



Hematopoiesis

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*Prepared and adapted for teaching by Prof. Dr. Heba Kalbouneh.
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Chromatin

Formed of DNA.

- 2 Forms:

- Euchromatin: extended active chromatin (pale).
- Heterochromatin: condensed inactive chromatin (dark)

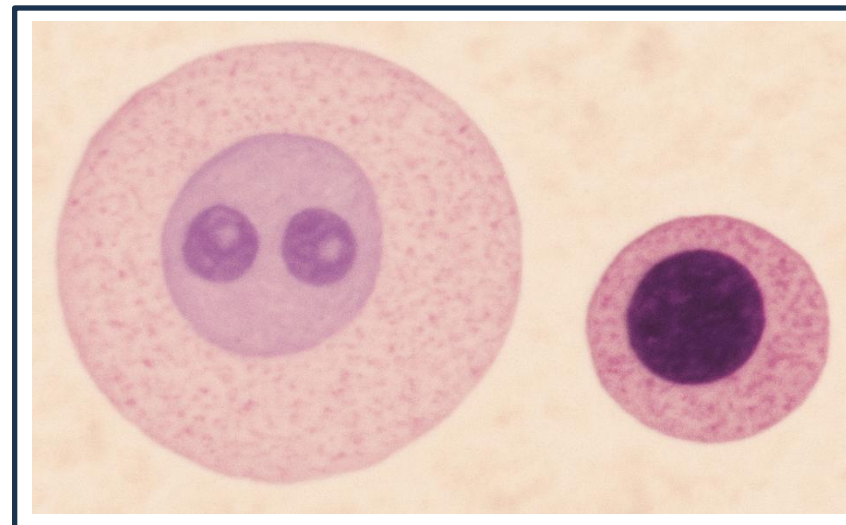
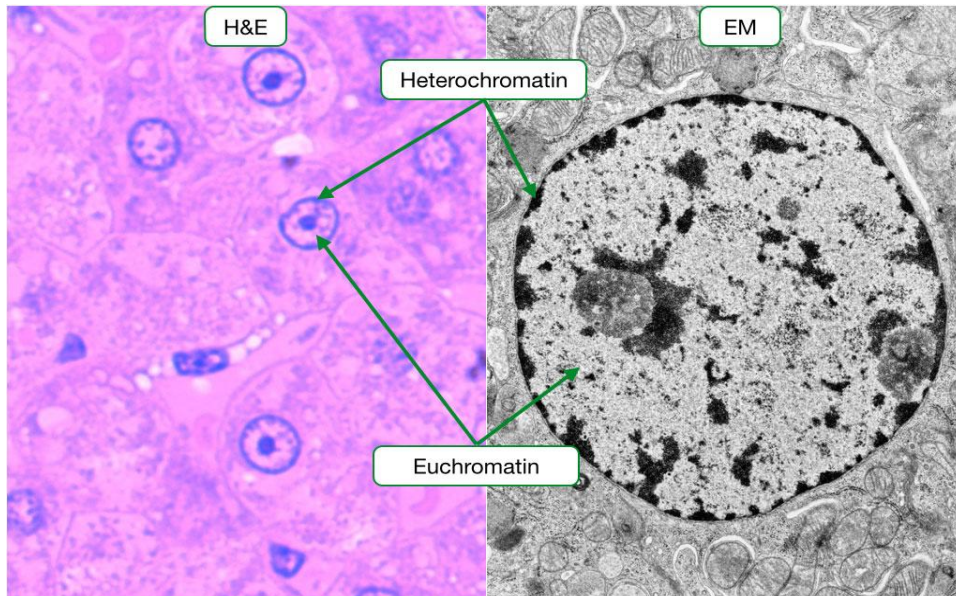
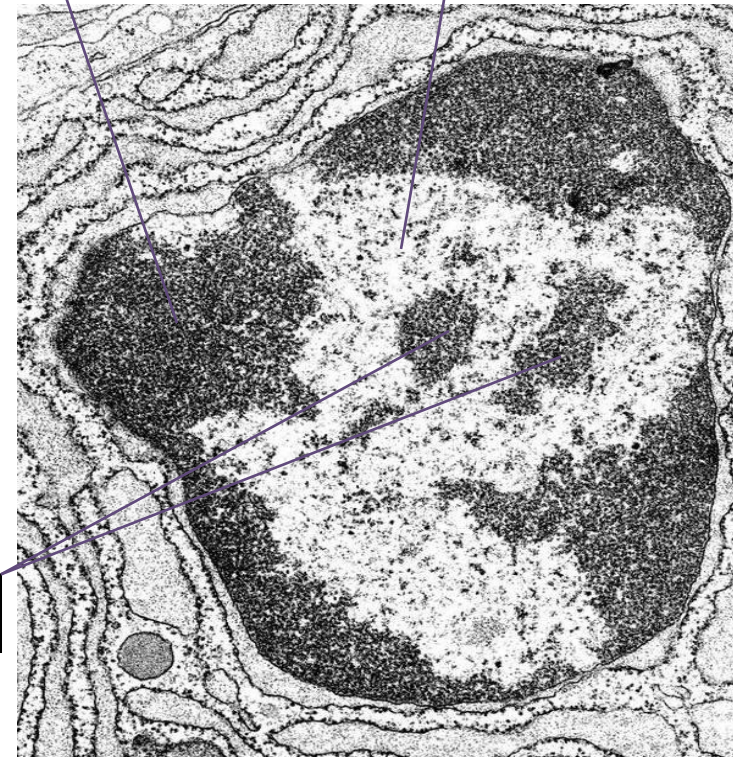
Nucleolus

- It is a spherical dark basophilic mass not surrounded by a membrane.
- Usually one.
- Function: formation and assembly of ribosomal RNA (rRNA), which is responsible for protein synthesis in the cytoplasm

Heterochromatin

Euchromatin

Nucleoli



Note: More active cells have paler, more euchromatic nuclei and more abundant cytoplasm, whereas less active cells have darker, more heterochromatic nuclei and less abundant cytoplasm.

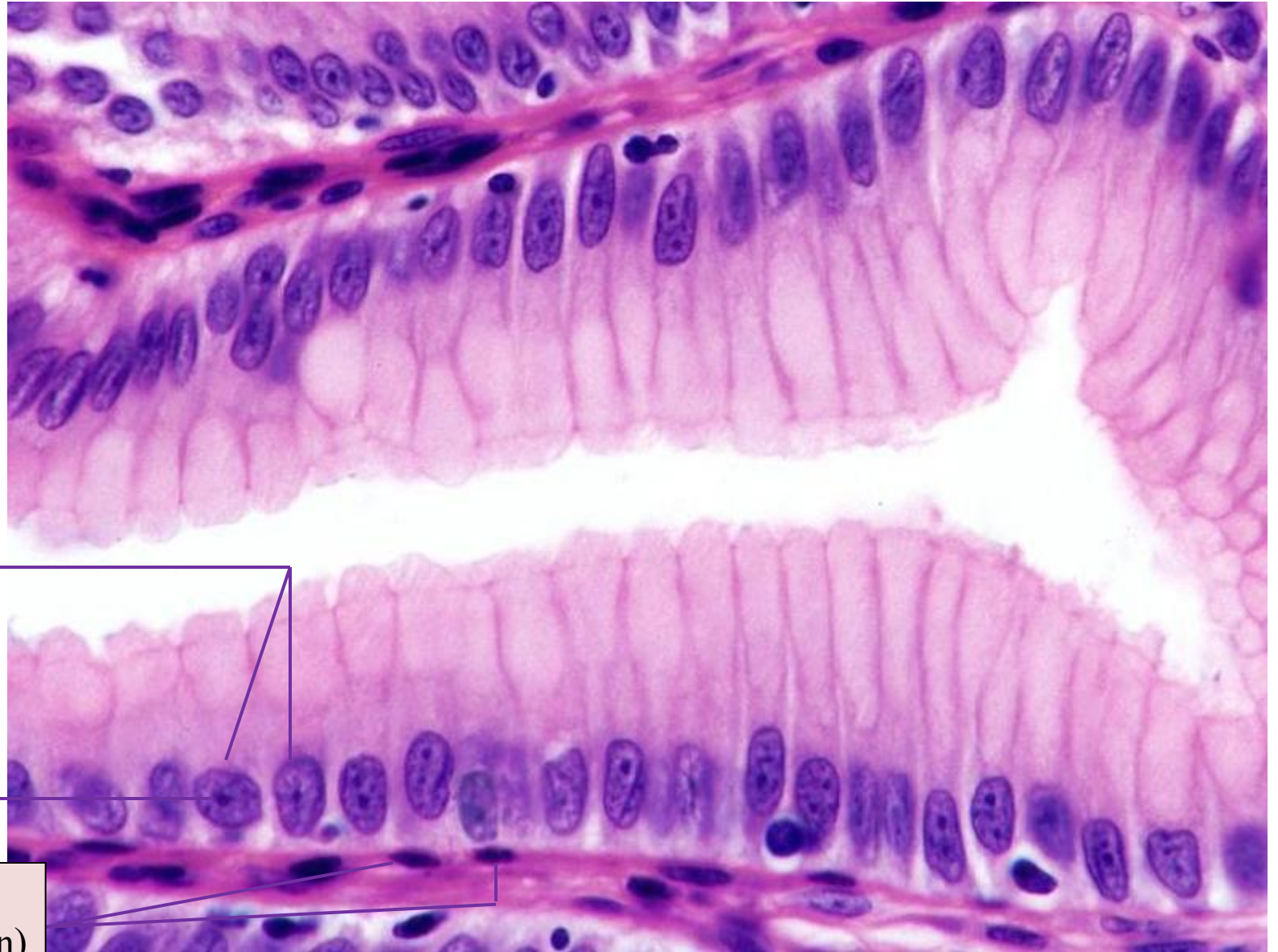
Note:
The nucleus stains **blue (basophilic)** using H&E

Lightly basophilic: active
Deeply basophilic and small: inactive

Active nucleus
(Euchromatin)

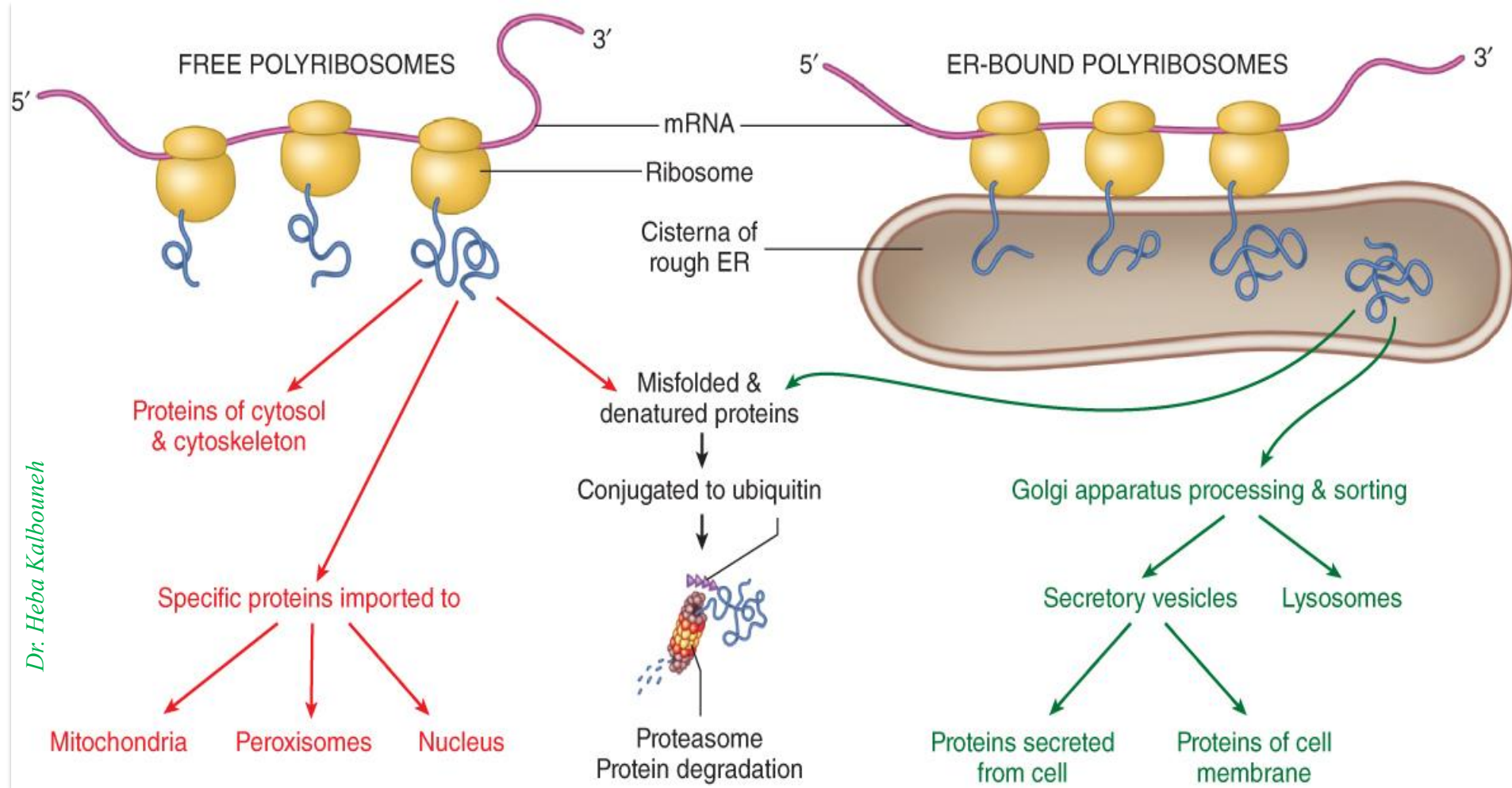
Nucleolus

Inactive nuclei
(Heterochromatin)



Note:

The cytoplasm stains **pink/red (acidophilic)** using H&E
The organelle (when prominent) that produces **basophilia** in the cytoplasm is the
ribosome

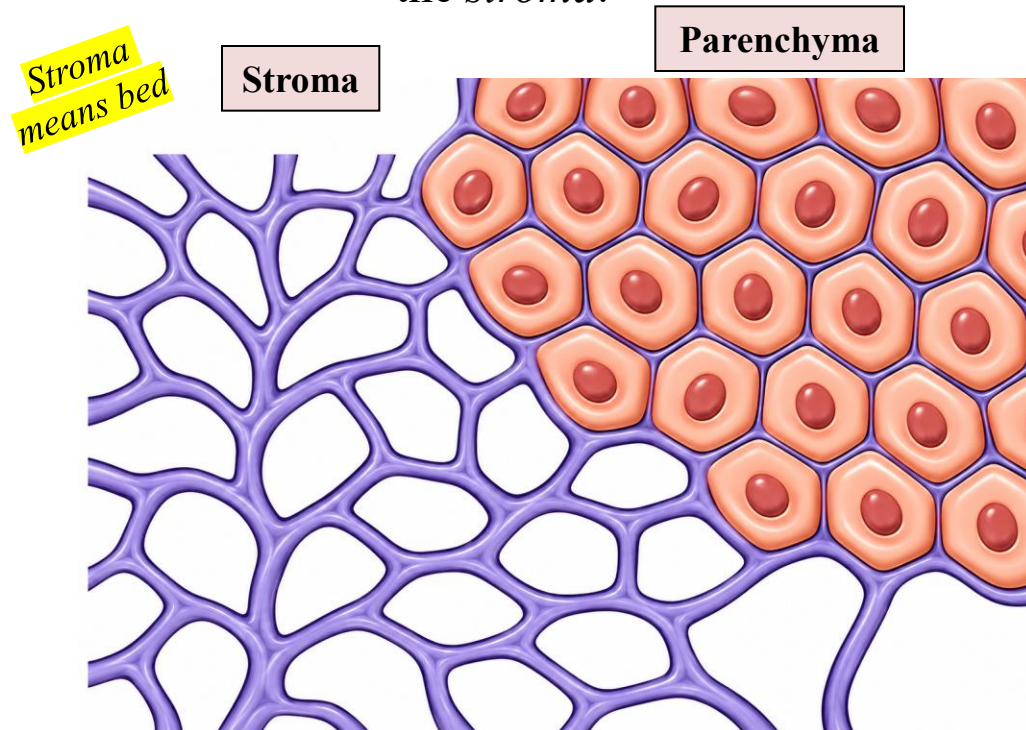


Parenchyma / Stroma:

