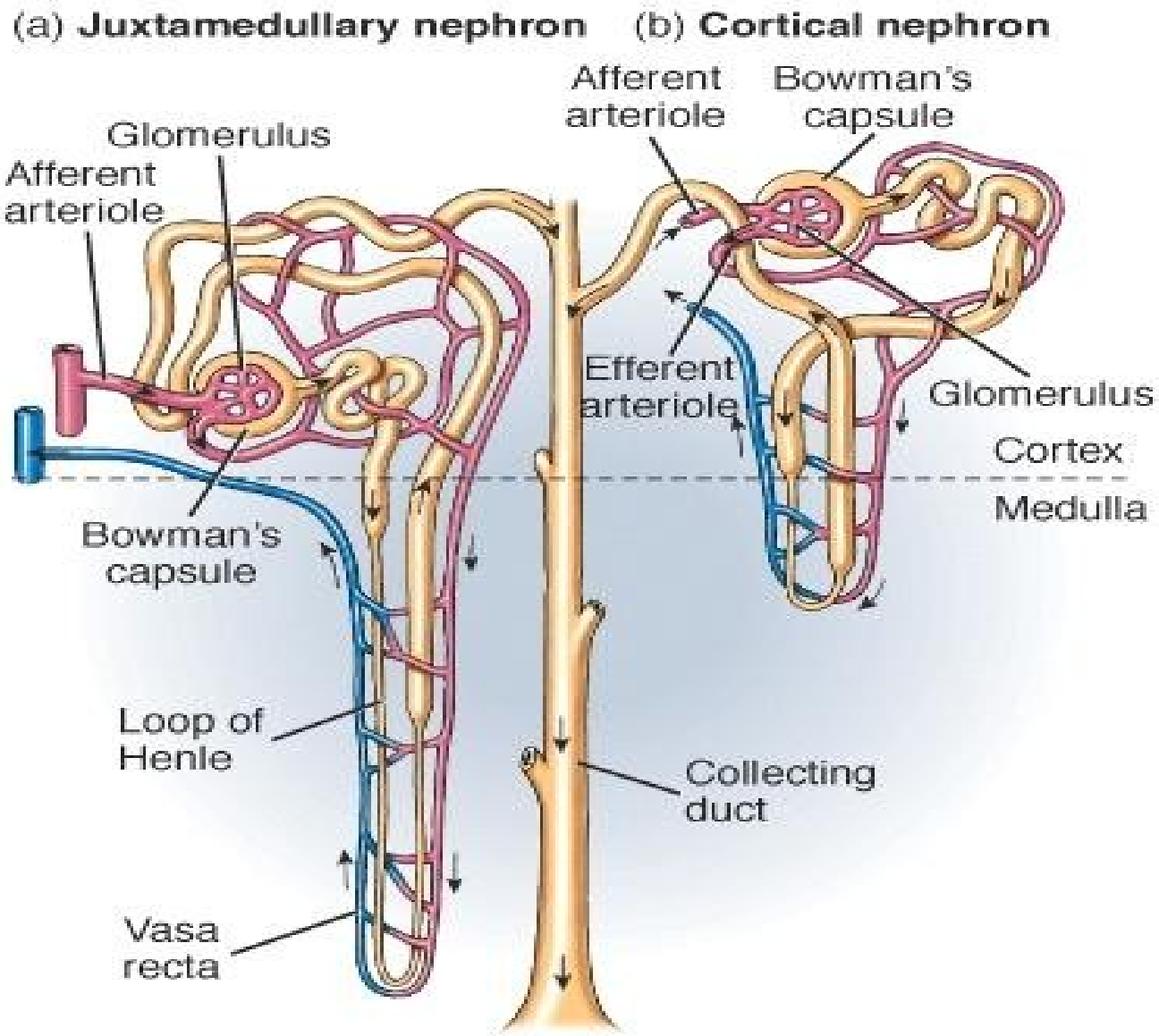
- Glycoprotein MW-34000 (165 AA residues)

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


(a) Juxtamedullary nephron
(b) Cortical nephron
Afferent arteriole
Bowman's capsule
Glomerulus
Afferent arteriole
Efferent arteriole
Glomerulus
Cortex
Medulla
Bowman's capsule
Loop of Henle
Collecting duct
Vasa recta

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 o diseases
- Catecholamines
- Prostaglandins

