Erythropoiesis

Dr.Ahmed Alsabih

Objectives;

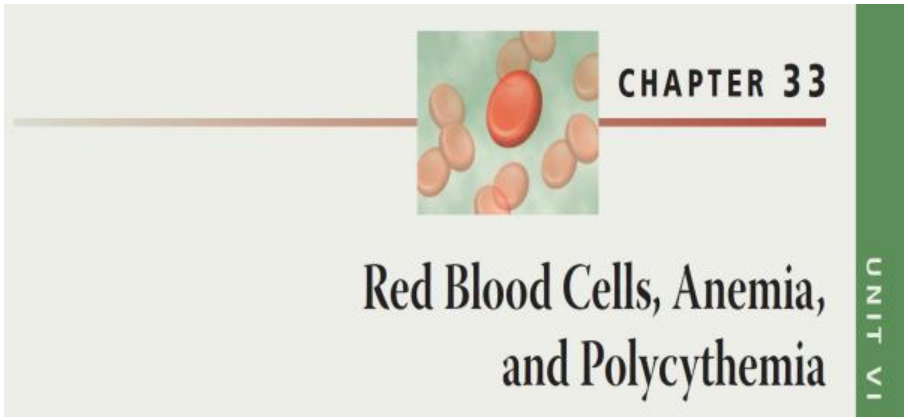
Intended learning outcomes (ILOs)

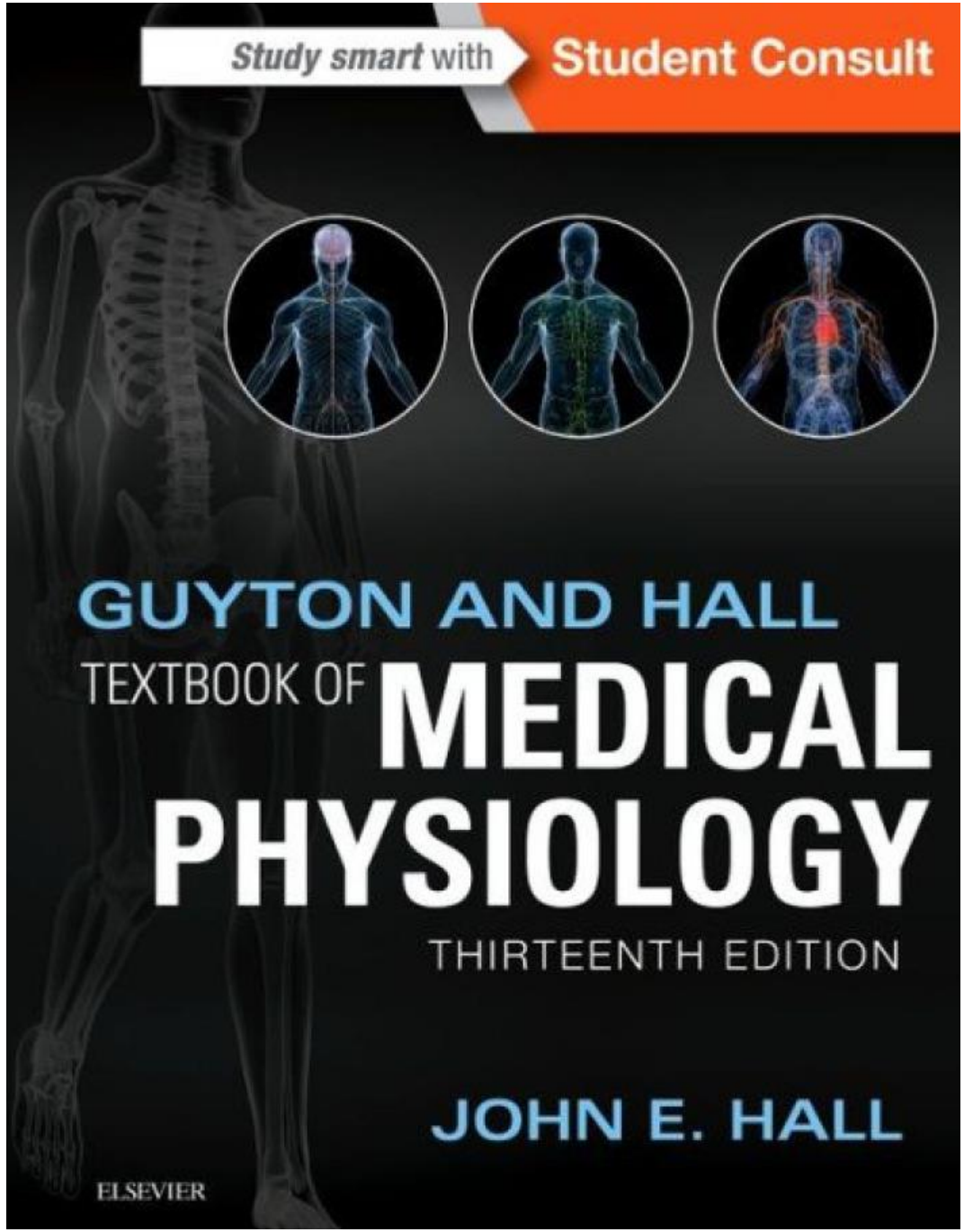
After reviewing the PowerPoint presentation and the associated learning resources, the student should be able to:

- Define erythropoiesis, leucopoiesis, and thrombopoiesis
- List the sites (areas) of the body that produce red blood cells
- Describe the steps involved in erythropoiesis from differentiation of stem cell to progenitor cell to final RBC
- Outline the features of RBC maturation
- Summarize the synthesis of Hemoglobin
- Recognize hemoglobin structure and its functions
- Describe the life cycle of normal RBCs

Learning Resources

- **Guyton and Hall, Textbook of Medical Physiology; 13th Edition; Unit VI-Chapter 33.**