The **parenchyma** of an organ consists of that tissue which conducts the specific function of the organ and which usually comprises the bulk of the organ. **Stroma** is everything else → connective tissue, blood vessels, nerves, ducts. It is made up of all the parts without specific functions of the organ

For Example:

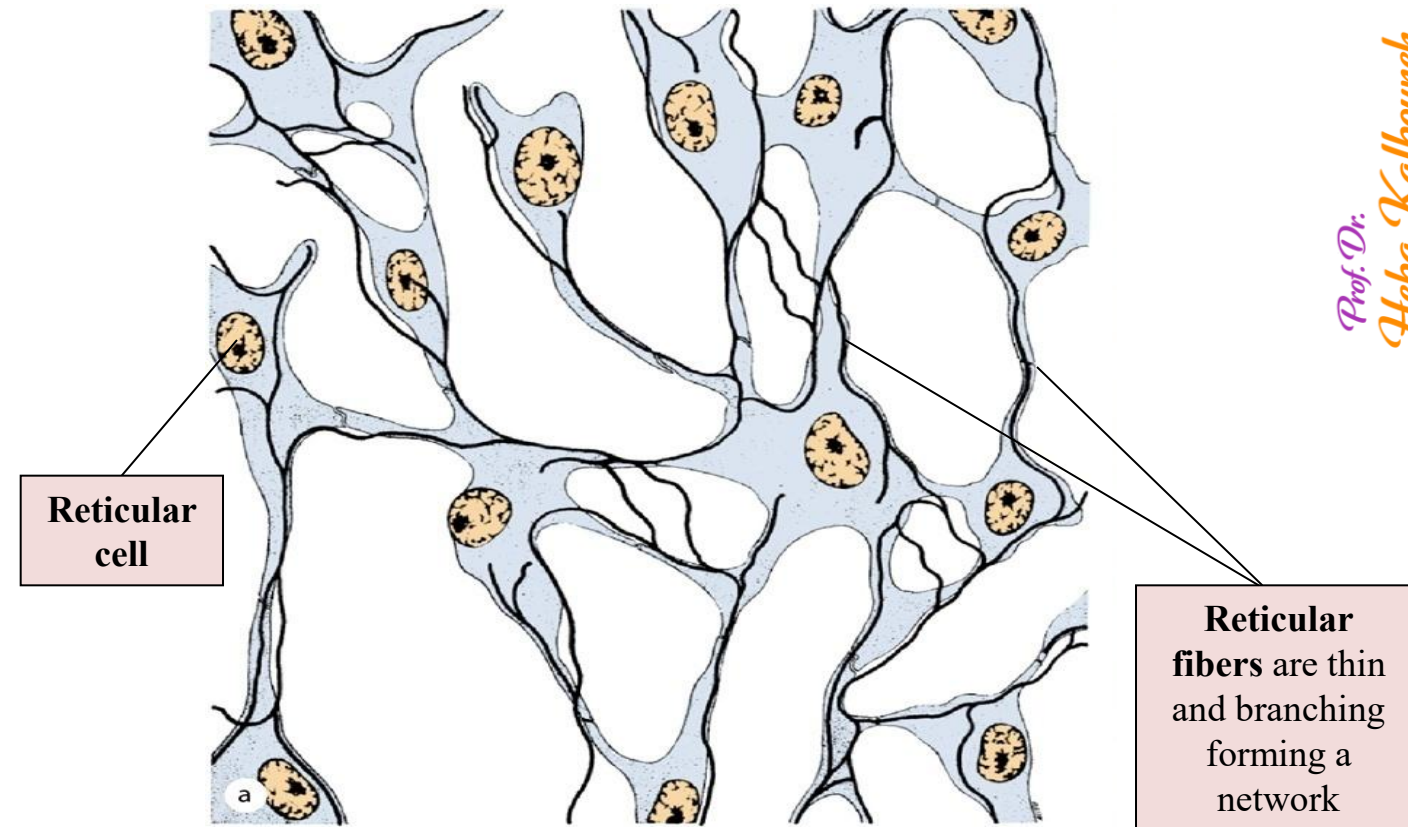
The *parenchyma* of the heart is **muscle tissue** (cardiac muscle cells). The nerves, intrinsic blood vessels, and connective tissue of the heart comprise the *stroma*.



Reticular connective tissue

- Consists of reticular cells (modified fibroblasts) and the network of reticular fibers formed by them
- Forms the structural framework (stroma) in which the cells of the organ are suspended
- In the **liver, bone marrow, lymph nodes and spleen**

(Mononuclear phagocyte system organs, Reticulo-Endothelial organs!!!)



Types of capillaries

Continuous capillaries

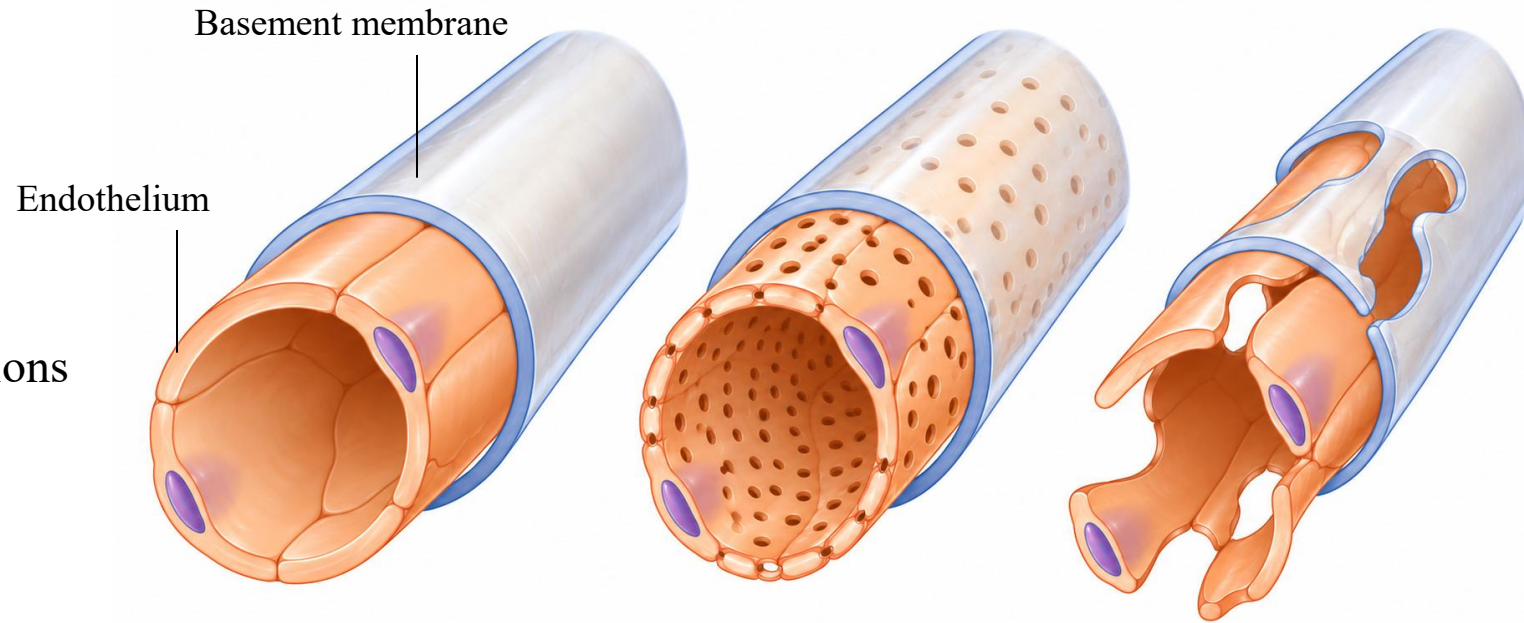
- Are most common
- Endothelium forms solid lining
- Adjacent cells are held together with tight junctions
- Found in most organs

Fenestrated capillaries

- Endothelium contains pores (fenestrations)
- Found wherever active capillary absorption or filtrate formation occurs
- Found in endocrine glands, small intestine, and kidney

Sinusoidal capillaries

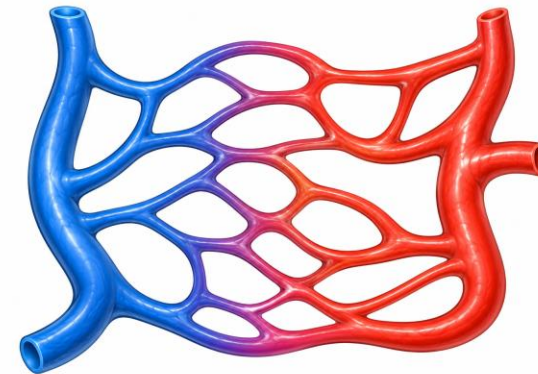
- Exhibit wide diameters with wide gaps between endothelial cells
- Basement membrane incomplete or absent
- Allow large molecules (proteins and blood cells) to pass between the blood and surrounding tissues
- Found in liver, spleen, and bone marrow



Continuous capillary

Fenestrated capillary

Sinusoid



Blood Cell Formation (Hematopoiesis)

Mature blood cells have a relatively short life span and must be continuously replaced with new cells from precursors developing during hemopoiesis/ hematopoiesis (Gr. haima, blood + poiesis, a making).

Early embryo

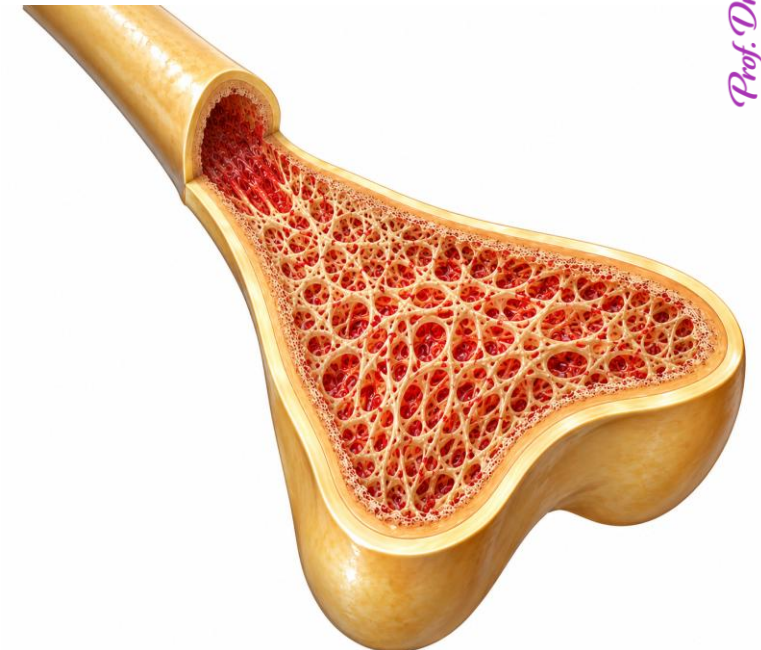
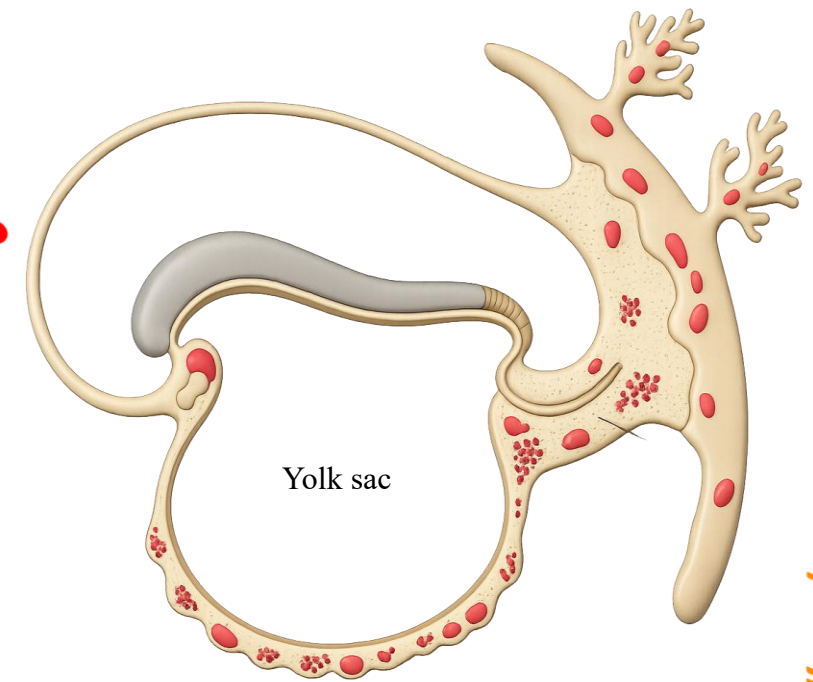
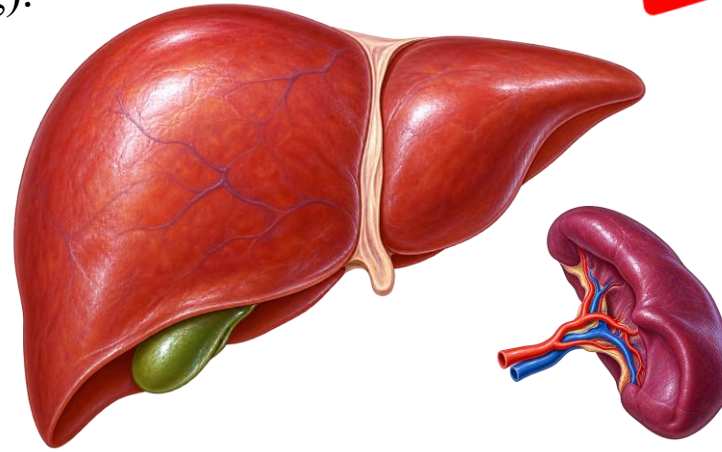
Yolk sac mesoderm