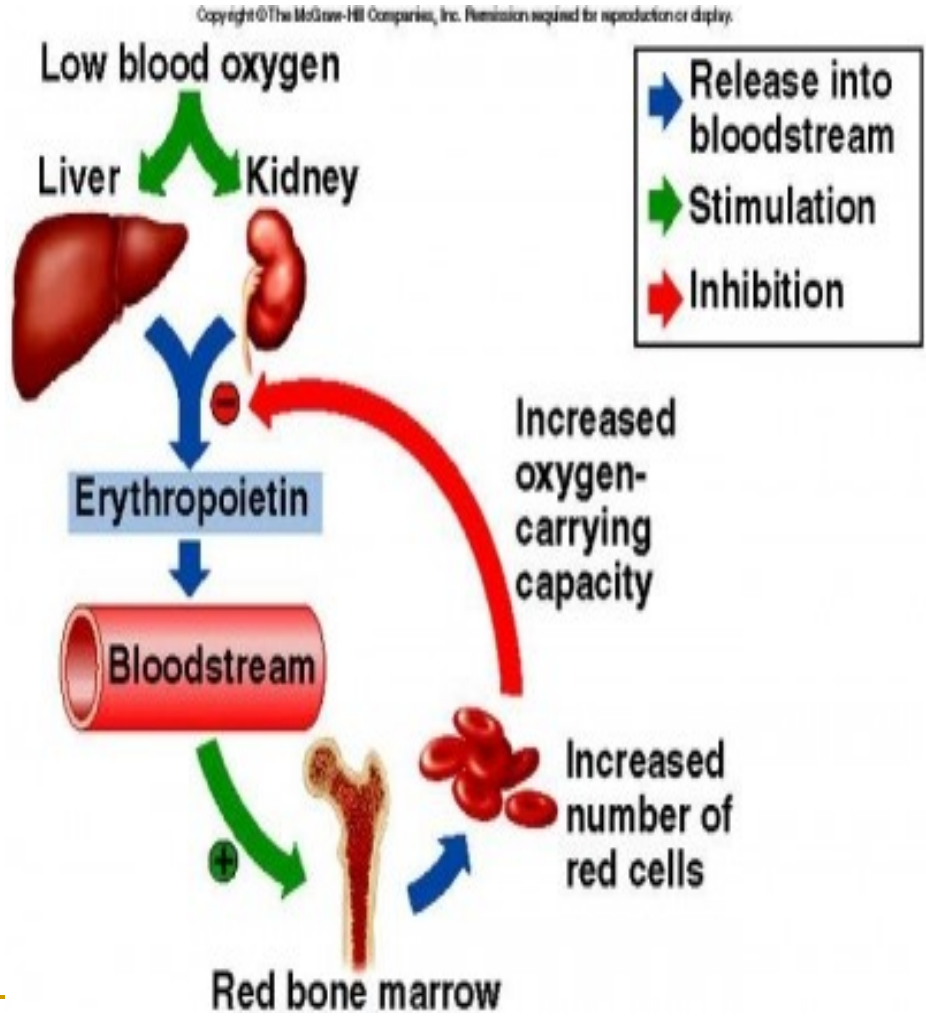
Androgens

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.