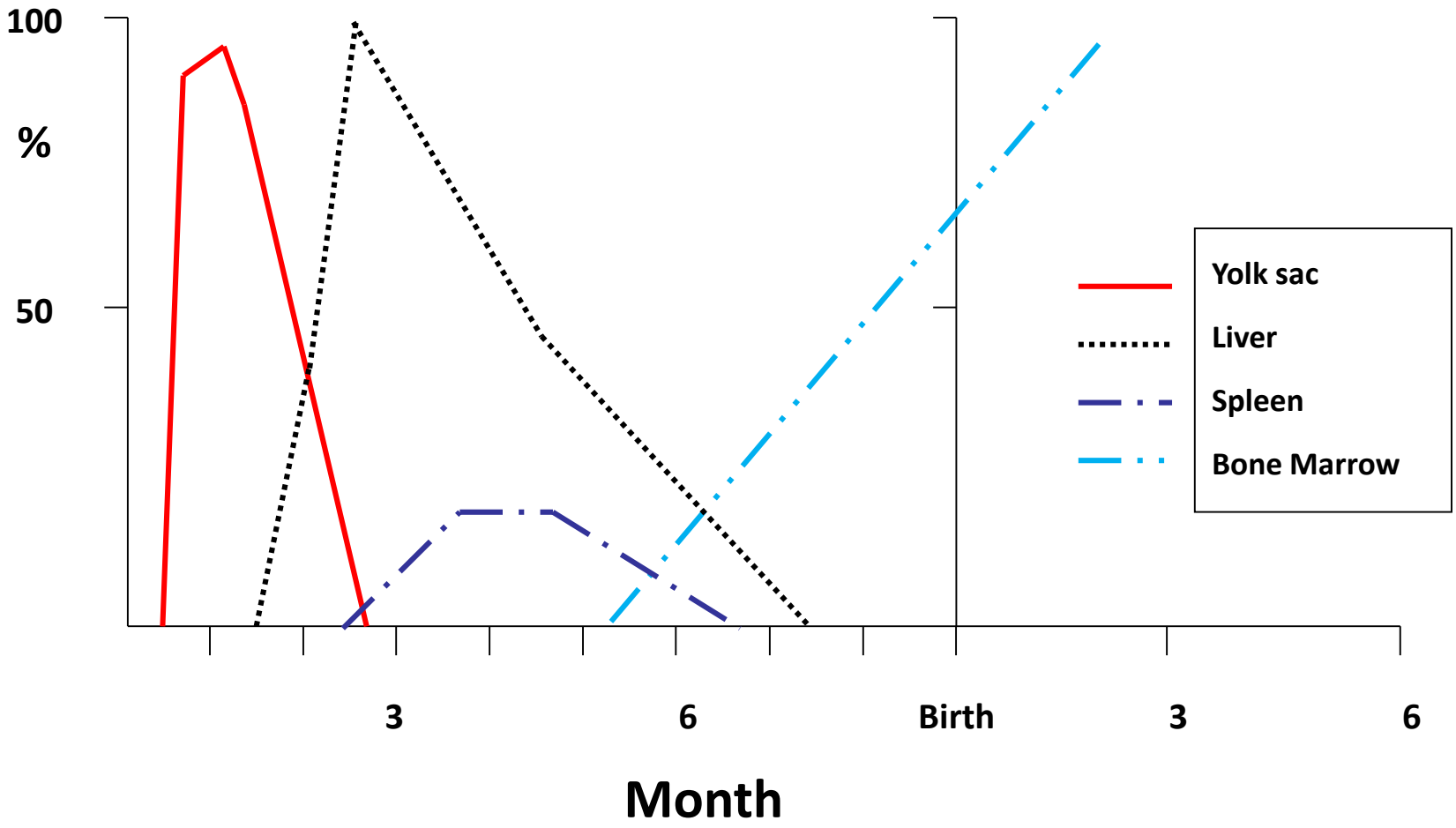
Formation of Blood Cells

- Formation of erythrocytes (RBC)
  - Erythropoiesis
- Formation of leucocytes (WBC)
  - Leucopoiesis
- Formation of thrombocytes (platelets)
  - Thrombopiesis
- Formation of blood
  - Haematopoiesis.

Locations of Erythropoiesis

- During the 1st 8 weeks of embryonic development, RBCs are formed in yolk sac
- During the 2nd to 5th months of embryonic development, RBCs are formed in liver (main supplier) and spleen
- From the 5th month on, RBCs formed in bone marrow
- After birth and in adults, RBCs are formed in red bone marrow
  - Portions of: vertebrae, ribs, scapulae, skull, pelvis, proximal heads of femur and humerus
  - Yellow marrow of medullary cavities can be converted back into red marrow, if needed

Locations of Erythropoiesis



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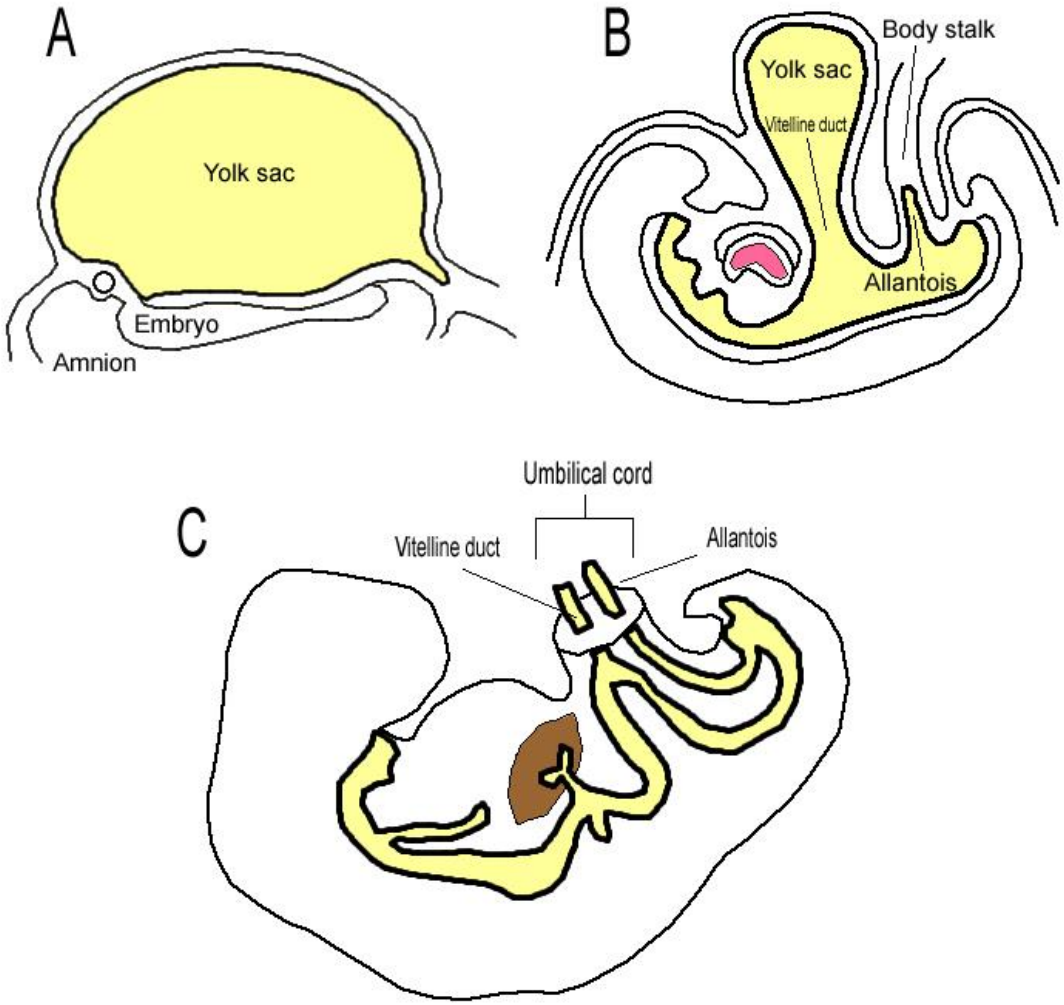
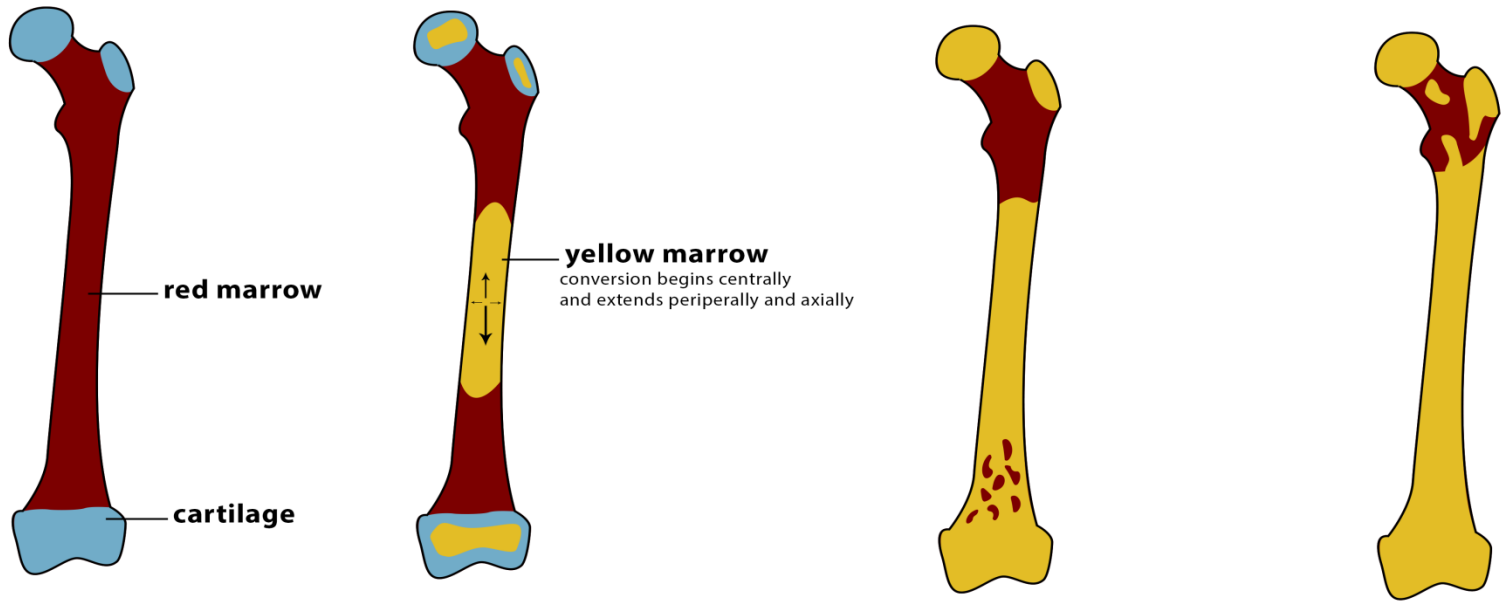
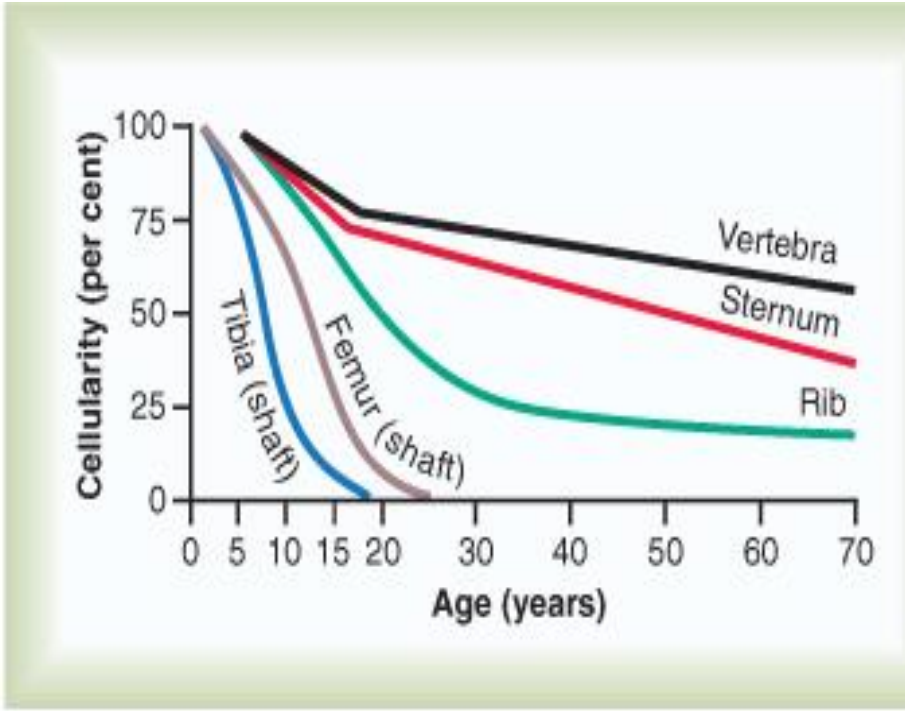