Second trimester

Developing liver and spleen

Third trimester

Bone marrow

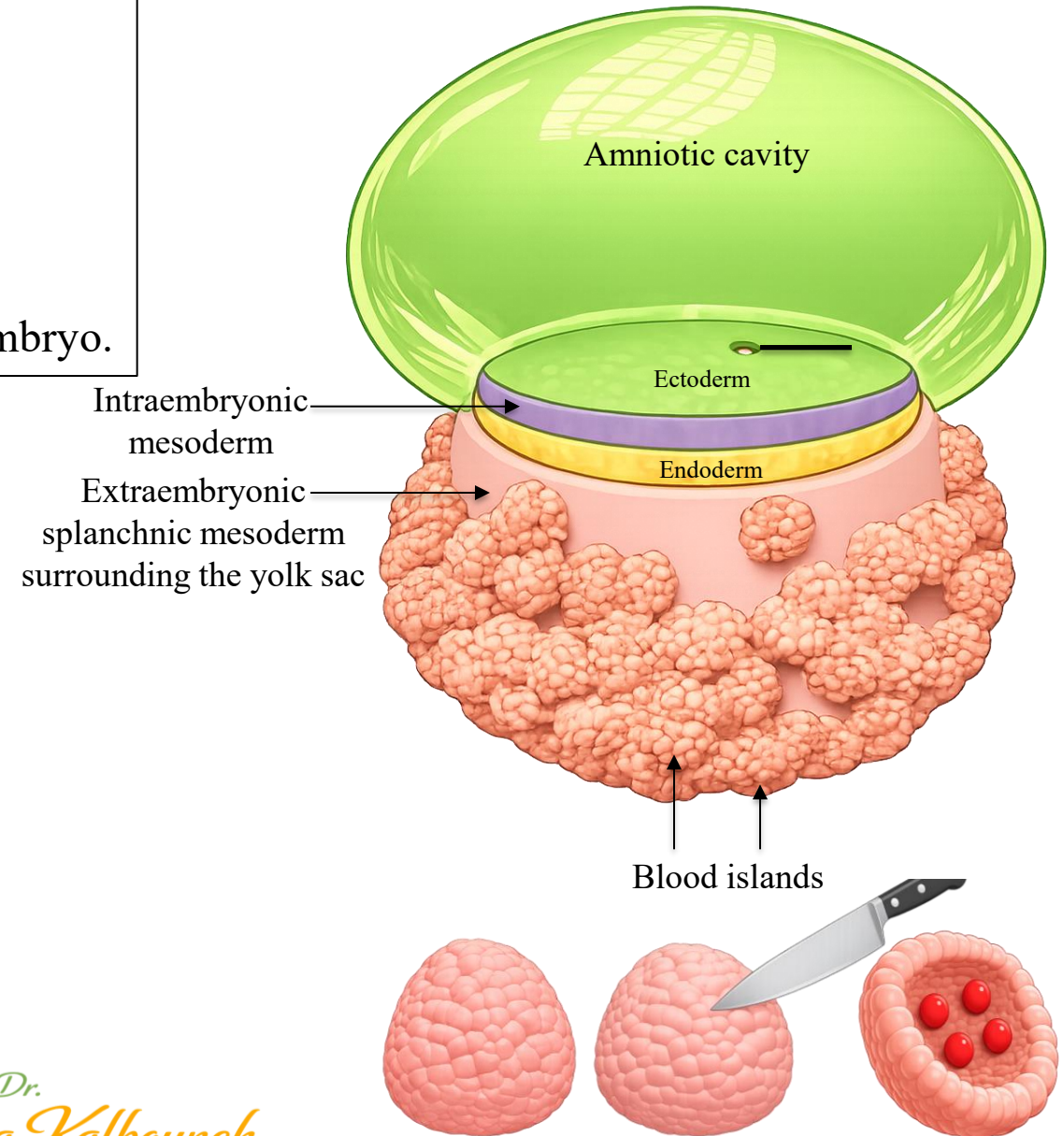
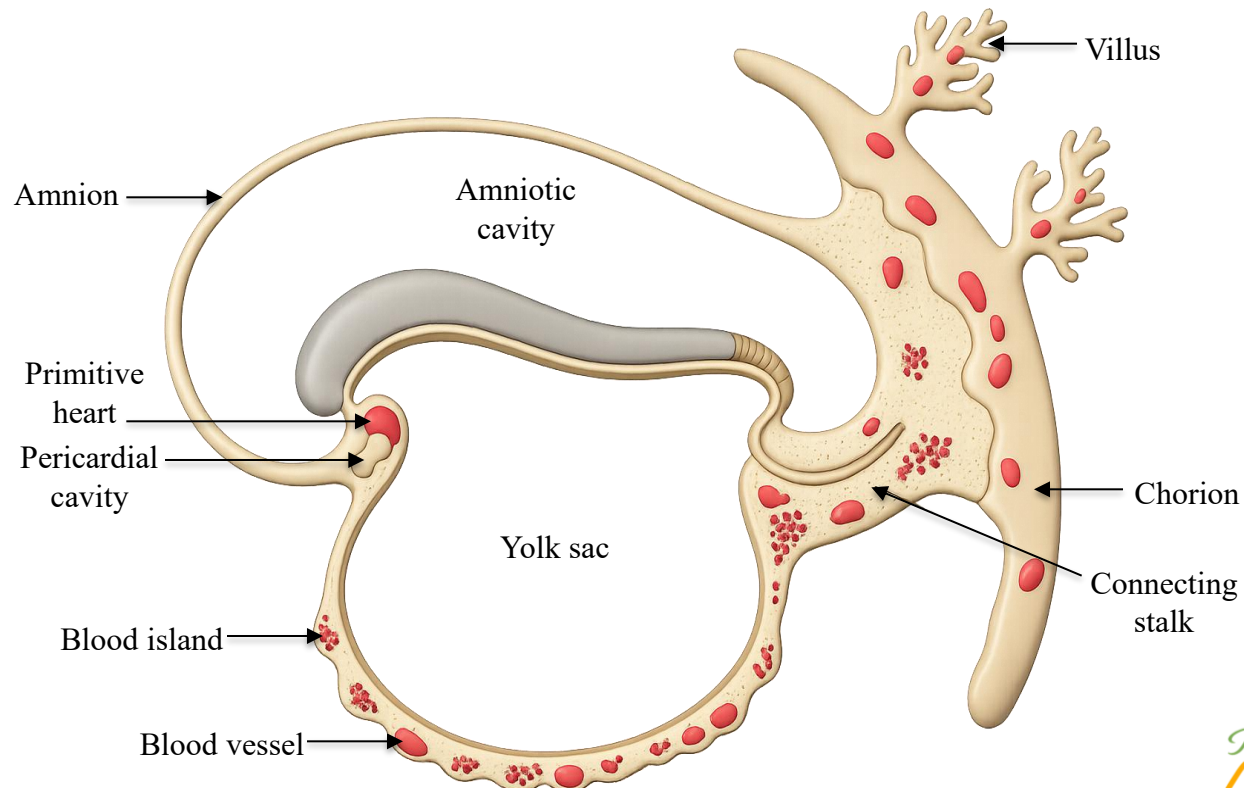


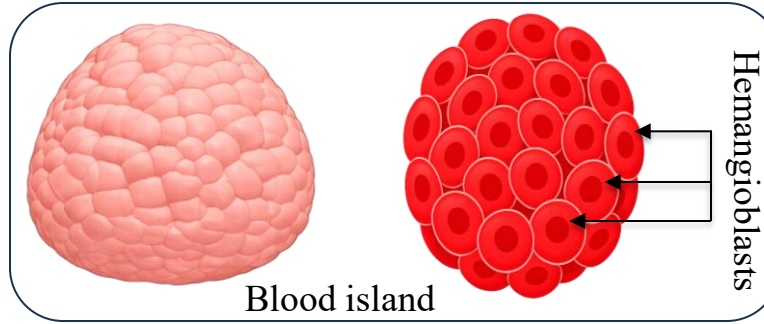
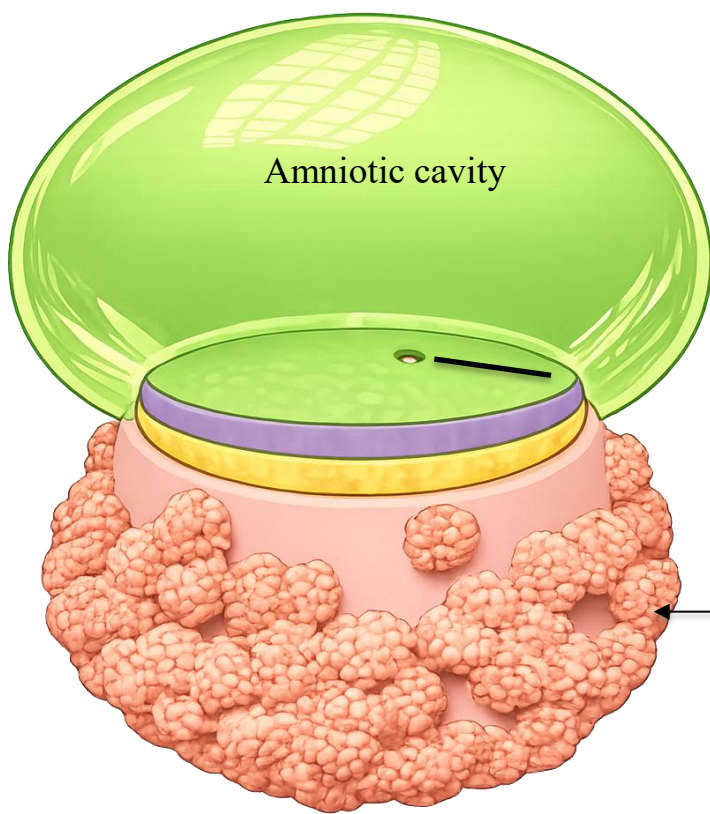
After birth, all blood cells originate in bone marrow
Medullary hematopoiesis

Development of the Cardiovascular System

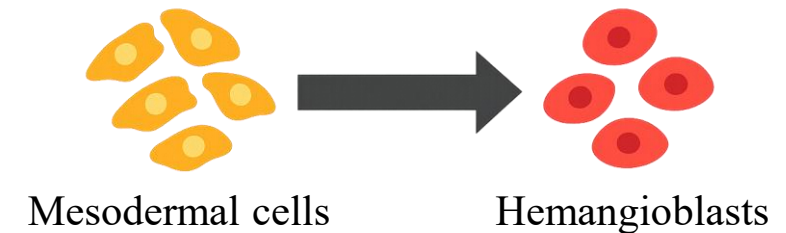
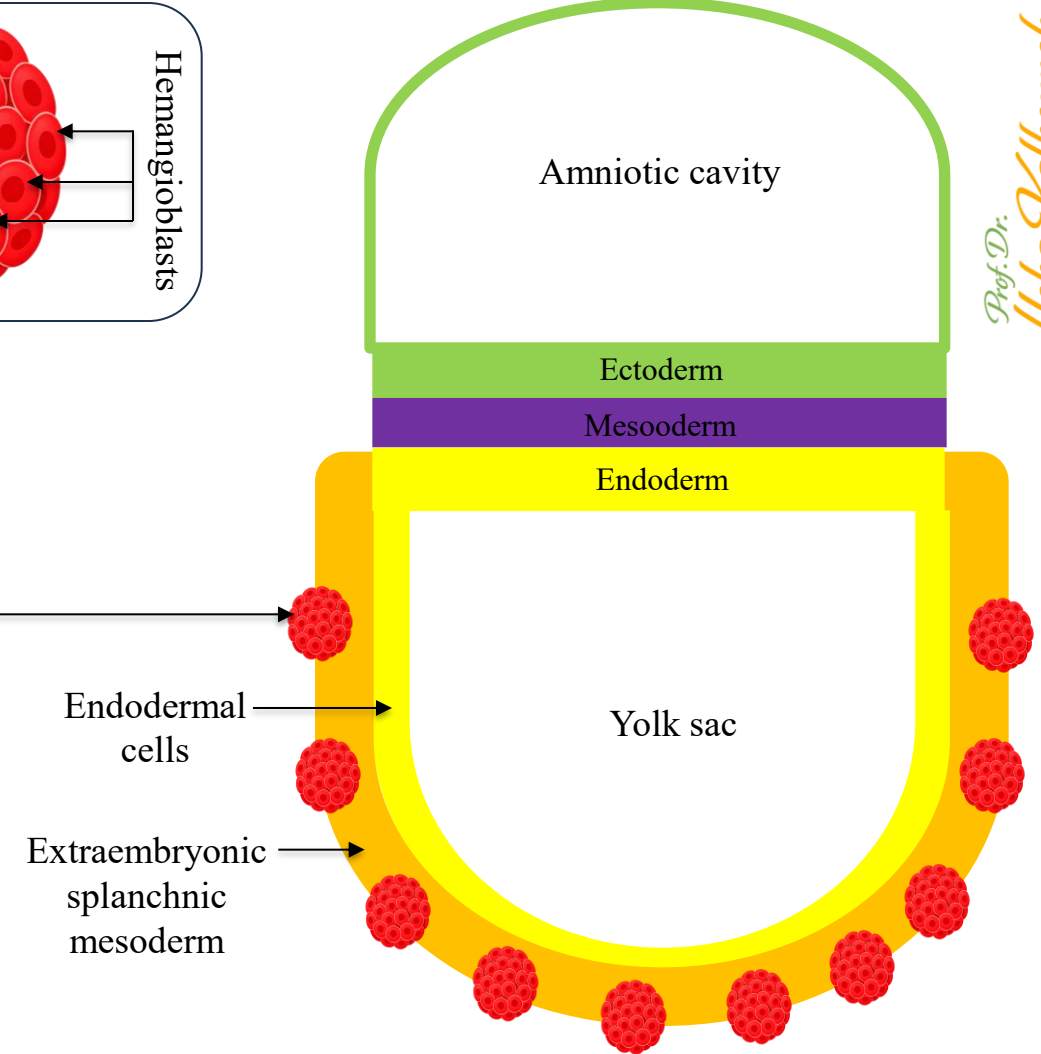
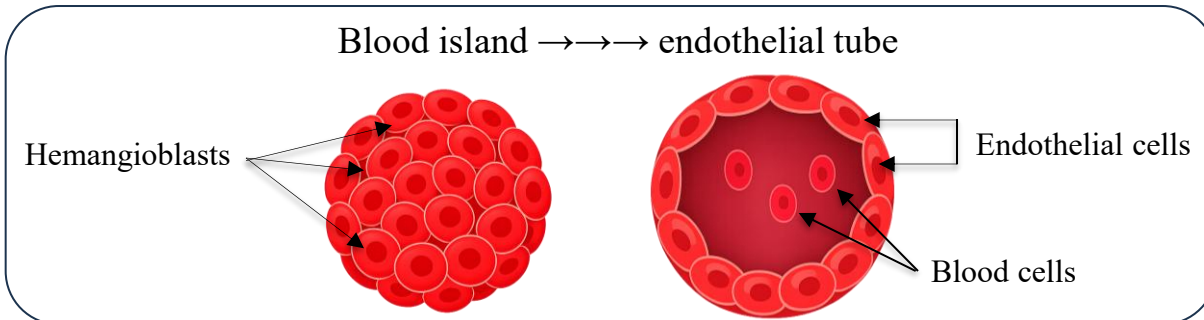
- ✓ Blood islands appear in:
 - Extraembryonic mesoderm (yolk sac wall, chorion)
 - Intraembryonic mesoderm
- ✓ These give rise to:
 - Blood cells
 - Endothelial cells
- ✓ The primitive heart tube begins to form by the end of week 3.
- ✓ The cardiovascular system is the first functional system in the embryo.