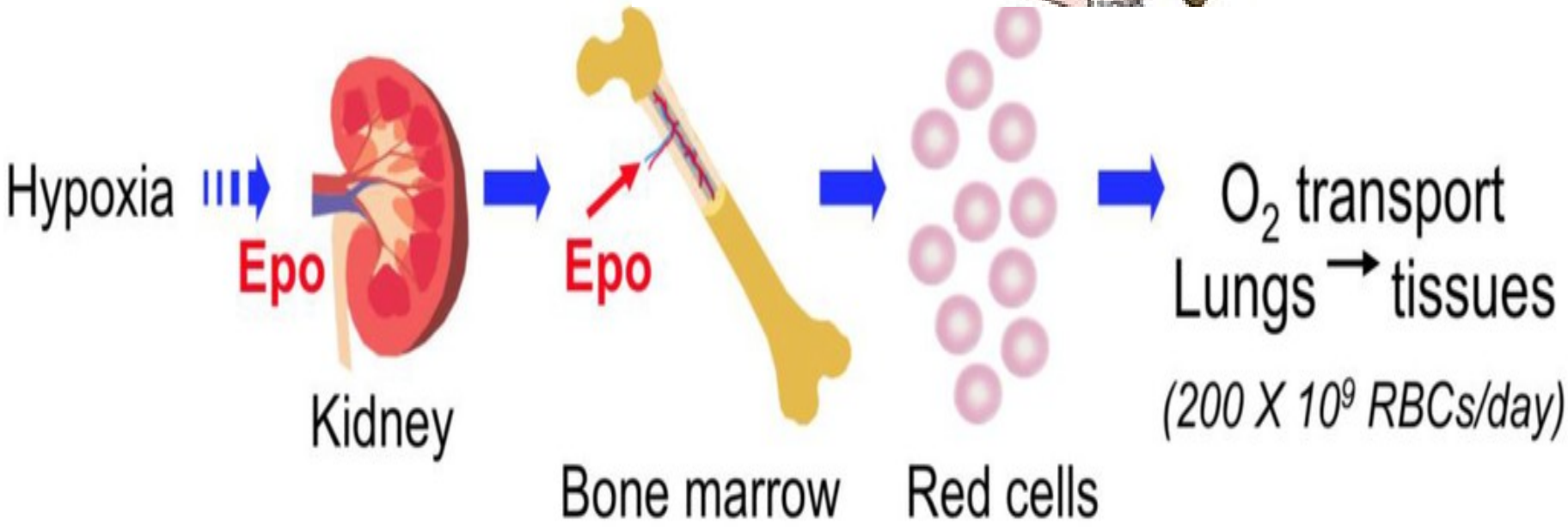


Renal failure

CHRONIC RENAL FAILURE (CRF)

- RENAL INSUFFICIENCY -

- Headaches
- ↓ Ability to Concentrate Urine
- Polyuria → Oliguria
- ↑ BUN & Serum Creatinine
- Edema
- GFR - progressively decreases from 90 to 30 ml/min
- Mild Anemia
- ↑ BP
- Weakness & Fatigue



Growth inducers/ Differentiation inducers

- Interleukin 1, 3, 6 (IL-3 is a growth inducer for all cell lines)
- CSF- E (colony stimulating factor – erythro)