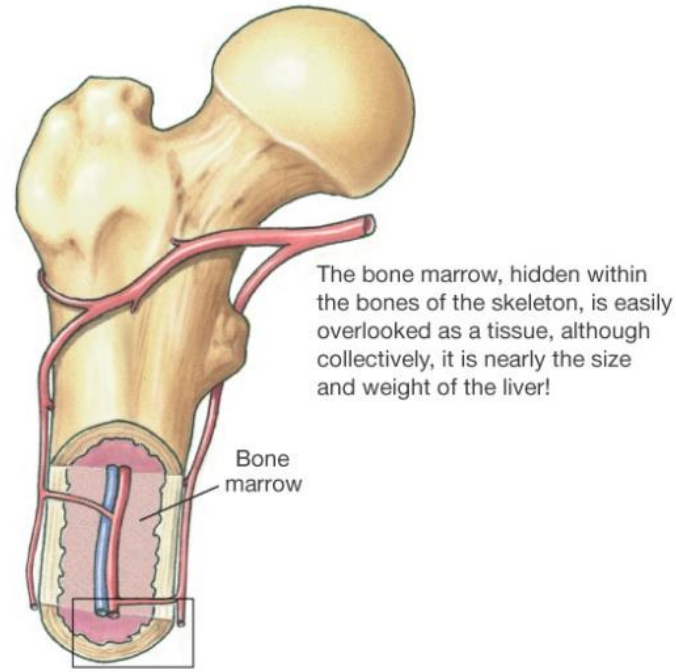
Locations of Erythropoiesis

Normal bone marrow conversion



Locations of Erythropoiesis





- Bone marrow of all bones produces red blood cells until a person is 5 years old.
- Bone marrow of long bones, except for the proximal portions of the humeri and tibiae, becomes quite fatty and produces no more red blood cells after about age 20 years.
- Beyond this age, most red cells continue to be produced in the marrow of the vertebrae, sternum and ribs.
- Yellow marrow of medullary cavities can be converted back into red marrow, if needed

Stages of Erythropoiesis

- **The blood cells begin their lives in the bone marrow from a single type of cell called the *pluripotential (pluripotent) hematopoietic stem cell (PHSC); hemocytoblast*, from which all the cells of the circulating blood are eventually derived.**

- **These PHSC are least differentiated and can develop into any blood cell.**

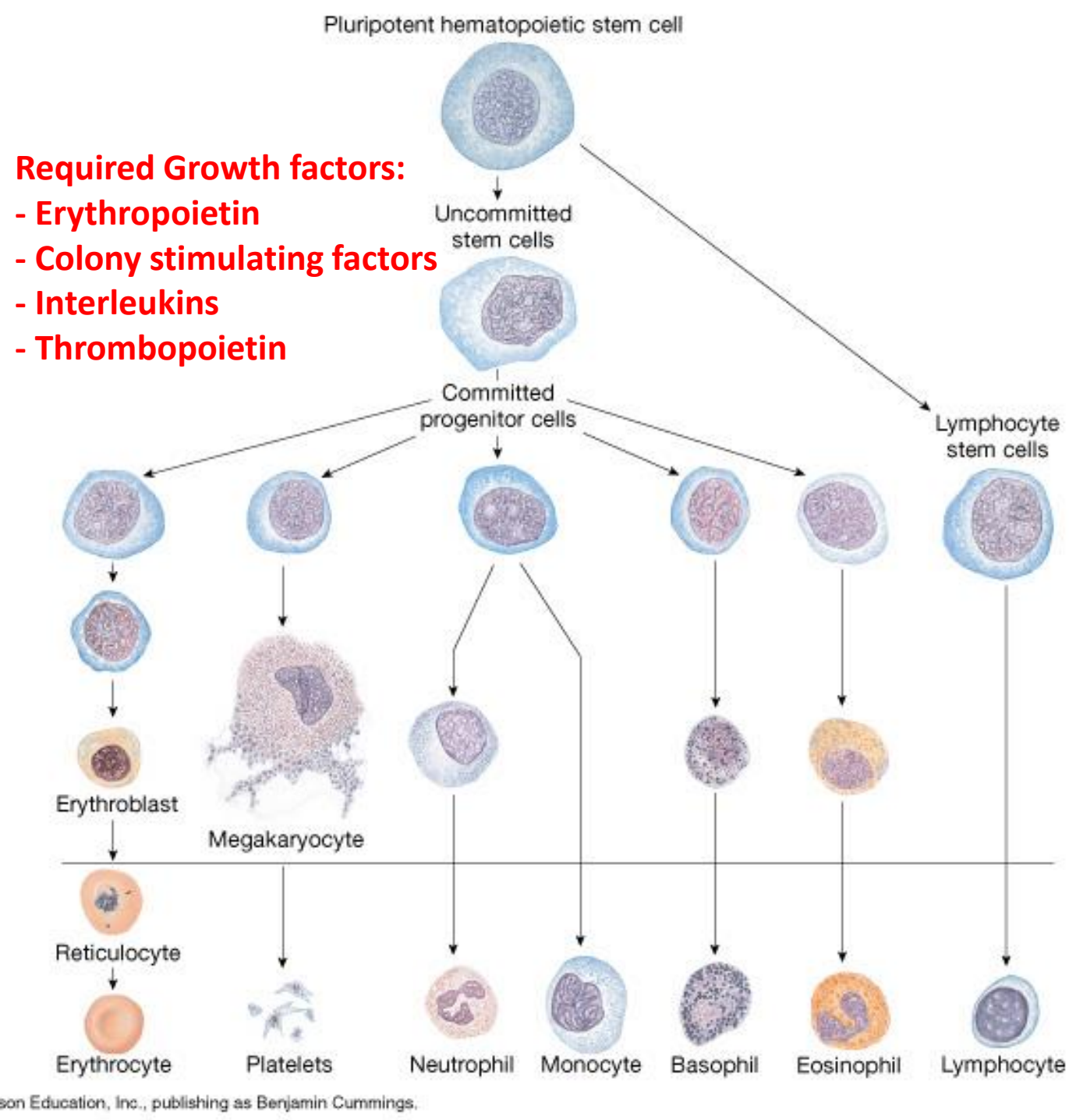
- **They give rise to uncommitted stem cells that in turn give rise to committed stem cells; committed progenitor cells; progenitor cells (colony-forming units).**