Remember: The yolk sac wall consists of two layers:
1. Endodermal cells (inner lining of the yolk sac)
2. Extraembryonic splanchnic mesoderm (outer layer)





- ✓ Mesodermal cells differentiate into hemangioblasts
- ✓ Hemangioblasts aggregate to form blood islands
- ✓ Cavities are formed inside blood island forming endothelial tube with:
 - Peripheral cells (angioblasts) → **endothelial cells**
 - Central cells (hemocytoblast) → **blood cells**



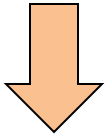
Bone marrow

The red bone marrow is a highly cellular structure that is located in the medullary cavities of the bone

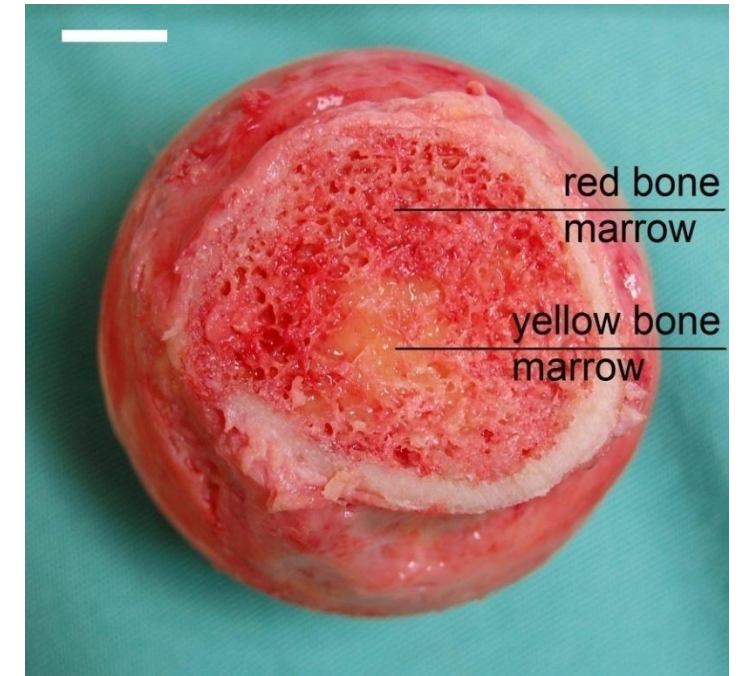
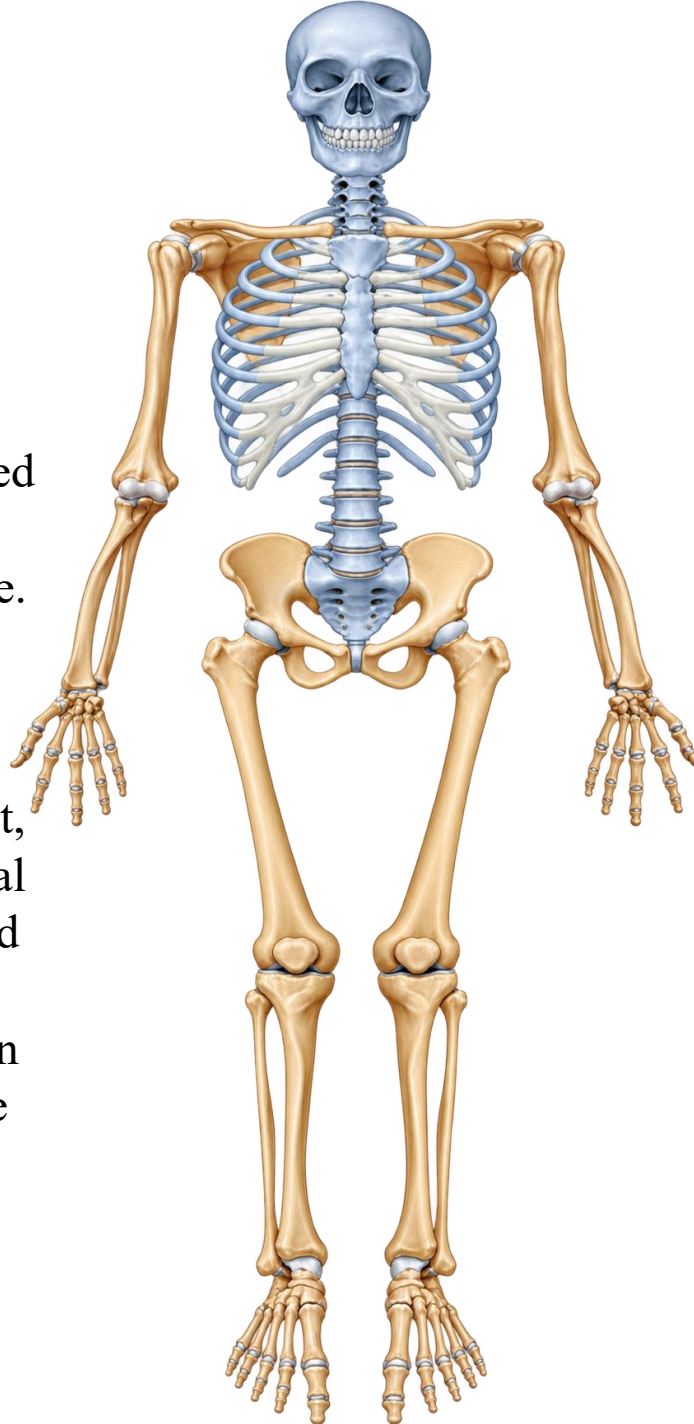
It consists of:

Hemopoietic stem cells

(the origin of different blood cells) surrounded by numerous macrophages and sinusoidal capillaries and supported by a reticular tissue.

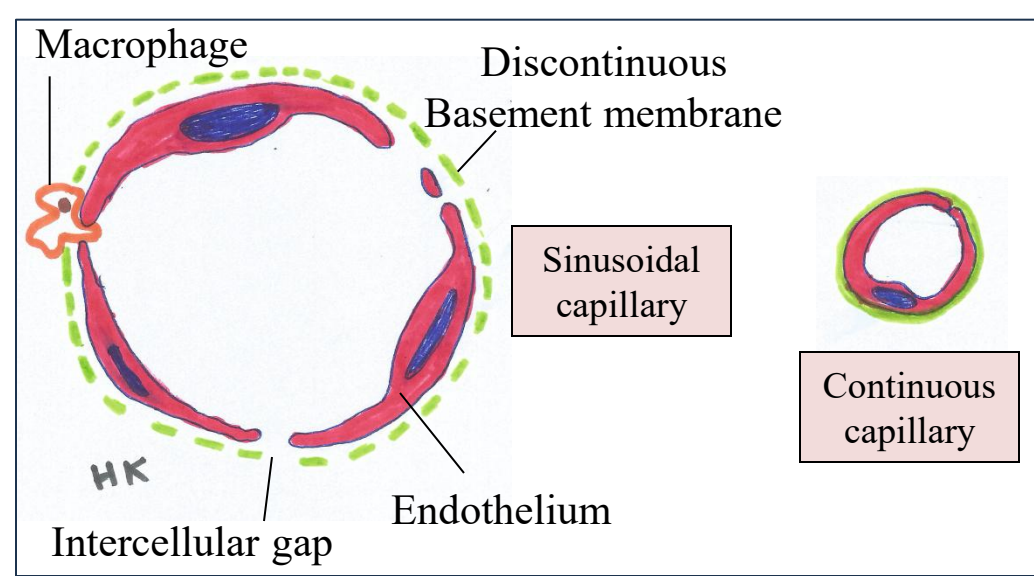


As the individual ages and becomes an adult, the red marrow is found primarily in the axial skeleton (flat bones of the skull, sternum and ribs, vertebrae, and pelvic bones). The remaining bones, primarily the long bones in the limbs of the body, gradually accumulate fat, and their marrow becomes yellow. Consequently, they lose the hemopoietic functions.

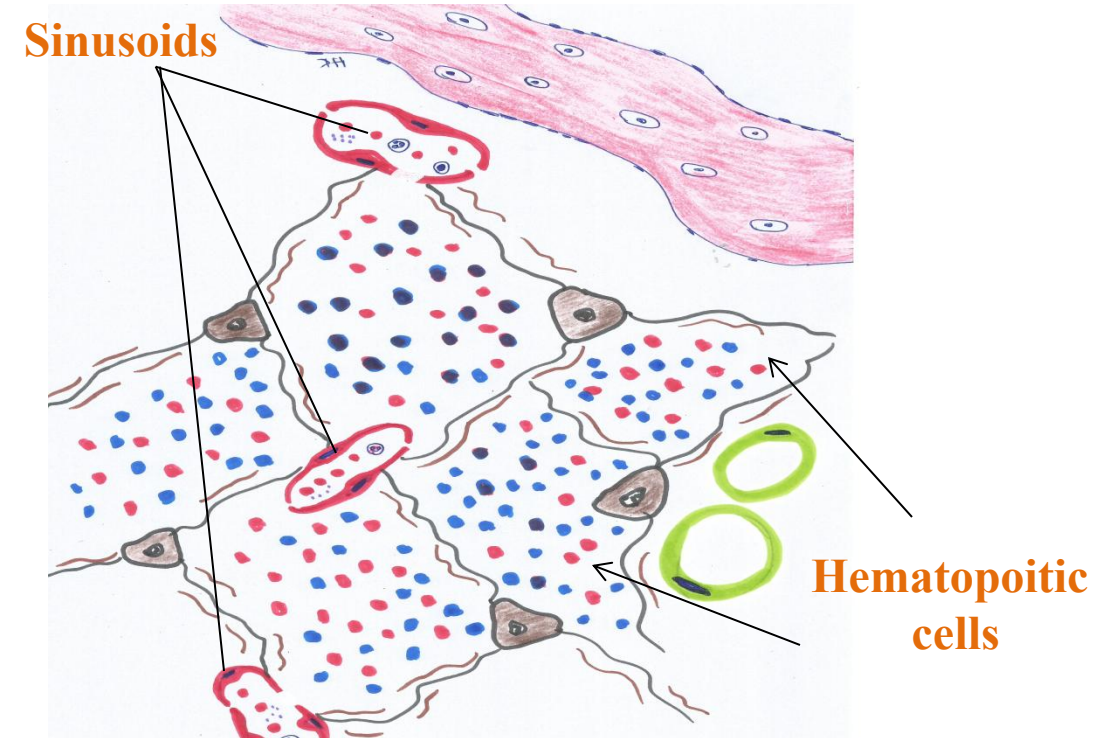
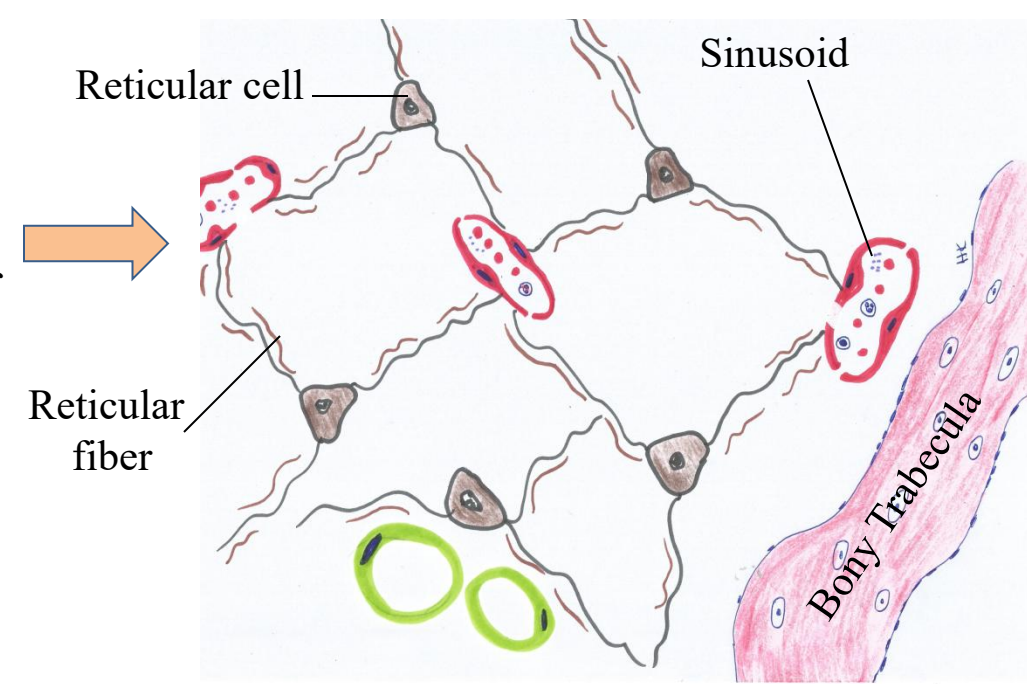


Extramedullary hematopoiesis refers to the hematopoiesis that occurs in organs other than bone marrow.
(fetal development, normal immune responses, and pathological circumstances)

*Under certain conditions
(severe bleeding or hypoxia),
yellow marrow reverts to red*



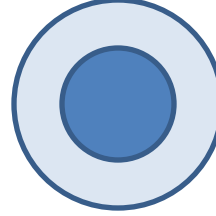
Reticular tissue
forming the stroma of
the bone marrow



Between the hematopoietic cells run the **sinusoids**, which have discontinuous endothelium, through which newly differentiated blood cells and platelets enter the circulation

Red marrow is also a site where older, defective erythrocytes undergo phagocytosis by macrophages, which then reprocess heme-bound iron for delivery to the differentiating erythrocytes.

Hematopoietic stem cell
(Pluripotent/Multipotent)

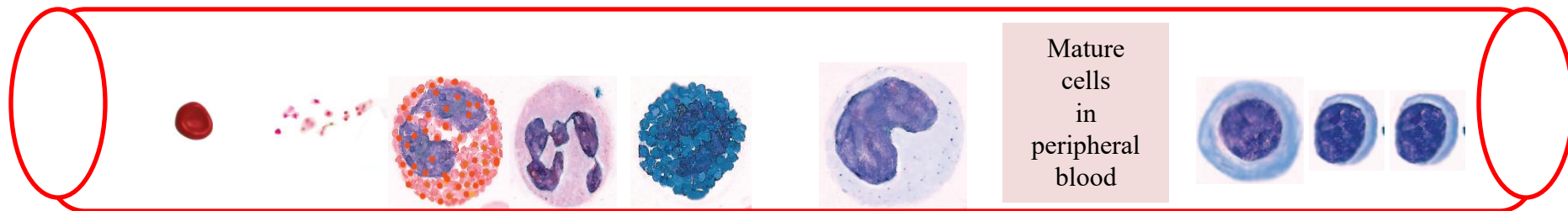


Pluripotent within blood lineages

Pluripotent refers to their ability to generate all hematopoietic lineages.

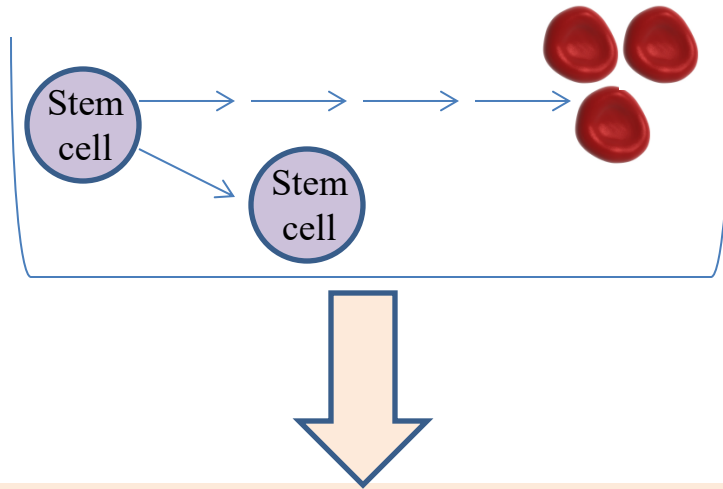
Pluripotent = can produce cells from all three germ layers (like embryonic stem cells)

Multipotent = can produce multiple related cell types within one system/tissue



Stem cells are capable of asymmetric division and self-renewal.