Maturation factors

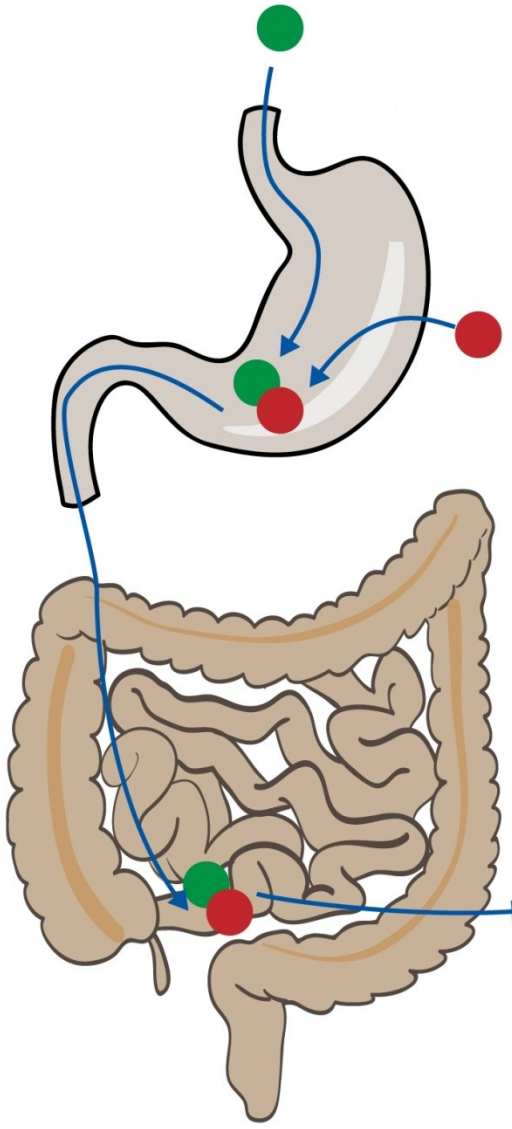
- Vitamin B 12
- Folic acid

Dietary factors - IRON

Vit B-12

- 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



stomach