- **A committed stem cell that produces erythrocytes is called a *colony-forming unit-erythrocyte (CFU-E).***

- **CFUs form differentiation lines leading to RBCs, megakaryocytes and most WBCs.**

- **Thus, the CFUs are specialized to form specific cell types.**

- **For example: CFU-E develops eventually into only red blood cells**



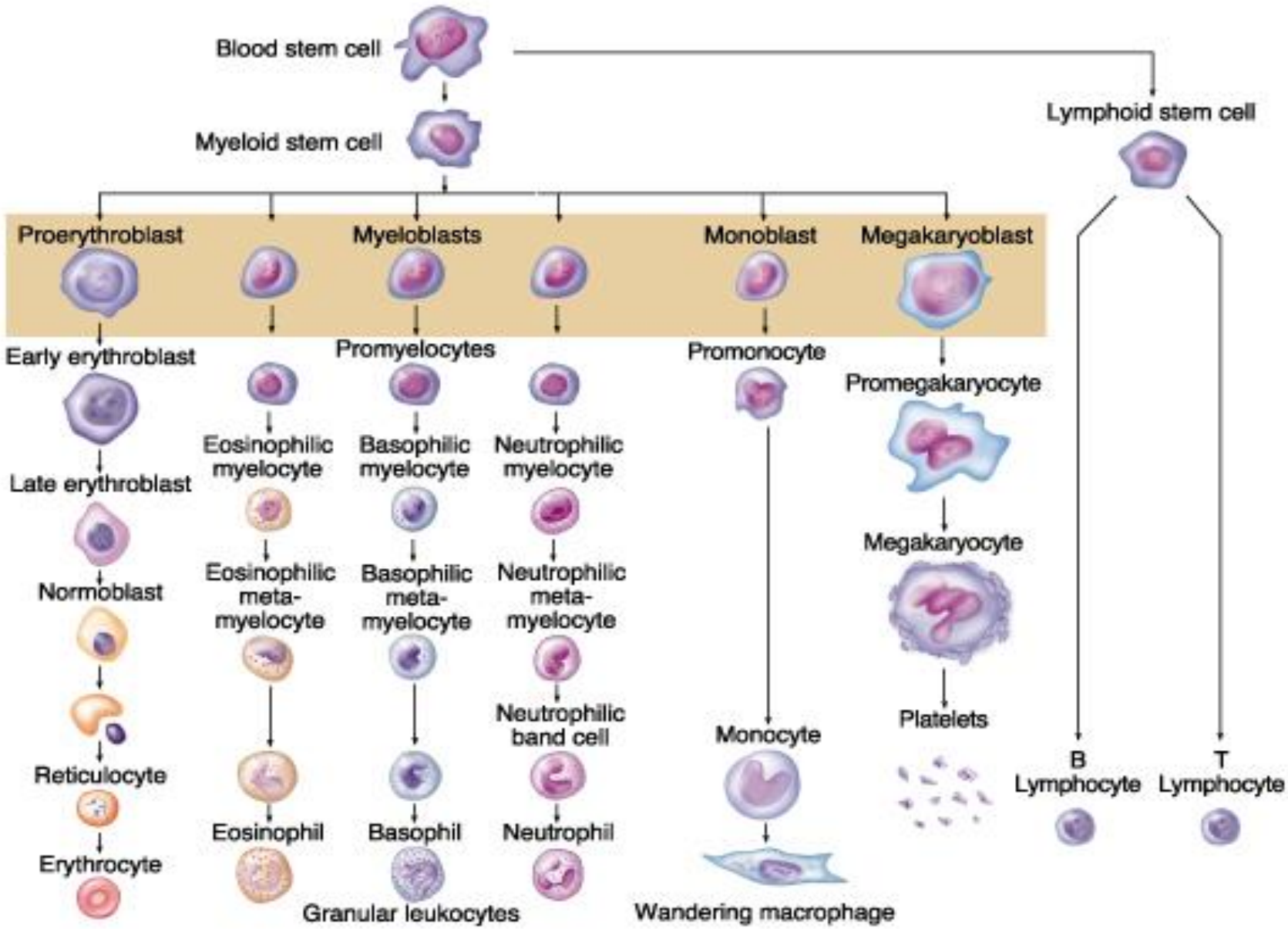
Required Growth factors:
- **Erythropoietin**
- **Colony stimulating factors**
- **Interleukins**
- **Thrombopoietin**

- **Growth and reproduction of the different stem cells are controlled by multiple proteins called growth inducers. One of these, interleukin-3, promotes growth and reproduction of virtually all the different types of committed stem cells, whereas the others induce growth of only specific types of cells.**

- **Differentiation of the cells is the function of another set of proteins called differentiation inducers. Each of these causes one type of committed stem cell to differentiate one or more steps toward a final adult blood cell.**

- **Formation of the growth inducers and differentiation inducers is itself controlled by factors outside the bone marrow. For instance, in the case of erythrocytes (red blood cells), exposure of the blood to low oxygen for a long time results in growth induction, differentiation, and production of greatly increased numbers of erythrocytes.**

Hematopoiesis



Stages of Differentiation of Red Blood Cells

- ❑ RBCs are formed from PHSC (hemocytoblasts).
- ❑ These give rise to uncommitted stem cells, which in turn give rise to committed stem (progenitor) cells (CFU-E), which give rise to proerythroblasts.
- ❑ The proerythroblasts are considered as differentiated RBC precursors. They are the first cells that can be identified as belonging to the red blood cell series.
- ❑ The proerythroblasts give rise to *basophil erythroblasts*