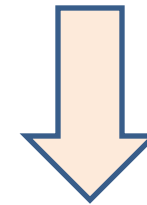
Stem cells can maintain the original population



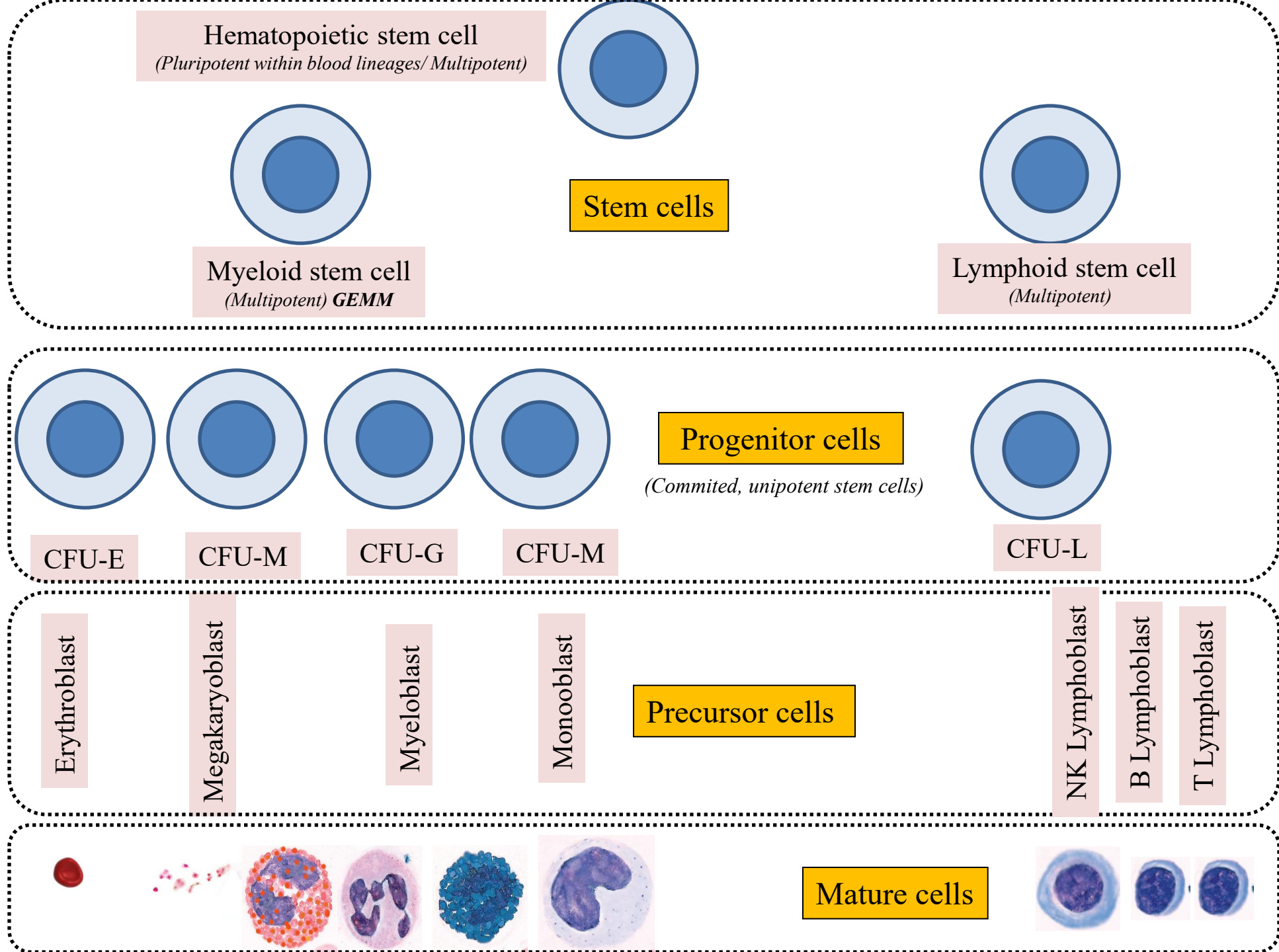
Every time the stem cell multiplies, it will give two cells, one differentiate into mature RBCs and the other cell add to the original population

Precursor cells produce only mature blood cells

Erythroblasts are precursor cells



All Erythroblasts multiply and differentiate into mature RBCs (erythrocytes) and **no** erythroblasts are left in the end



Hematopoietic stem cells



Note:

Stem cells and progenitor cells cannot be morphologically distinguished and resemble **large lymphocytes**

Myeloid stem cells



Lymphoid stem cells



Rate of cell division:

Slow in Stem cells

Rapid in progenitor and precursor cells

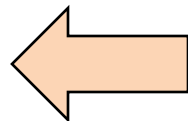
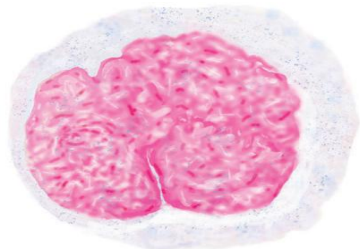
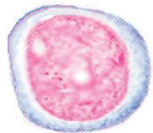
Progenitor cells/ CFUs



All progenitor cells (CFUs) produce precursor cells (or blasts)

Precursor cells/ Blasts

Selected precursors of different blood cells



Precursor cells gradually assume the morphologic characteristics of the mature, functional cell types they will become

While stem cells divide at a rate only sufficient to maintain their relatively small population, progenitor and precursor cells divide more rapidly, producing large numbers of differentiated, mature cells

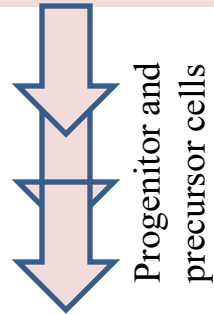
Hematopoietic stem cells

All blood cells arise from a single type of stem cell in the bone marrow called pluripotent/ multipotent stem cell
It can produce ALL BLOOD CELL TYPES

Note: Pluripotent within blood lineages

It proliferates and forms two major cell lineages

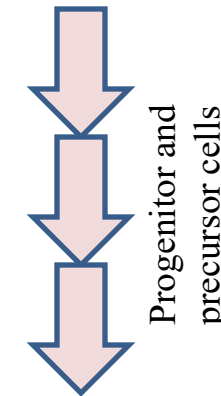
Myeloid stem cells



Granulocytes
-Neutrophils
-Basophils
-Eosinophils
Erythrocytes
Megakaryocytes
Monocytes

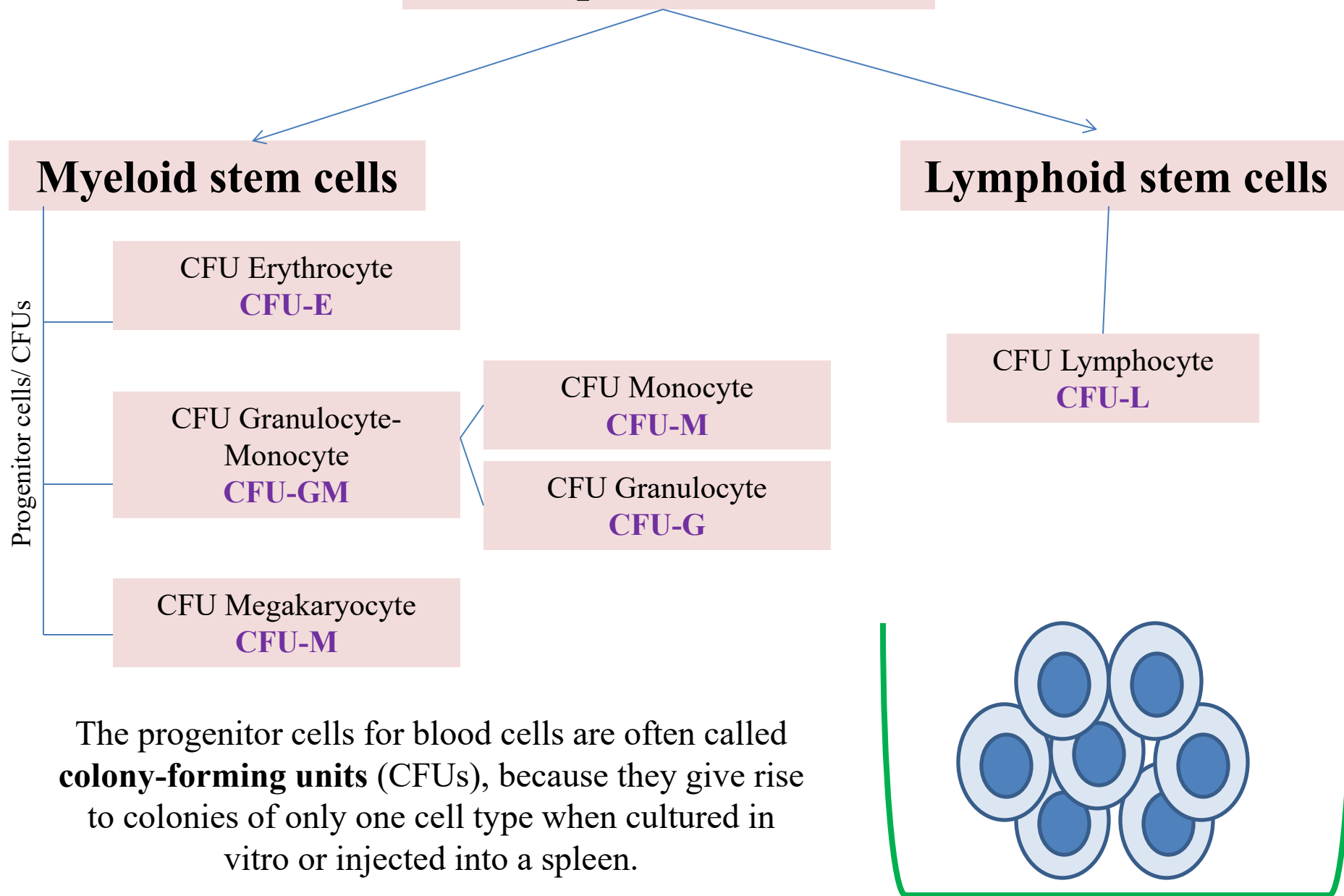
Lymphoid stem cells

Note: pre T-cells (precursor T cells, T lymphoblasts) migrate to the thymus where they proliferate and differentiate.



T lymphocyte
B lymphocyte
Natural killer cells

Hematopoietic stem cells



Blood Cell Formation (Hematopoiesis)

Throughout childhood and adult life, erythrocytes, granulocytes, monocytes, and platelets continue to form from stem cells located in bone marrow

Important & required

Erythropoiesis: the process which produces erythrocytes

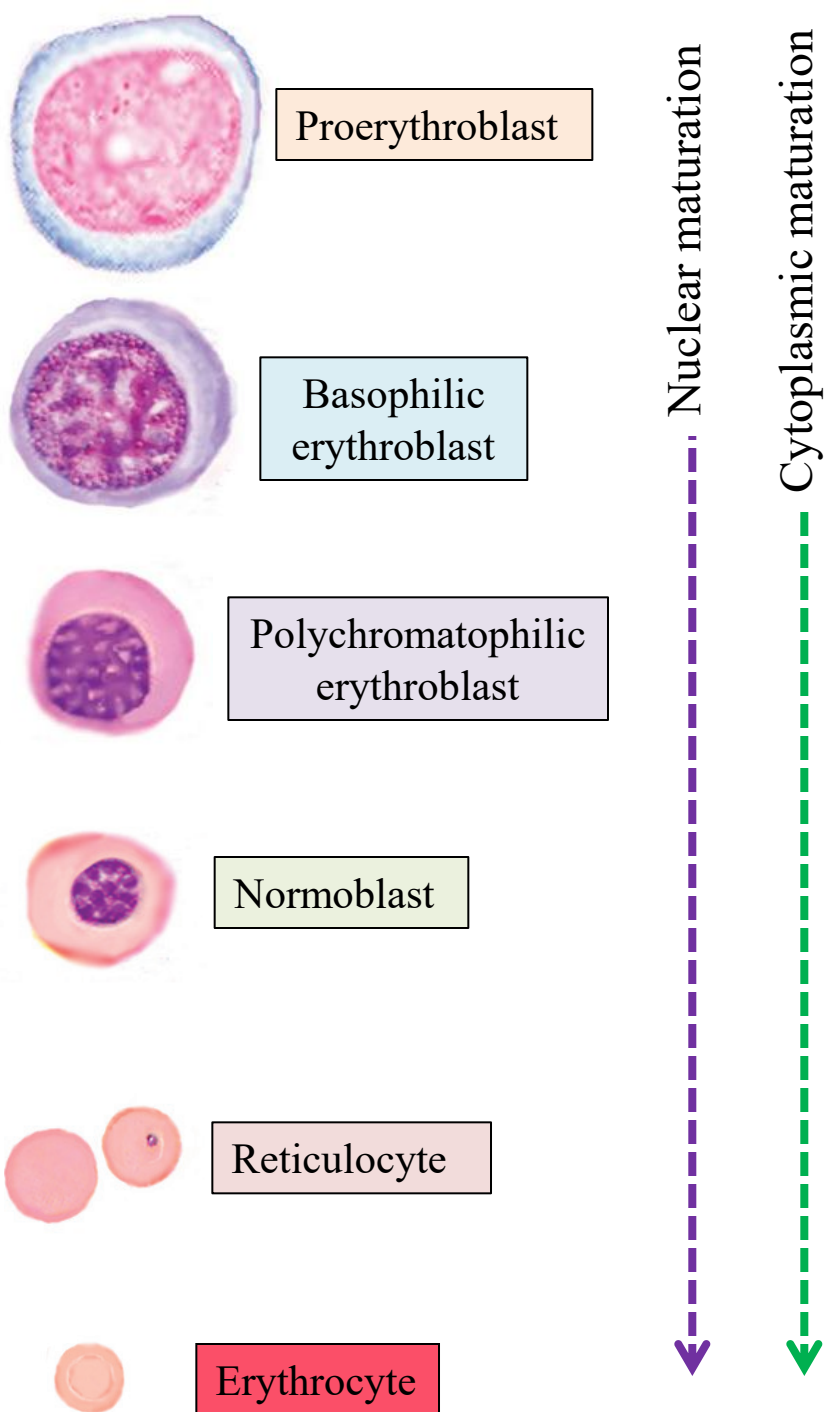
Granulopoiesis: the process which produces granulocytes

Thrombopoiesis: the process which produces thrombocytes

Lymphopoiesis: the process which produces lymphocytes

Monocytopoiesis: the process which produces monocytes

Remember
Lymphopoiesis occurs in the marrow and in the lymphoid organs to which precursor cells migrate from marrow.