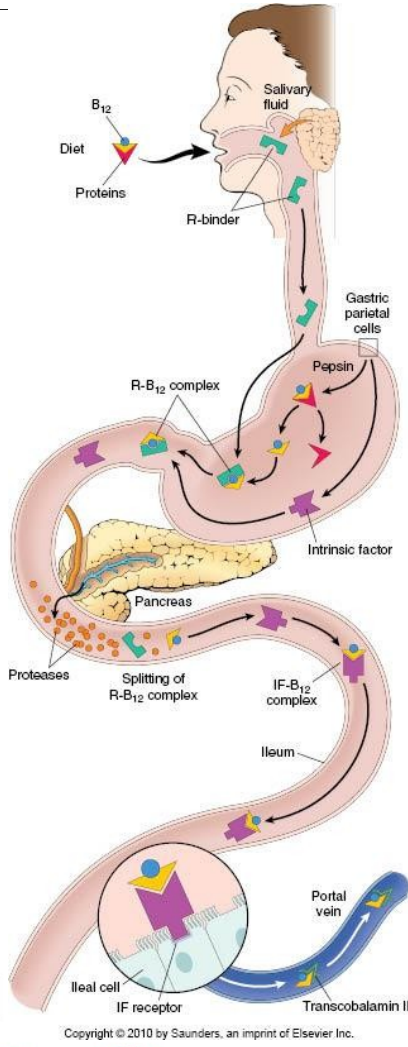
intrinsic factor

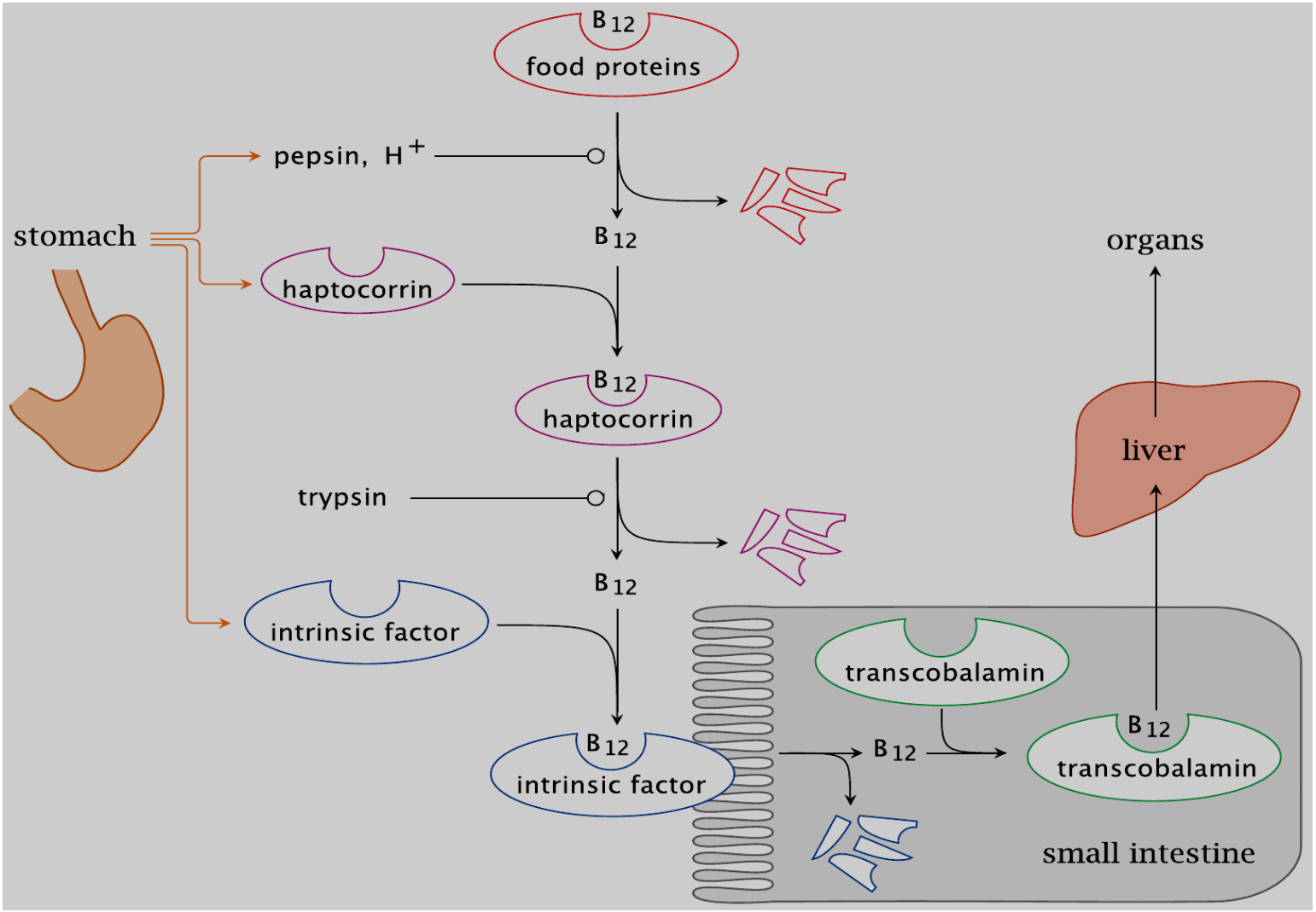
terminal ileum

transcobalamin II

blood transport

cell

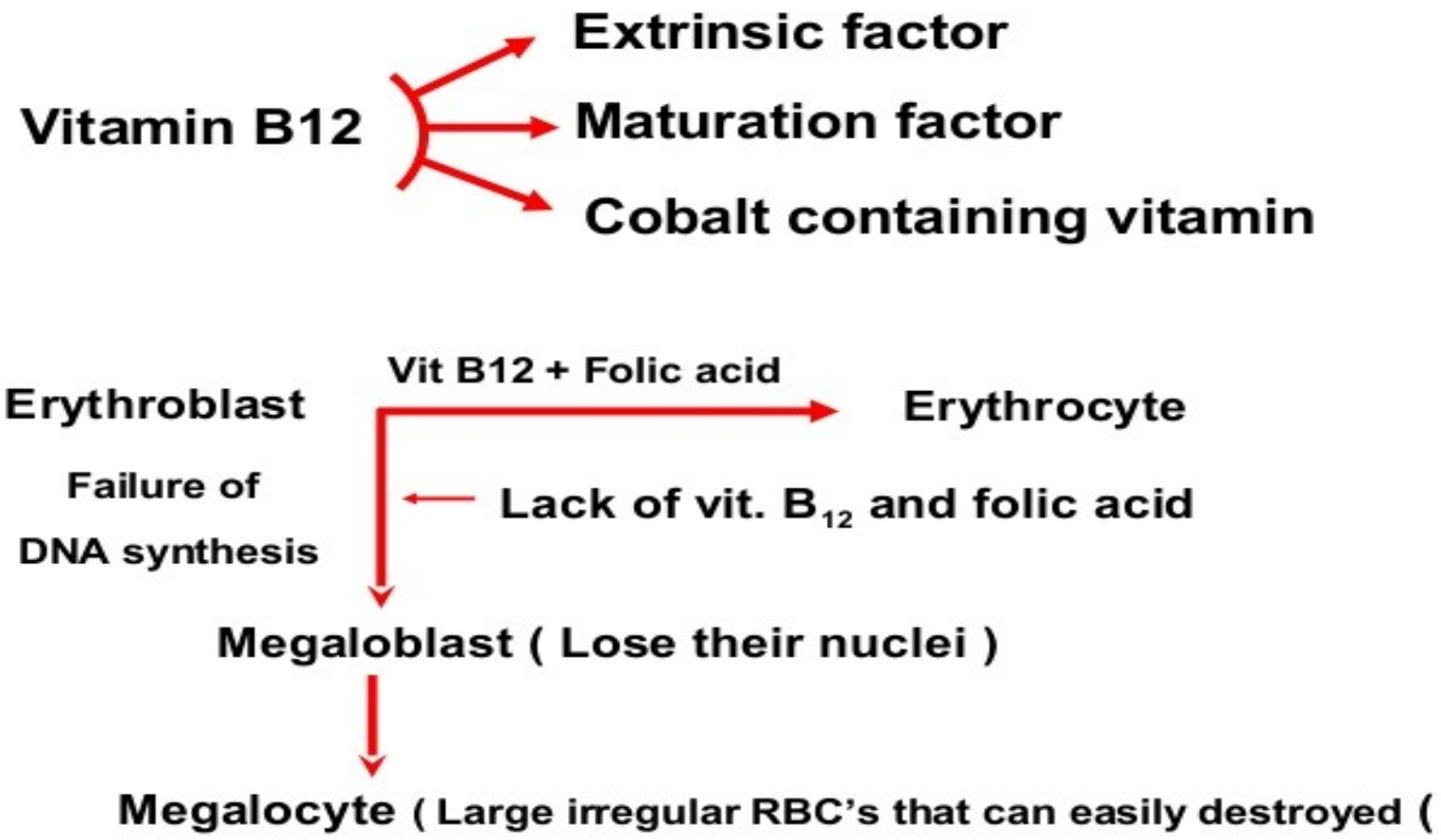