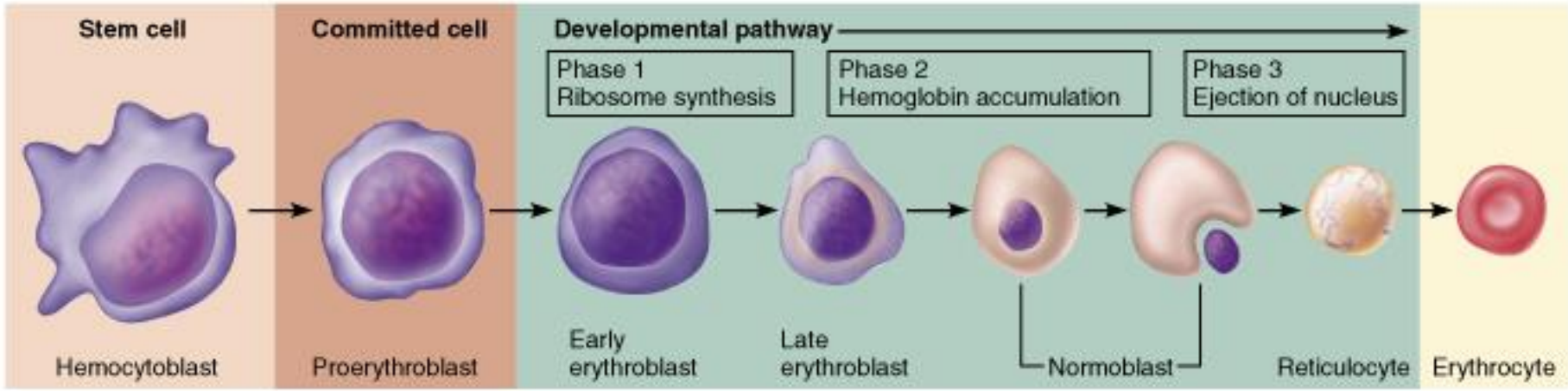
→ erythroblasts: synthesize Hb

→ normoblasts: lose nucleus , some mitochondria

→ Reticulocytes contain ribosomes and mitochondria (but no nucleus)

reticulocyte count: normally 0.8-2.0% of RBC population

In 1-2 days, reticulocytes eject the remaining organelles to become a mature RBC

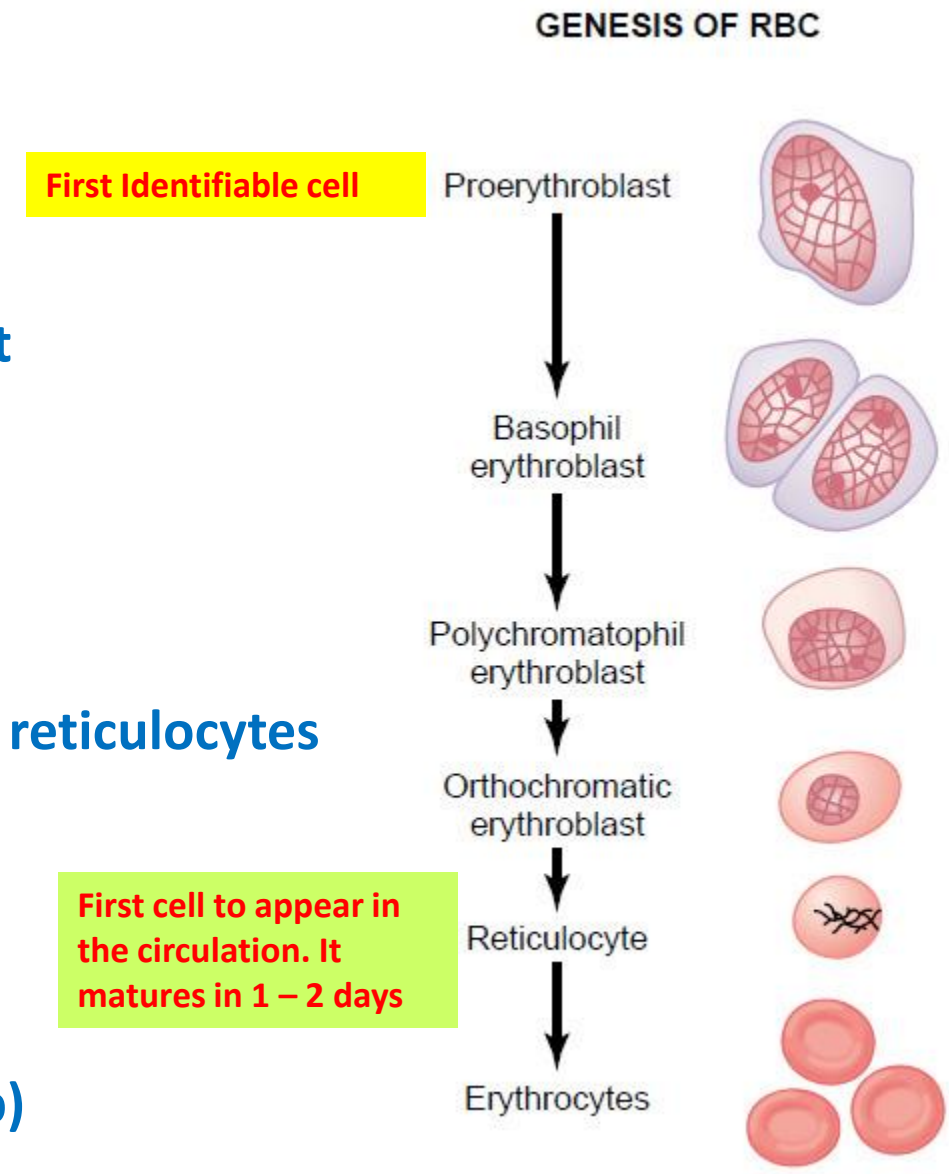


Stages of Differentiation of Red Blood Cells

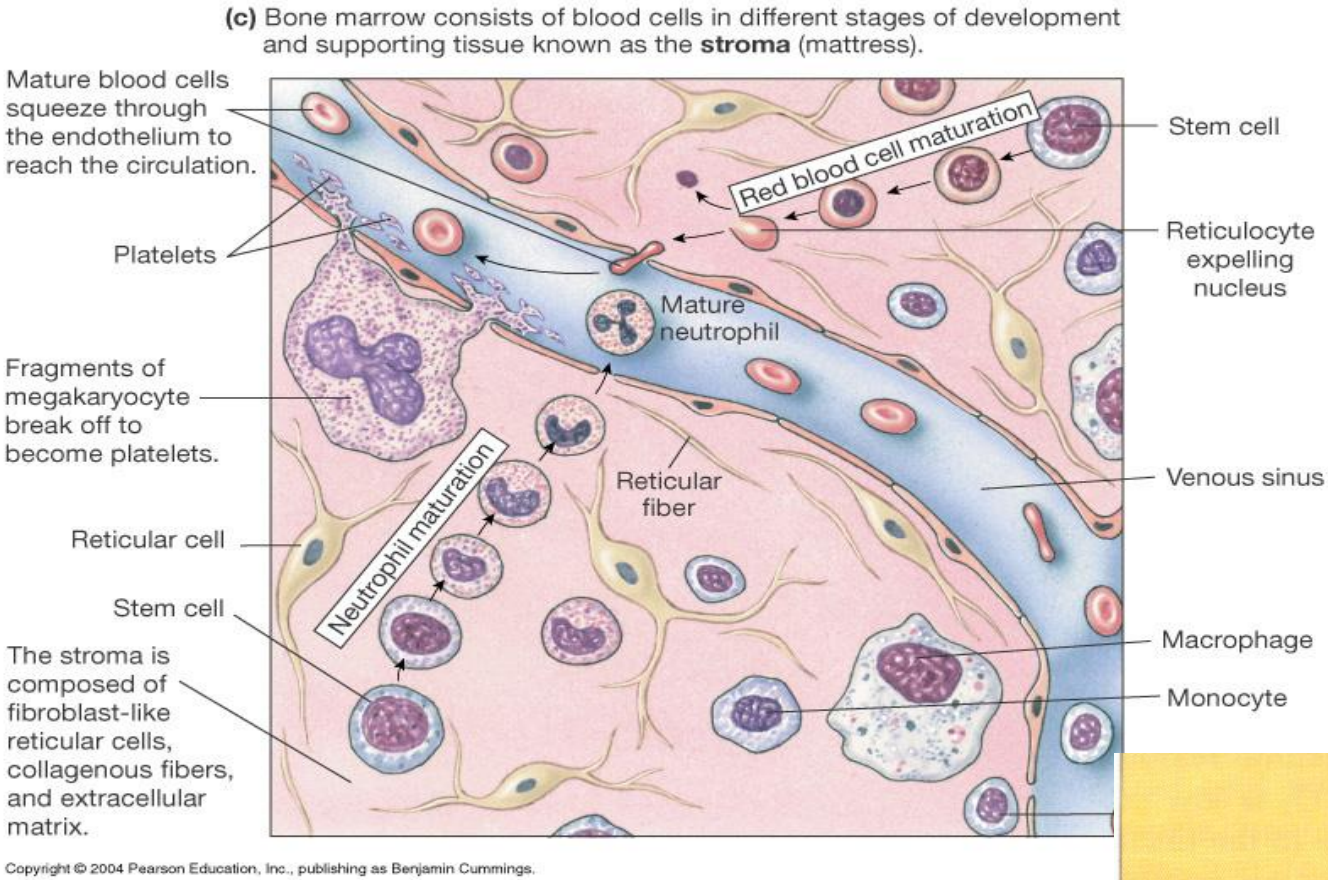
- Stages of RBC development:
  - Committed stem cell
    - Proerthroblast
    - Basophil erythroblast
    - Polychromatophil erythroblast
    - Orthochromatic erythroblast
    - Reticulocytes
    - Mature erythrocytes