Erythropoiesis (red cell formation)

- ✓ Takes about 1 week
- ✓ Rate is controlled by the hormone erythropoietin (secreted by the kidney cells) and the availability of iron, folic acid, vitamin B12, protein precursors

Stages of differentiation are characterized by:

- 1- Decreasing cell size
- 2- Progressive loss of organelles

Presence of free ribosomes at early stages

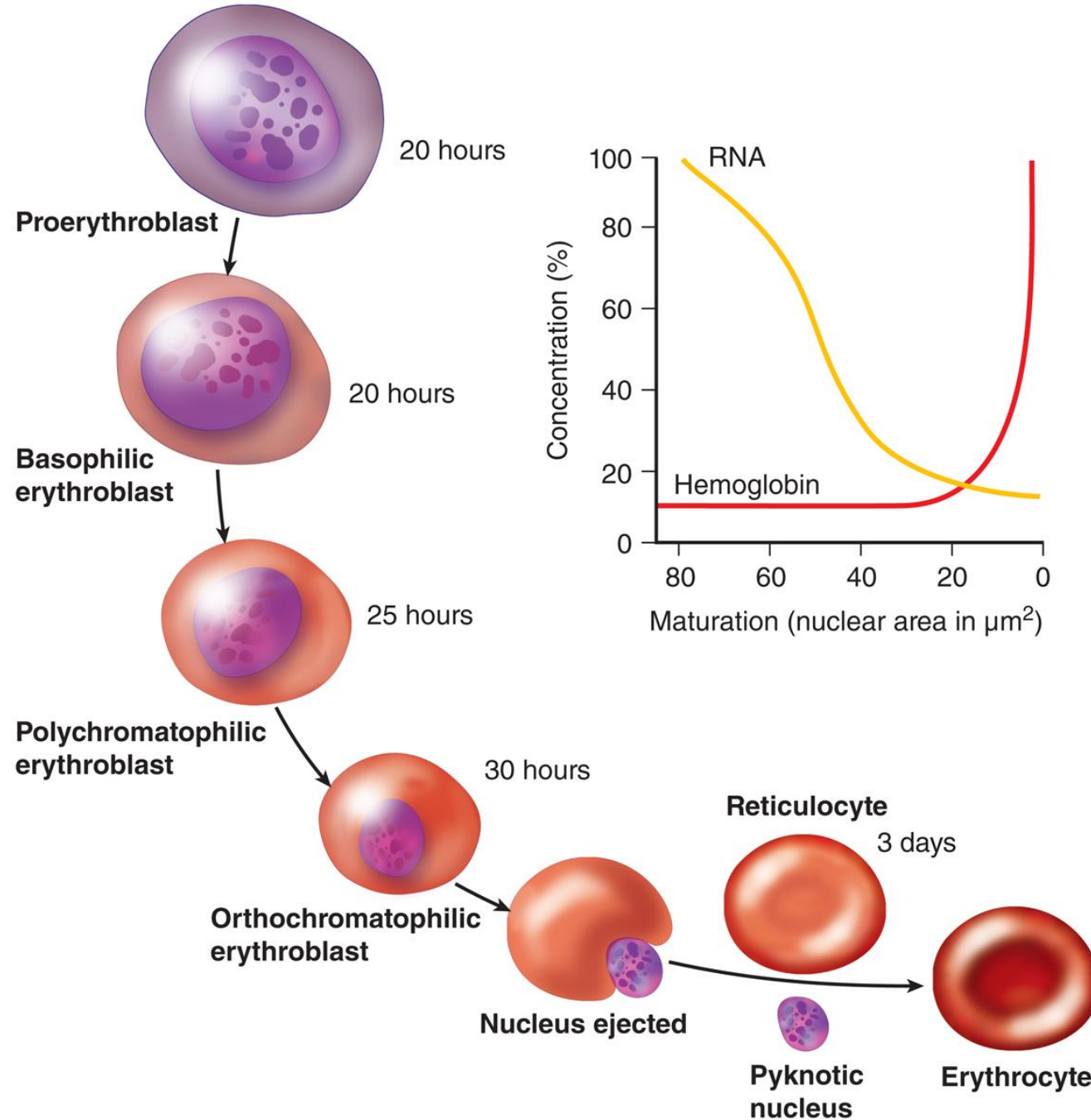


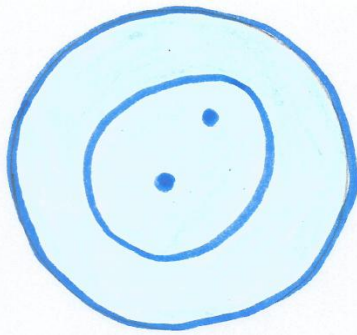
Accounts for the marked cytoplasmic basophilia (**blue**)

- 3- Progressive increase in hemoglobin content



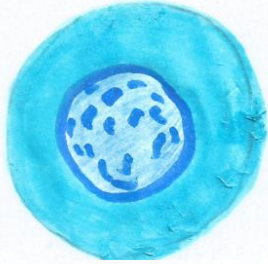
Accounts for increasing eosinophilia (**pink/red**)





Proerythroblast

- ✓ The first recognizable erythrocyte precursor
- ✓ Largest cell (17um)
- ✓ Large pale nucleus with prominent nucleolus
- ✓ Pale basophilic cytoplasm



Basophilic erythroblast

- ✓ The cell becomes smaller (15um)
- ✓ Nucleus: smaller and darker
- ✓ Deeply basophilic cytoplasm (high in ribosomes)



Polychromatophilic erythroblast

- ✓ The cell becomes smaller (13um)
- ✓ Nucleus: smaller and darker
- ✓ Cytoplasm becomes violet
- ✓ Takes basic (ribosomes) and acidic stains (Hb)



Normoblast

- ✓ The cell becomes smaller (11um)
- ✓ Nucleus: smaller, darker and eccentric to be expelled outside
- ✓ Cytoplasm is acidophilic (Hb)

The nucleus is extruded at this stage



Reticulocyte

- ✓ Immature erythrocyte but slightly larger (9um)
- ✓ No nucleus
- ✓ Cytoplasm is acidophilic (Hb) but contains remnants of ribosomes forming reticulum
- ✓ Can be stained by supravital stains (brilliant cresyl blue)

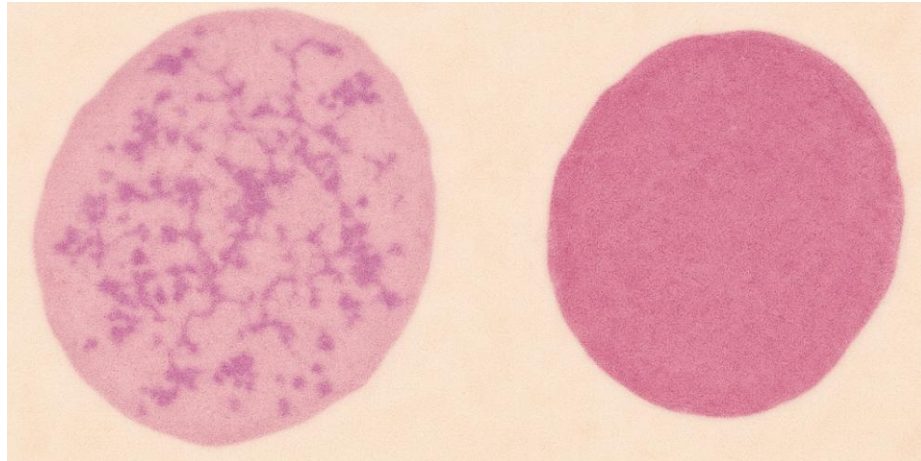


Erythrocyte

Reticulocytes

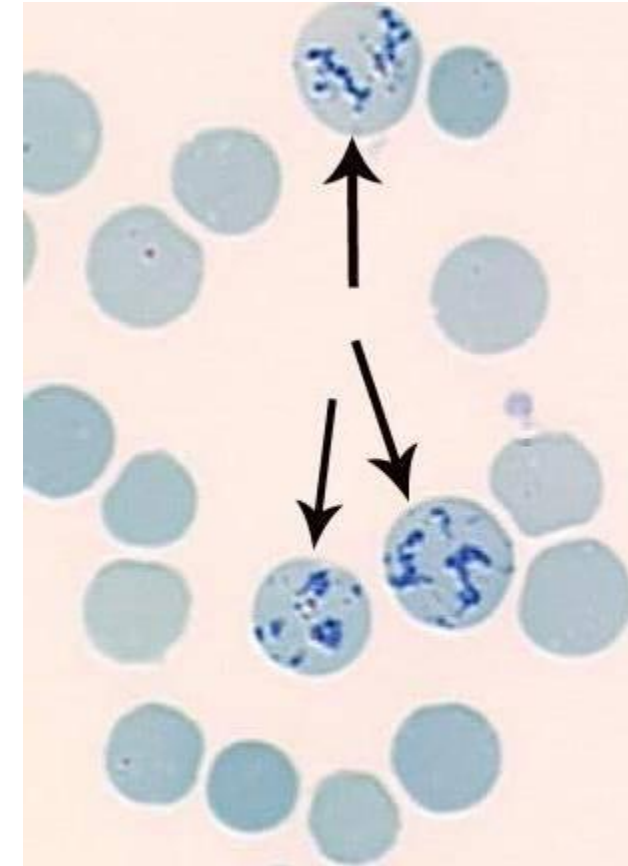
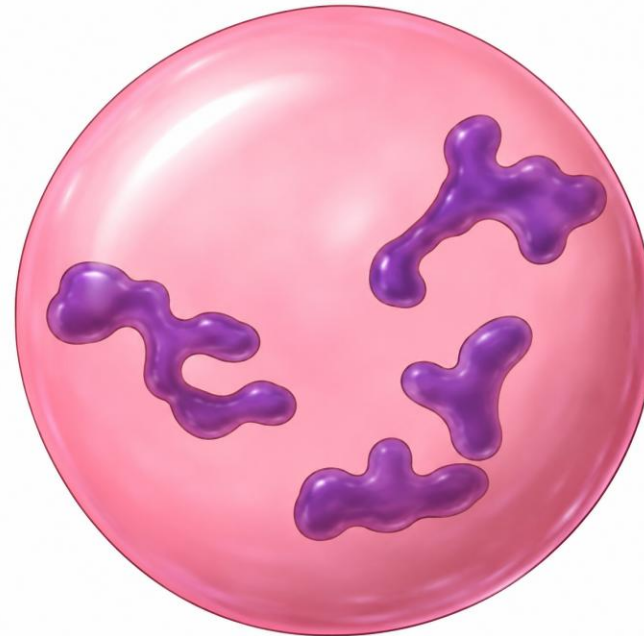
Very important
CLINICALLY

- Are immature red blood cells (last stage)
- The cell has extruded its nucleus, but is still capable of producing hemoglobin. **WHY??**
- Supravital dye: precipitation of reticulum in the cytoplasm (brilliant cresyl blue)
- Normally, only about 1% of all red blood cells in the bloodstream are reticulocytes
- They circulate for about 1-2 days before developing into mature red blood cells
- An increase in reticulocytes ---- blood loss (hemorrhage)



Reticulocyte

Mature Erythrocyte



Granulopoiesis (Neutrophils, Eosinophils and Basophils formation)

✓ Takes about 2 weeks

Stages of differentiation are characterized by:

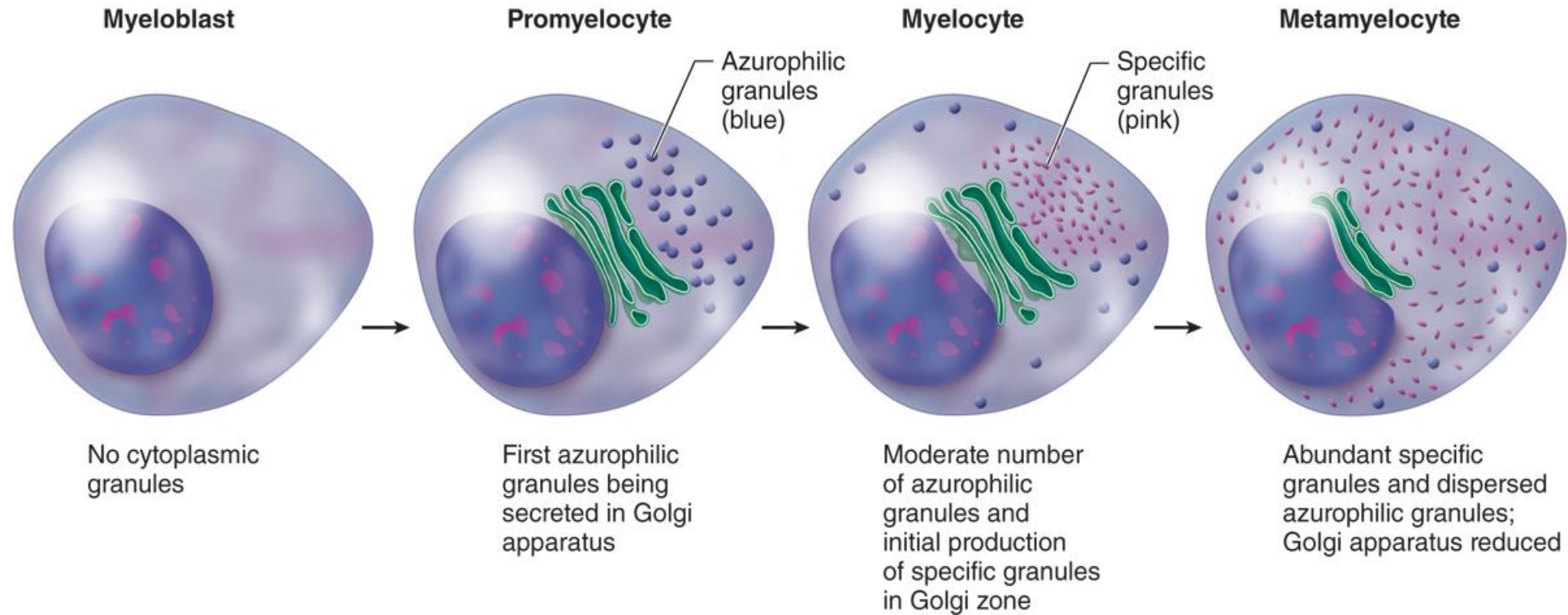
1- Cytoplasmic changes dominated by synthesis of azurophilic granules and specific granules.