Absorption of Vitamin B12 and the role of Intrinsic factor

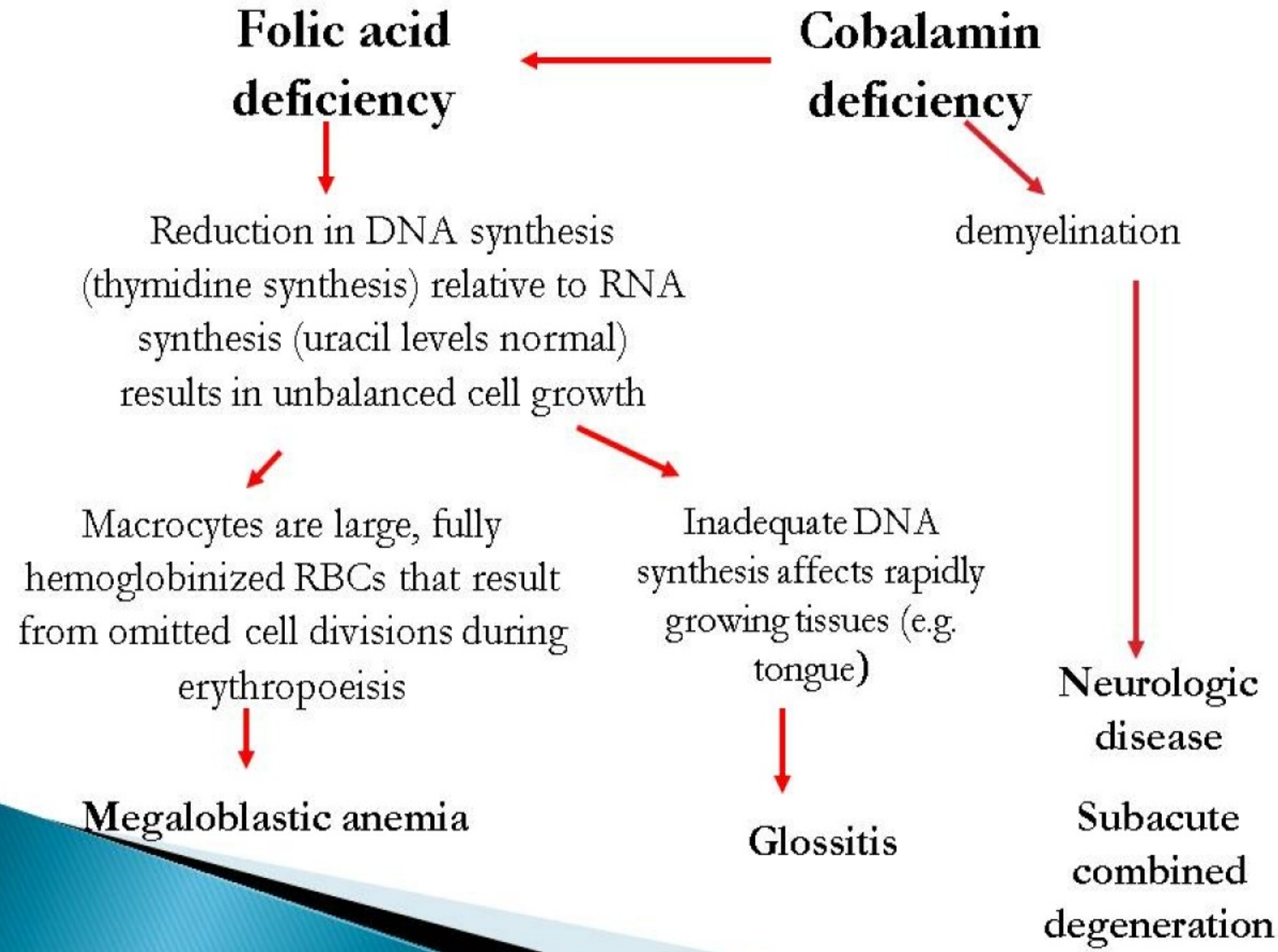
Folic acid

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