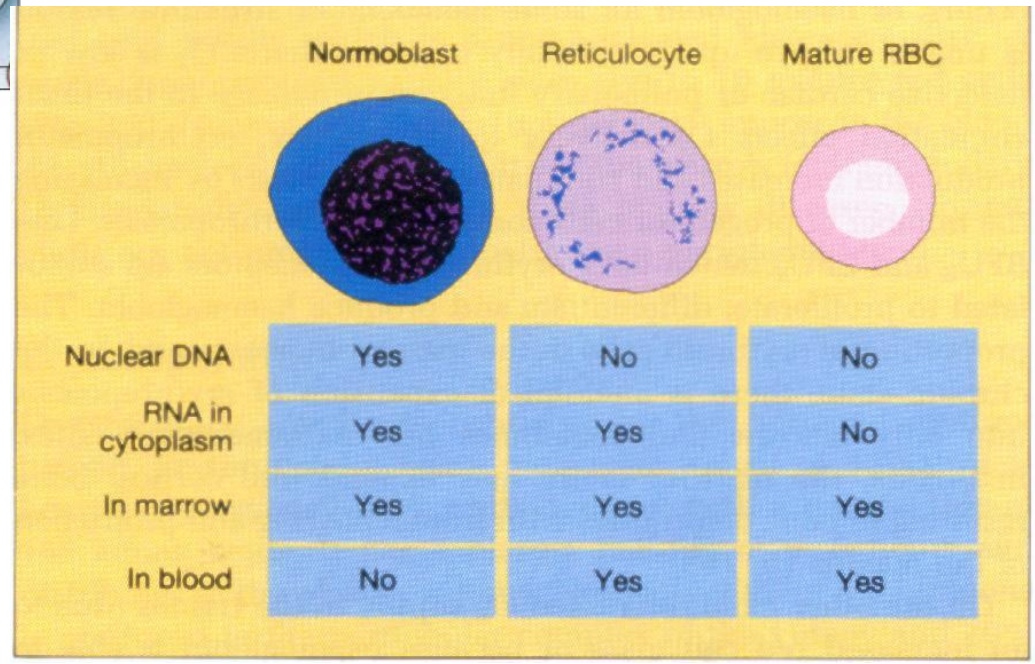
- In cases of rapid RBC production → ↑ reticulocytes in the circulation.

- RBC maturation is characterize by:
  - Decrease in cell size.
  - Appearance of hemoglobin (Hb)
  - Disappearance of nucleus.



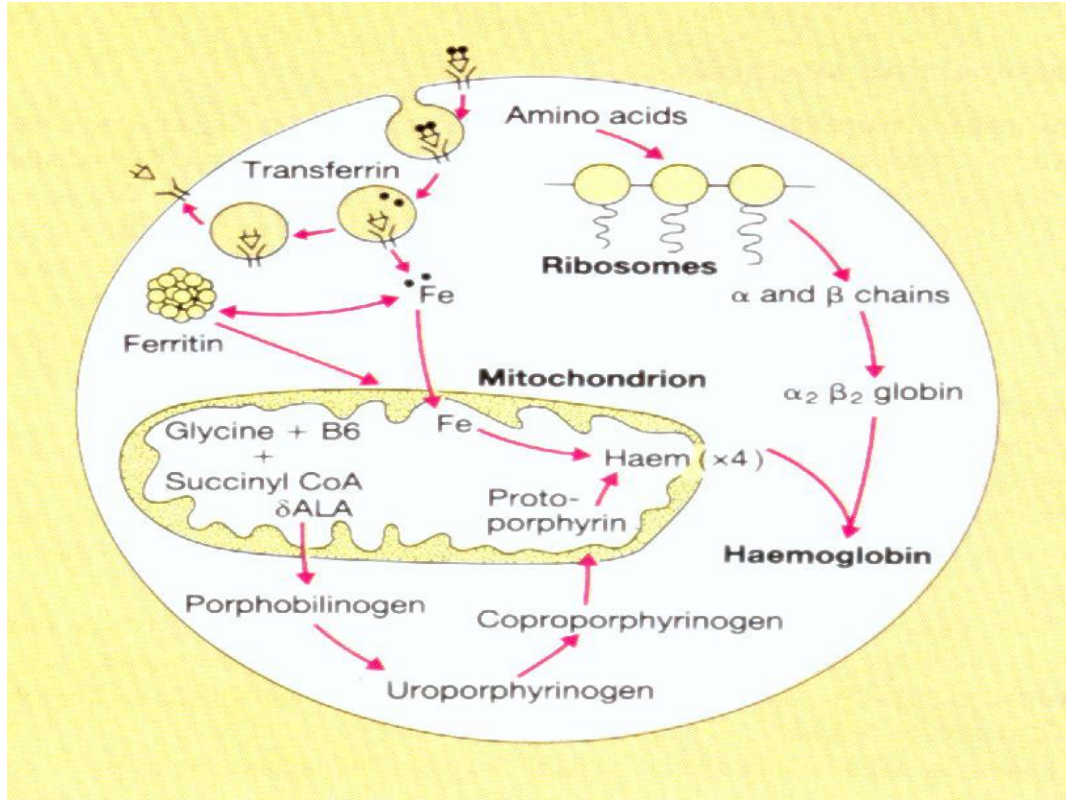
Stages of Erythropoiesis





Hemoglobin (Hb) Synthesis

- Hemoglobin synthesis occurs in the mitochondria of the developing RBC in bone marrow
- Transferrin attaches to surface receptor
- Iron is released and transported to mitochondria where it combines with protoporphyrin to form heme
- Heme combines with α and β protein chains formed on the ribosomes to make hemoglobin
- Functions of Hb:
  - Carriage of O_2 and CO_2
  - Buffer
  - Binds CO_2 in Smokers