First, formation of the azurophilic granules (similar in all three types of granulocytes)

Second, formation of the specific granules (differ in each of the three types of granulocytes)

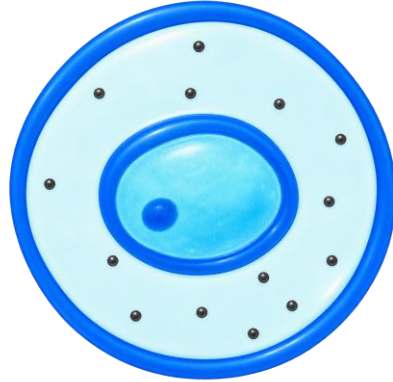
2- Condensation, indentation and segmentation of the nucleus



Myeloblast



Promyelocyte



Neutrophilic

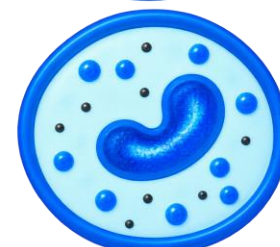
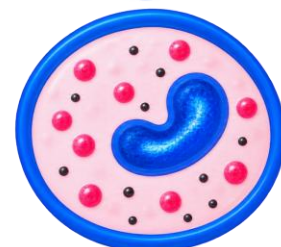
Eosinophilic

Basophilic

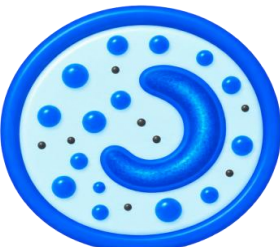
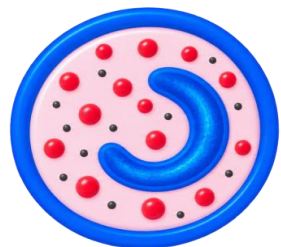
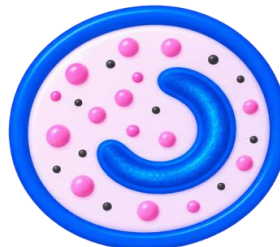
Myelocyte



Metamyelocyte



Band cell



Myeloblast

- ✓ The first recognizable precursor

Promyelocyte

- ✓ The largest (20um)
- ✓ Azurophilic granules start to appear

Myelocyte

- ✓ 3 types
- ✓ The cell becomes smaller
- ✓ The nucleus becomes smaller and darker
- ✓ Specific granules start to appear

Metamyelocyte

- ✓ 3 types
- ✓ Cannot divide
- ✓ Undergoes metamorphosis
- ✓ Nucleus becomes indented (kidney shaped)
- ✓ Specific granules increase in number

Band cell (stab cell)

- ✓ 3 types
- ✓ Nucleus becomes curved horseshoe/band in shape

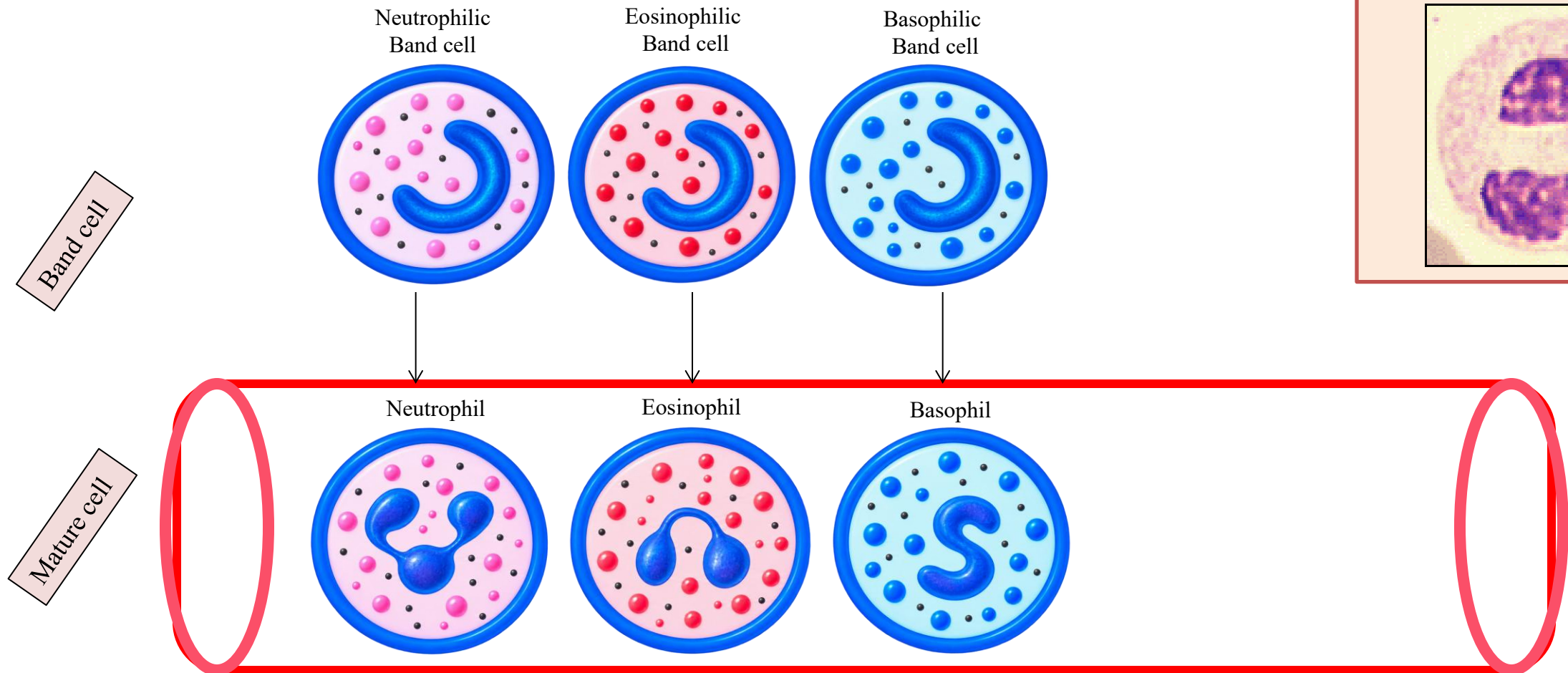
Neutrophilic band cells (important CLINICALLY)



Band cells normally account for no more than 5% of leukocytes in peripheral blood
An increased number of band cells (left shift) commonly indicates **acute bacterial infection** but may also occur in severe inflammation or tissue injury.

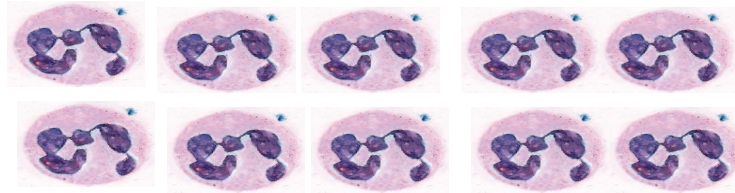
➡ This means that the bone marrow has been signaled to release more neutrophils and increase production of neutrophils

A band cell is a **nearly** mature neutrophil that differs primarily from a mature segmented neutrophil by having a nonsegmented, band-shaped nucleus.

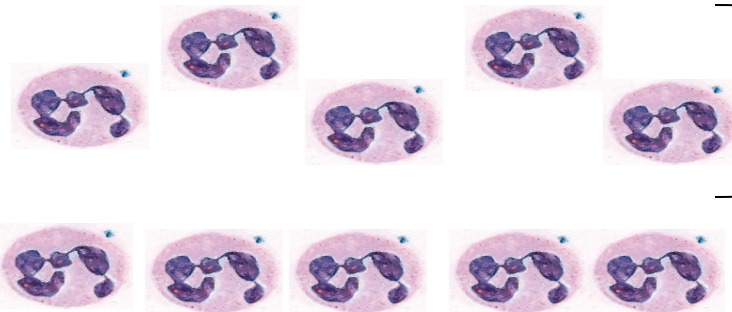


Bone marrow pool

Myeloblast
Promyelocyte
Myelocyte
Metamyelocyte
Band cell
Neutrophil



Circulating pool



Marginating pool

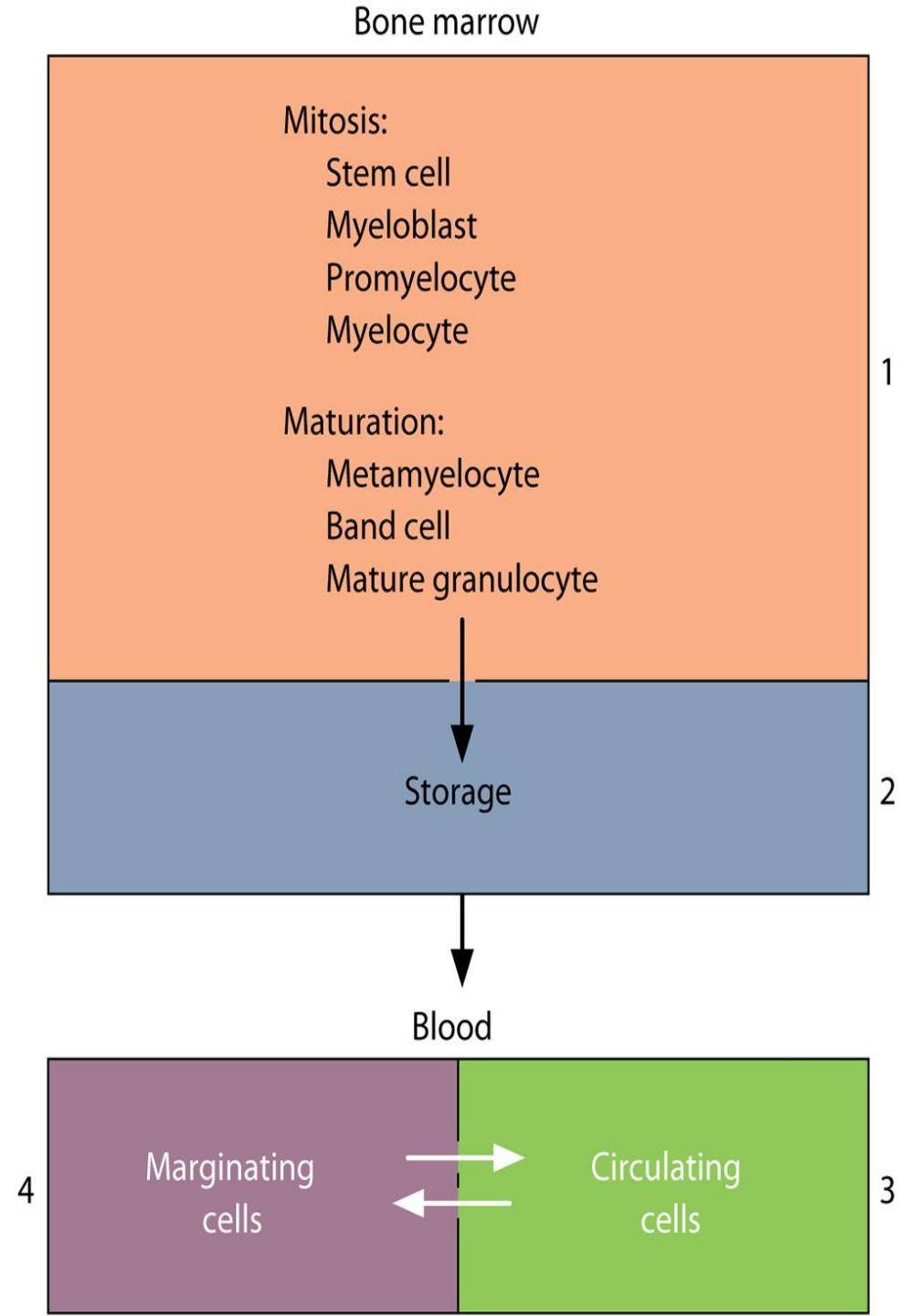
Developing and mature neutrophils exist in **four functionally and anatomically defined compartments:**

- (1) The granulopoietic compartment in active marrow
- (2) Storage as mature cells in marrow until release
- (3) The circulating population
- (4) A population undergoing margination



Margination is a process in which neutrophils adhere loosely and accumulate transiently along the endothelial surface in venules and small veins.

Note: Margination of neutrophils in some organs can persist for several hours and is not always followed by the cells' emigration from the microvasculature.



At sites of injury or infection, neutrophils and other granulocytes enter the connective tissues by migrating through intercellular junctions between endothelial cells of postcapillary venules in diapedesis.



Inflamed connective tissues thus form a fifth terminal compartment for neutrophils, where the cells reside for a few days and then die by apoptosis, regardless of whether they have performed their major function of bacterial phagocytosis.

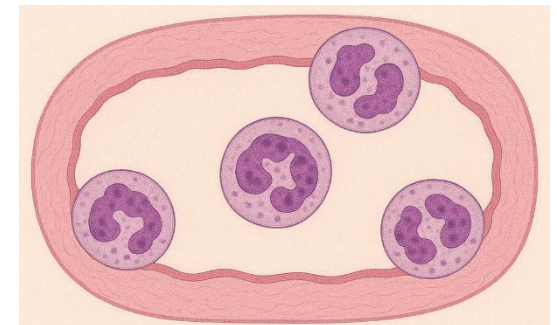
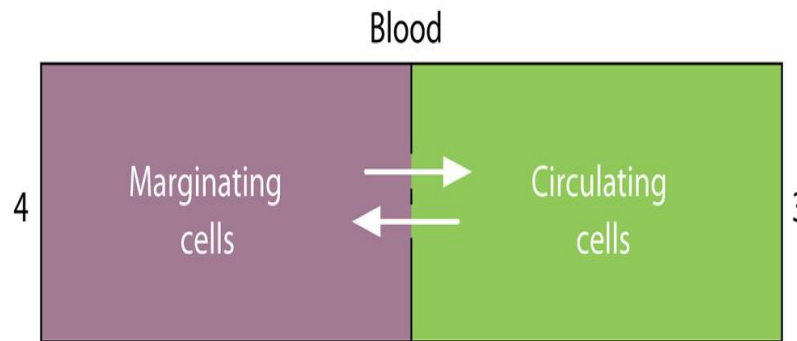
Changes in the number of neutrophils in the blood must be evaluated by taking all their compartments into consideration.

Thus, **neutrophilia** (an increase in the number of circulating neutrophils) does not necessarily imply an increase in granulopoiesis.

Intense muscular activity or the administration of epinephrine can cause neutrophils in the **marginating pool** to move into the **circulating pool**, producing transient neutrophilia without an increase in granulopoiesis.

Glucocorticoids, such as cortisol, also cause neutrophilia, primarily by promoting **demargination of neutrophils**, reducing their migration from the blood into tissues, and increasing their release from the bone marrow. Therefore, glucocorticoid-induced neutrophilia does not necessarily indicate increased granulopoiesis.

Epinephrine → rapid demargination → neutrophilia
Glucocorticoids → demargination + ↓ tissue migration
+ ↑ marrow release → neutrophilia
Infection/inflammation → ↑ granulopoiesis + ↑ marrow
release → neutrophilia (often with a left shift).



How many RBCs are in 1 ul of peripheral blood?

5 million/ul

How many WBCs are in 1 ul of peripheral blood?

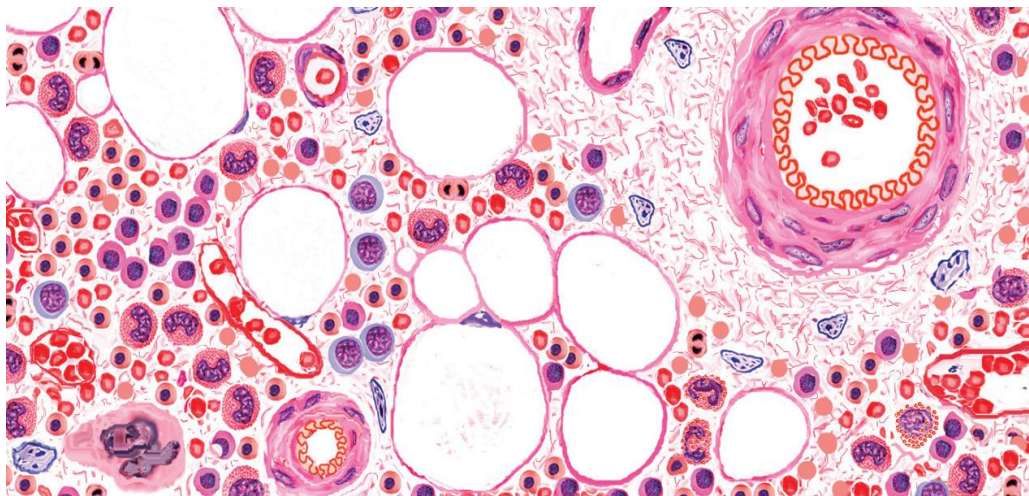
4500-11000/ul

But in the bone marrow (myeloid tissue)!!!

Myeloid: Erythroid

3:1

Remember the life span!!!!



White blood cell abnormalities

Increased numbers of white cells appear in the peripheral blood in a variety of disorders and provide a useful clue to the underlying disease.