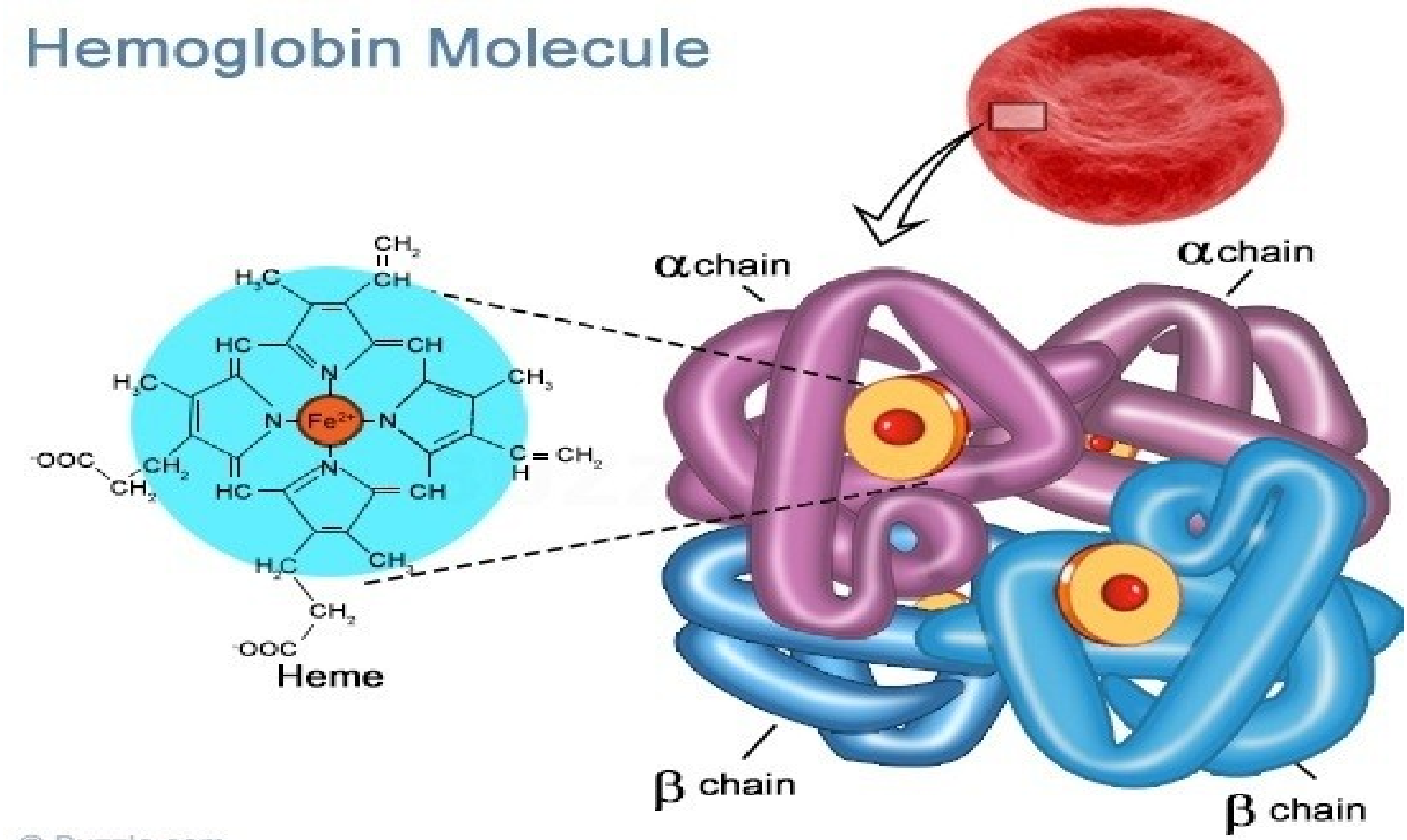


LIFE SPAN OF MEGALOBLAST IS 40 DAYS

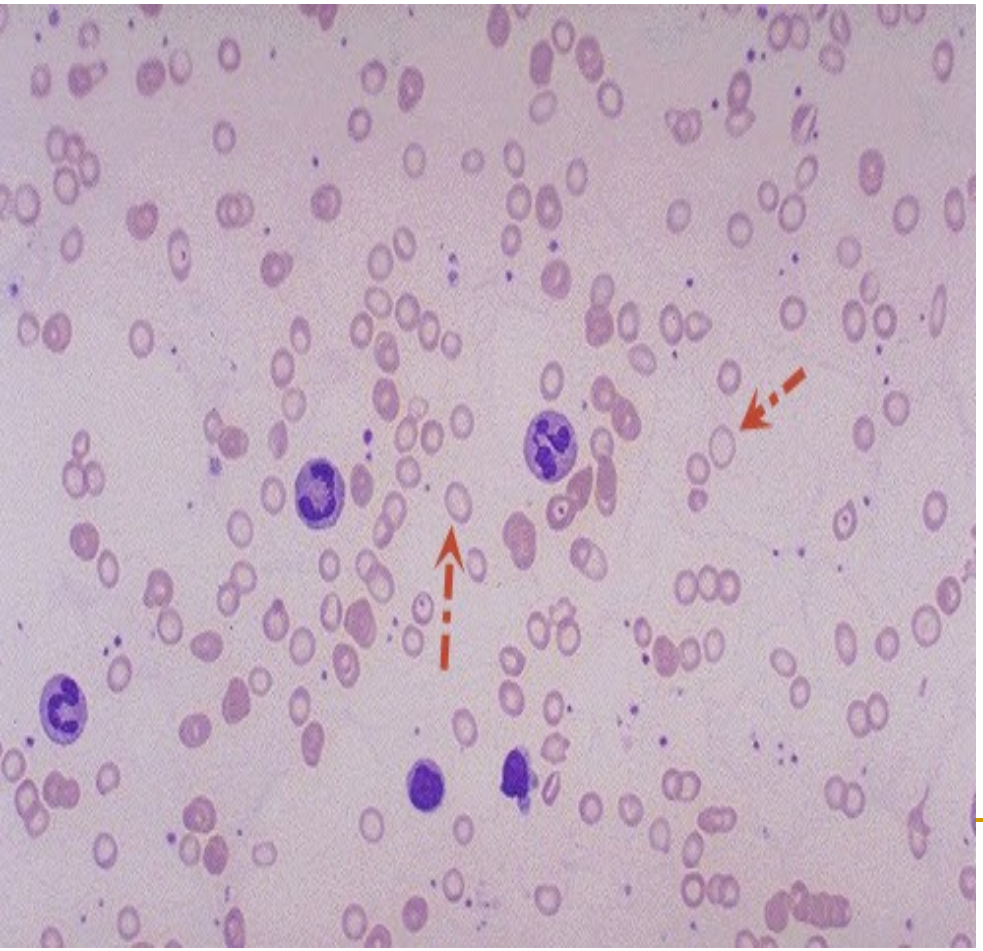
Relationship between cobalamin and folate deficiency