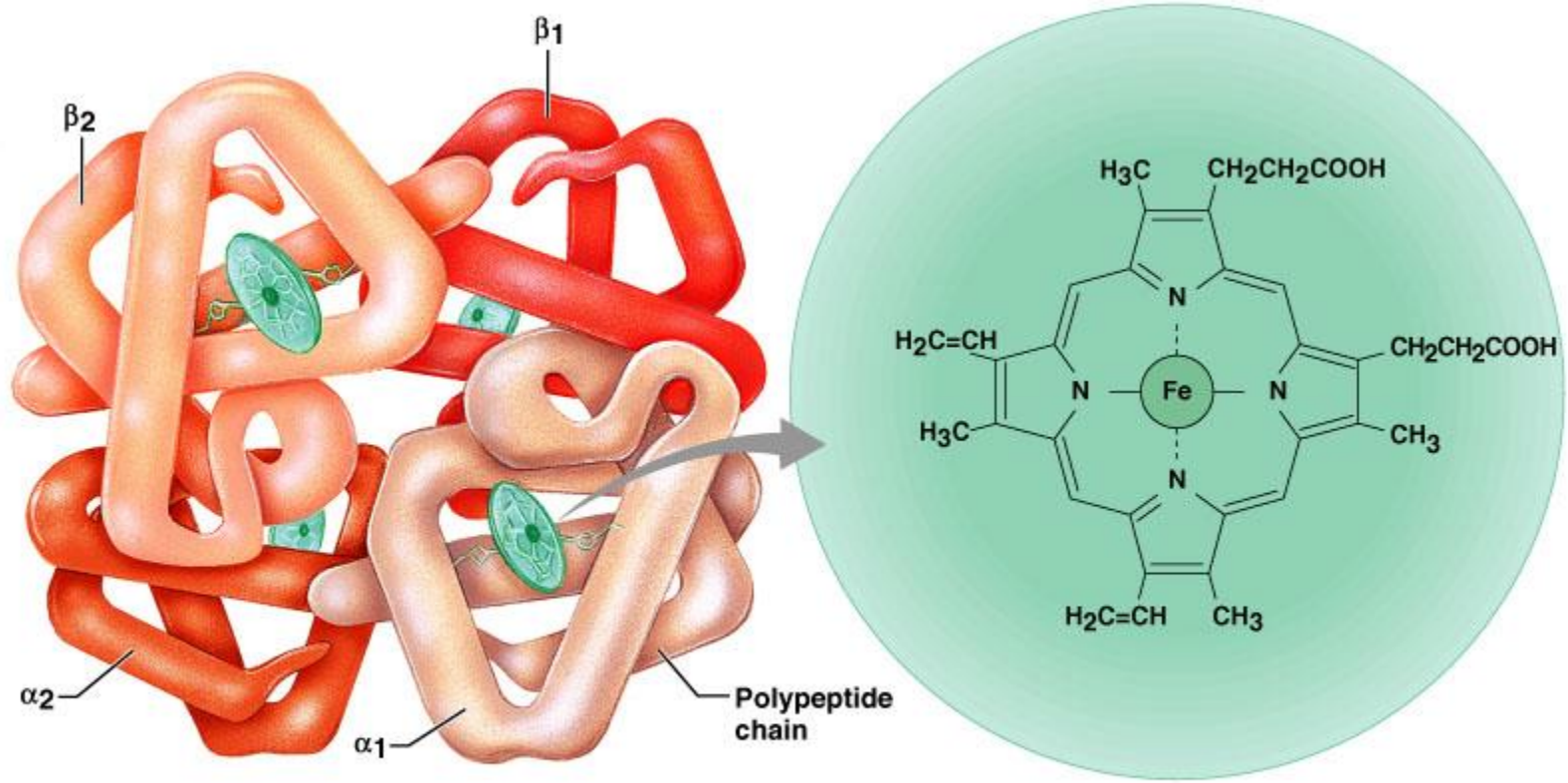
Hemoglobin (Hb)

Adult human Hb:

tetrameric protein $\alpha_2\beta_2$

alpha 141 aa residues

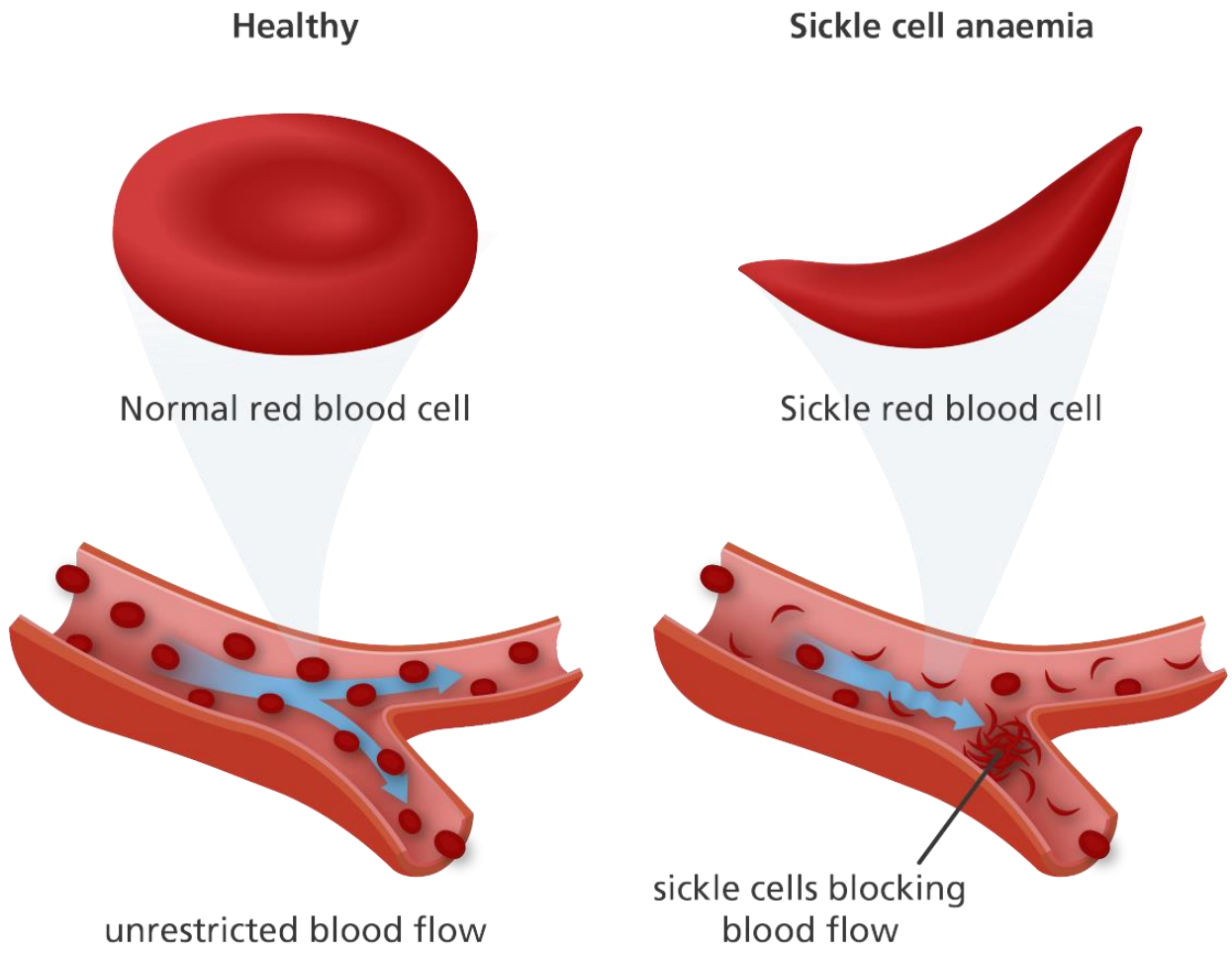
beta 146 aa residues



(a) Hemoglobin **(b) Iron-containing heme group**

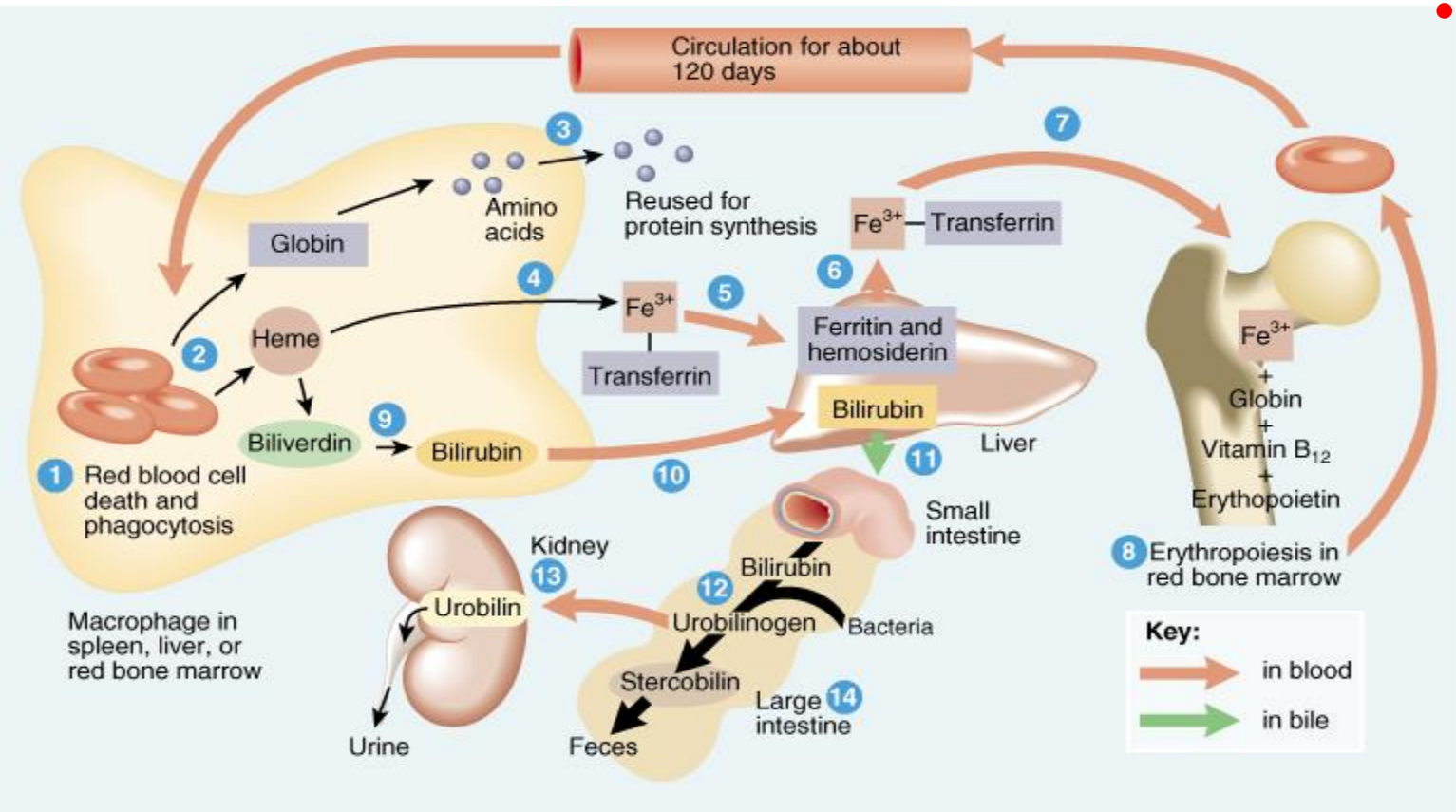
Types of Hemoglobin (Hb)

- **HbA (Adult Hemoglobin): This accounts for about 98% of adult Hb. Its polypeptide chains are ($\alpha_2\beta_2$)**
- **HbA2 (Minor Adult Form). This accounts for about 2.5% of adult Hb. Its polypeptide chains are ($\alpha_2\delta_2$)**
- **HbF (Fetal Hemoglobin): This a accounts for 80-90% of fetal Hb at birth. Its polypeptide chains ($\alpha_2\gamma_2$)**
- **Abnormality in the polypeptide chain α & β results in abnormal Hb (hemoglobinopathies) e.g thalassemias, sickle cell anemia**



RBC Life Cycle

- RBCs live only 120 days (cells need to be continually replaced)
- Cells wear out from bending to fit through capillaries
- Repair is not possible due to lack of organelles
- Worn out cells are removed by macrophages in spleen and liver
- Breakdown products are recycled



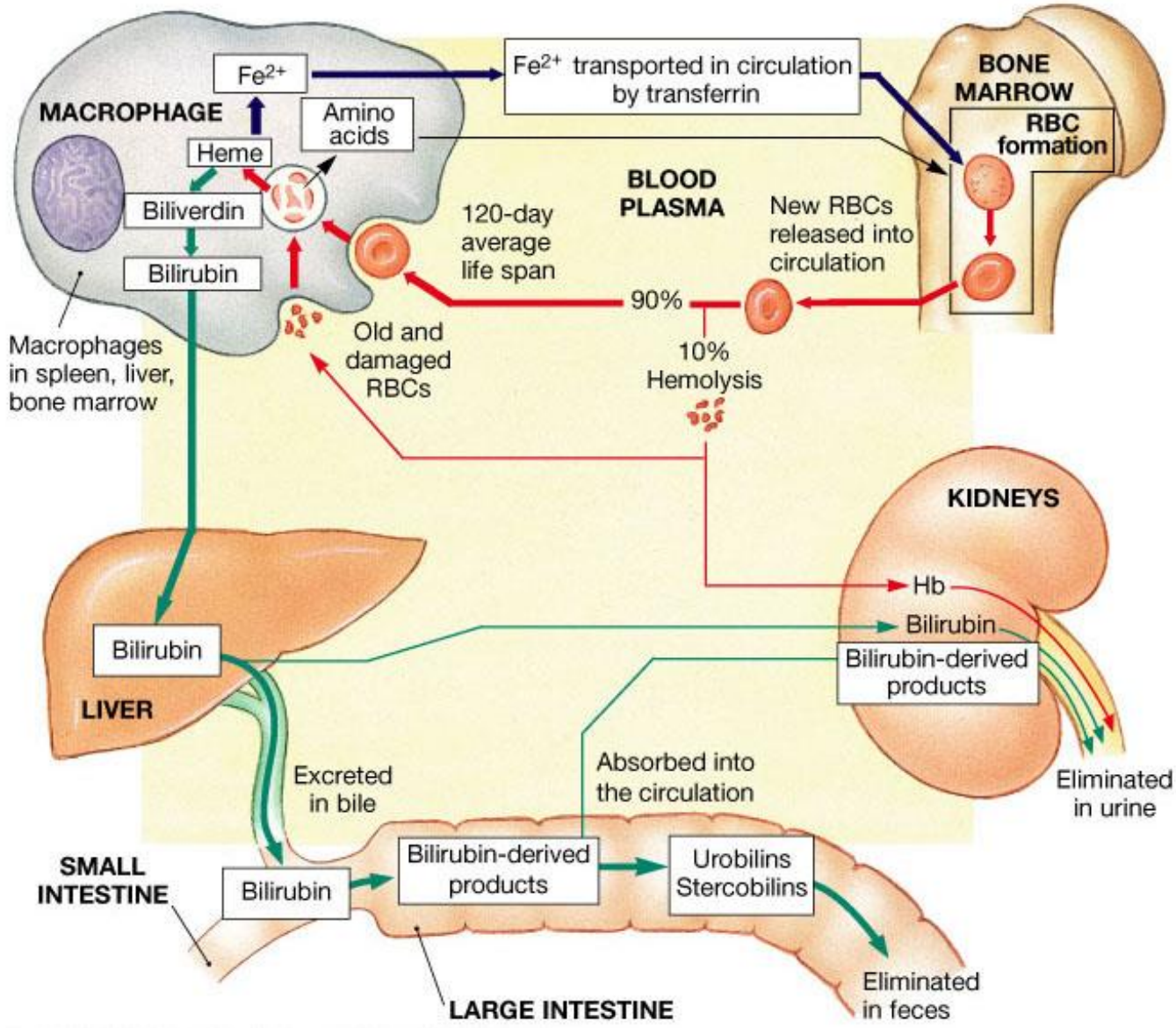
- In macrophages of liver or spleen:
  - Globin portion is broken down into amino acids and recycled
  - Heme portion is split into iron (Fe^{+3}) and biliverdin (green pigment)

Fate of Components of Heme

- Iron(Fe^{+3})
  - Transported in blood attached to transferrin protein
  - Stored in liver
    * attached to ferritin or hemosiderin protein
  - In bone marrow, iron is used for hemoglobin synthesis

- Biliverdin (green) is converted to bilirubin (yellow)
  - bilirubin is secreted by liver into bile
    * converted to urobilinogen then stercobilin (brown pigment in feces) by bacteria of large intestine
    * if urobilinogen is reabsorbed from intestines into blood is converted to a yellow pigment, urobilin and excreted in urine

Fate of Components of Heme



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