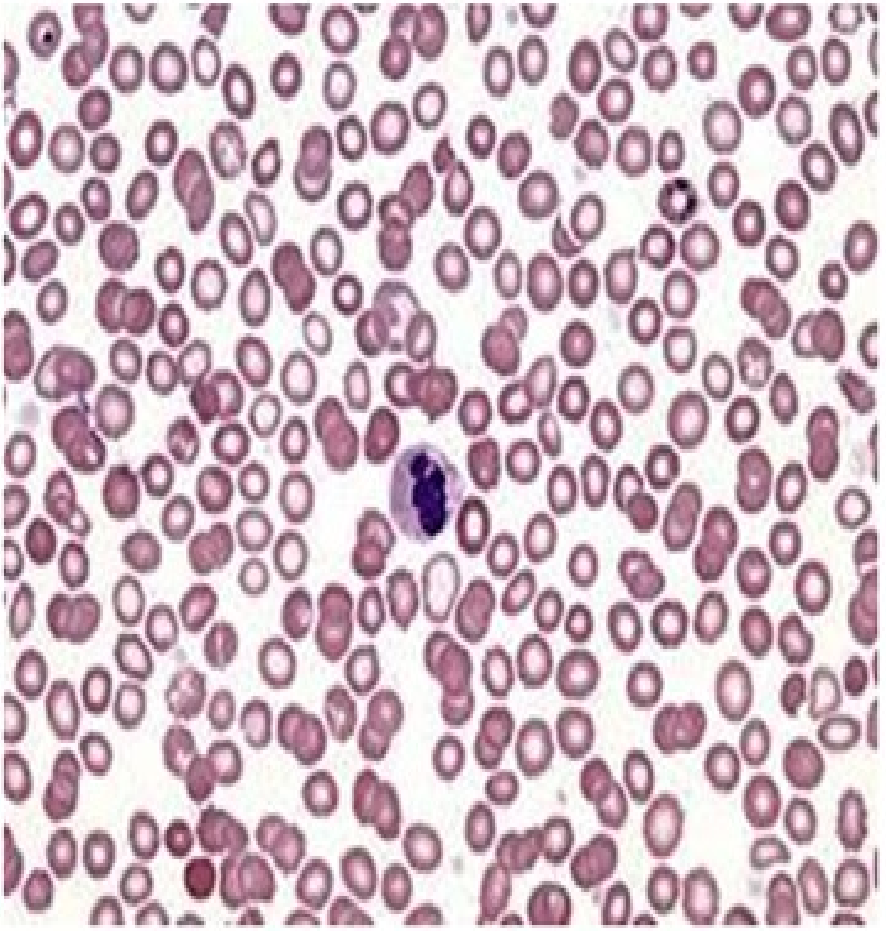


Iron


Hemoglobin Molecule
Heme
α chain
α chain
β chain
β chain
© Buzzle.com

IRON DEFICENCY ANEMIA





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