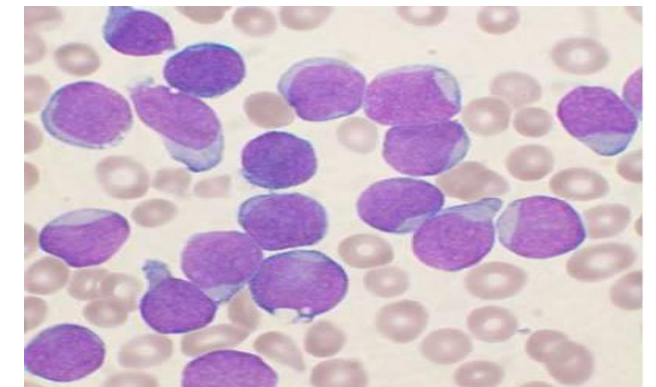
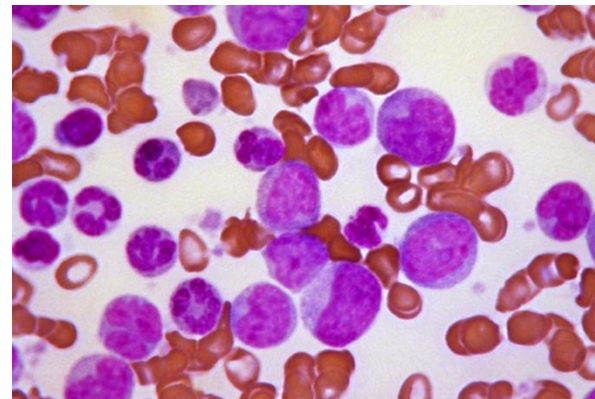
A considerable and sustained increase of circulating **neutrophils** in **bacterial infection**

An increase of circulating **eosinophils** in **parasitic infection and some allergies**

Leukemia is a malignant clonal proliferation of hematopoietic cells or their precursors, primarily involving the bone marrow.



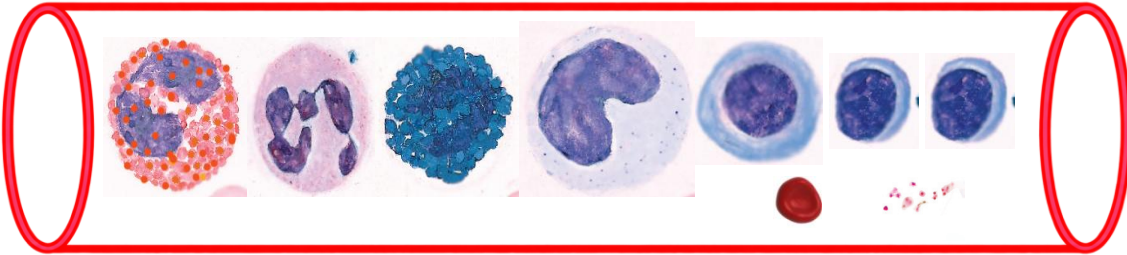
Abnormal leukemic cells proliferate in the bone marrow and may spill over into the peripheral blood.



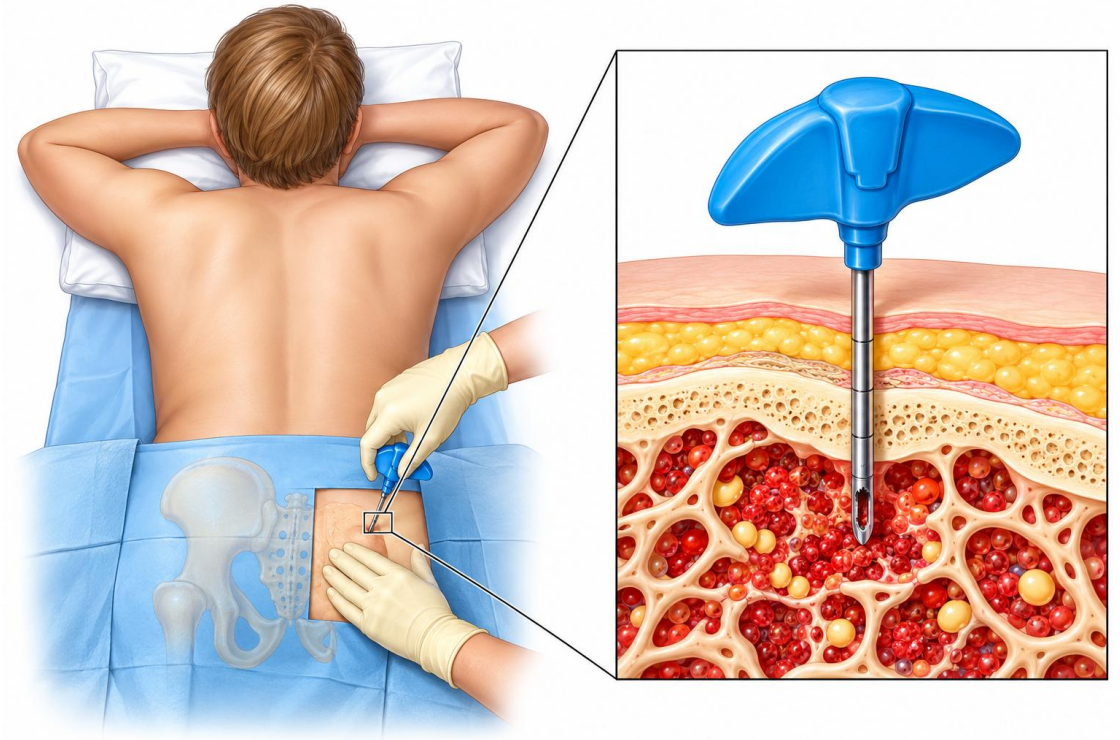
Stem cells
Progenitor cells
Precursor cells

Bone marrow

Peripheral blood



Blood film/ smear



Bone marrow Aspirate or biopsy

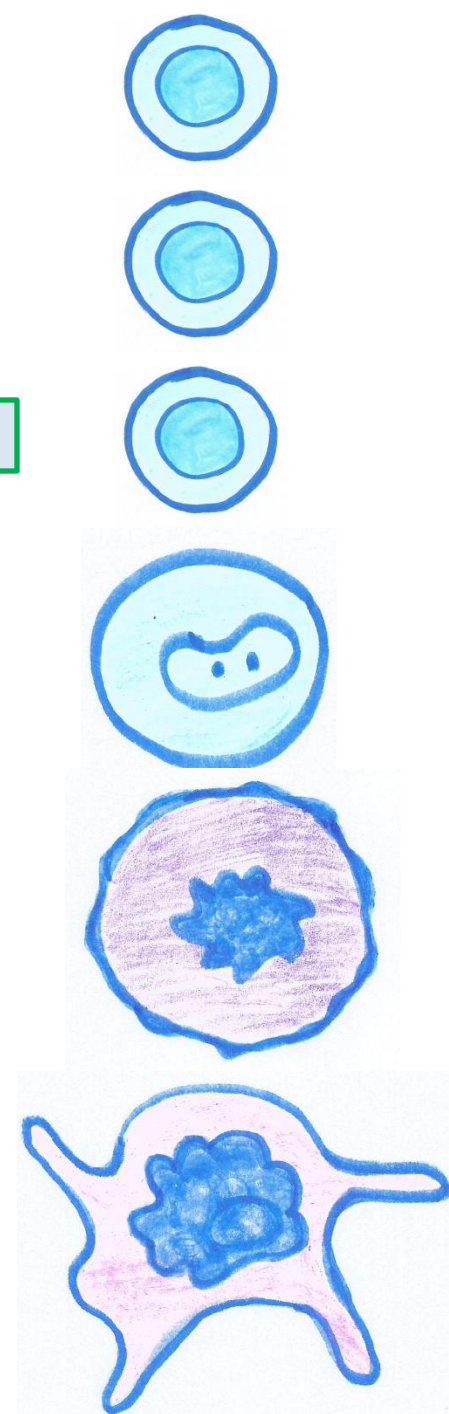
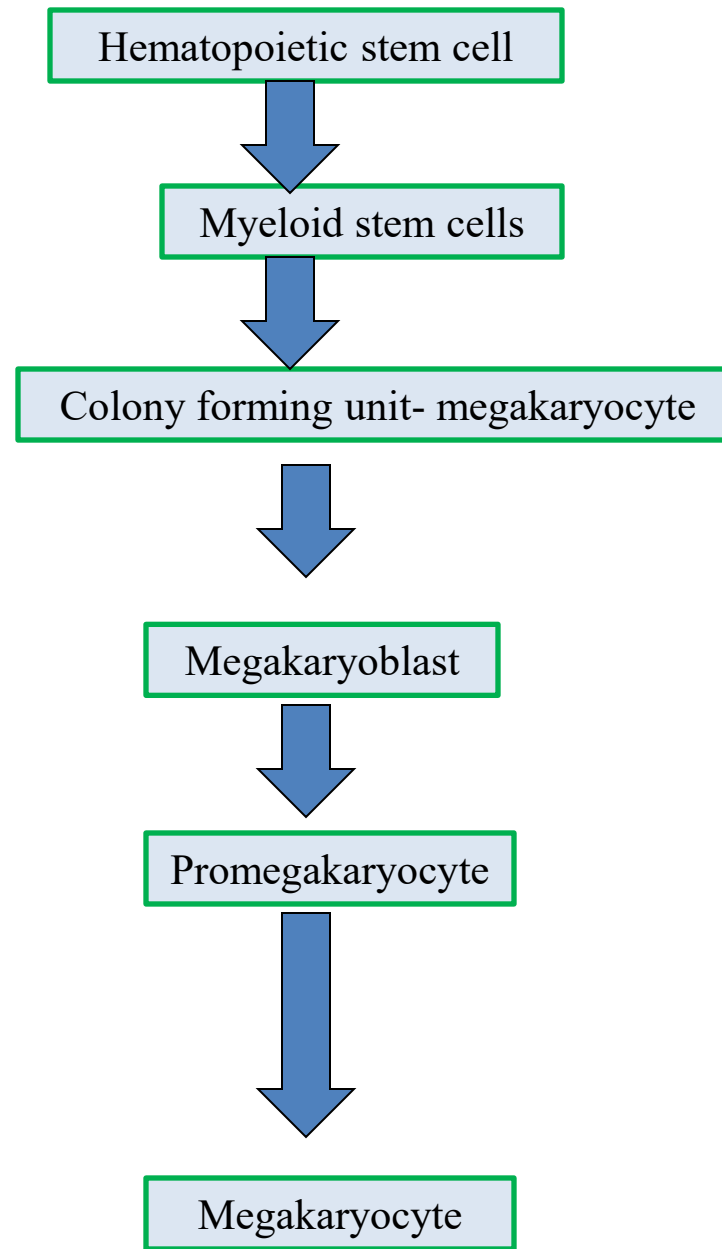
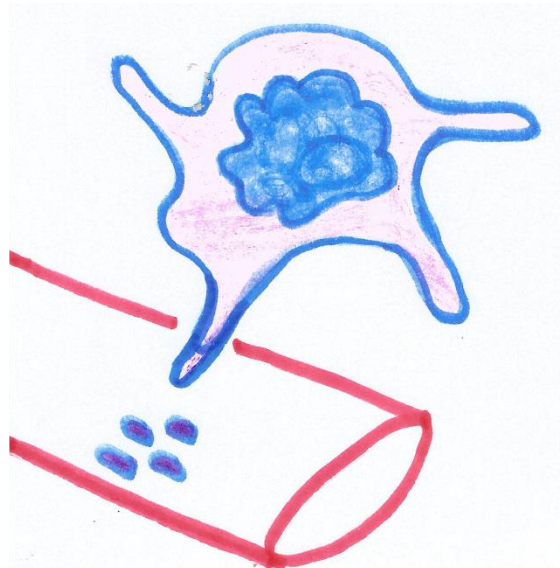
Used to diagnose bone marrow disorders such as aplastic anemia and leukemia.

Aspiration is best for examining individual marrow cells and their morphology, whereas core biopsy shows the marrow architecture and cellularity. In suspected aplastic anemia, the biopsy is particularly important because it demonstrates markedly hypocellular marrow.

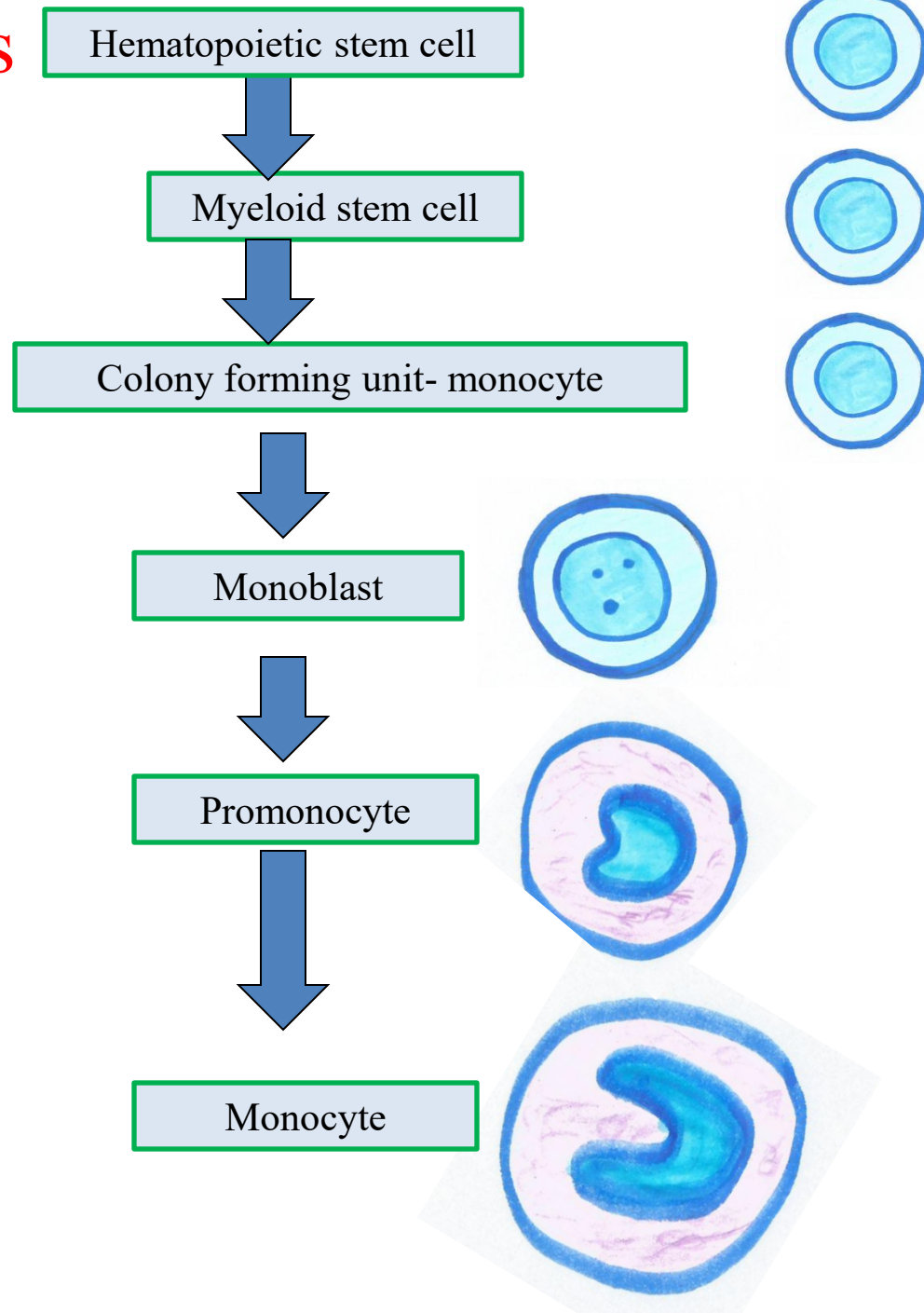
Bone marrow transplantation

Used to treat bone marrow and hematologic diseases, such as leukemia. Hematopoietic stem cells are infused intravenously to restore normal blood cell production after diseased or abnormal bone marrow has been eliminated or suppressed.

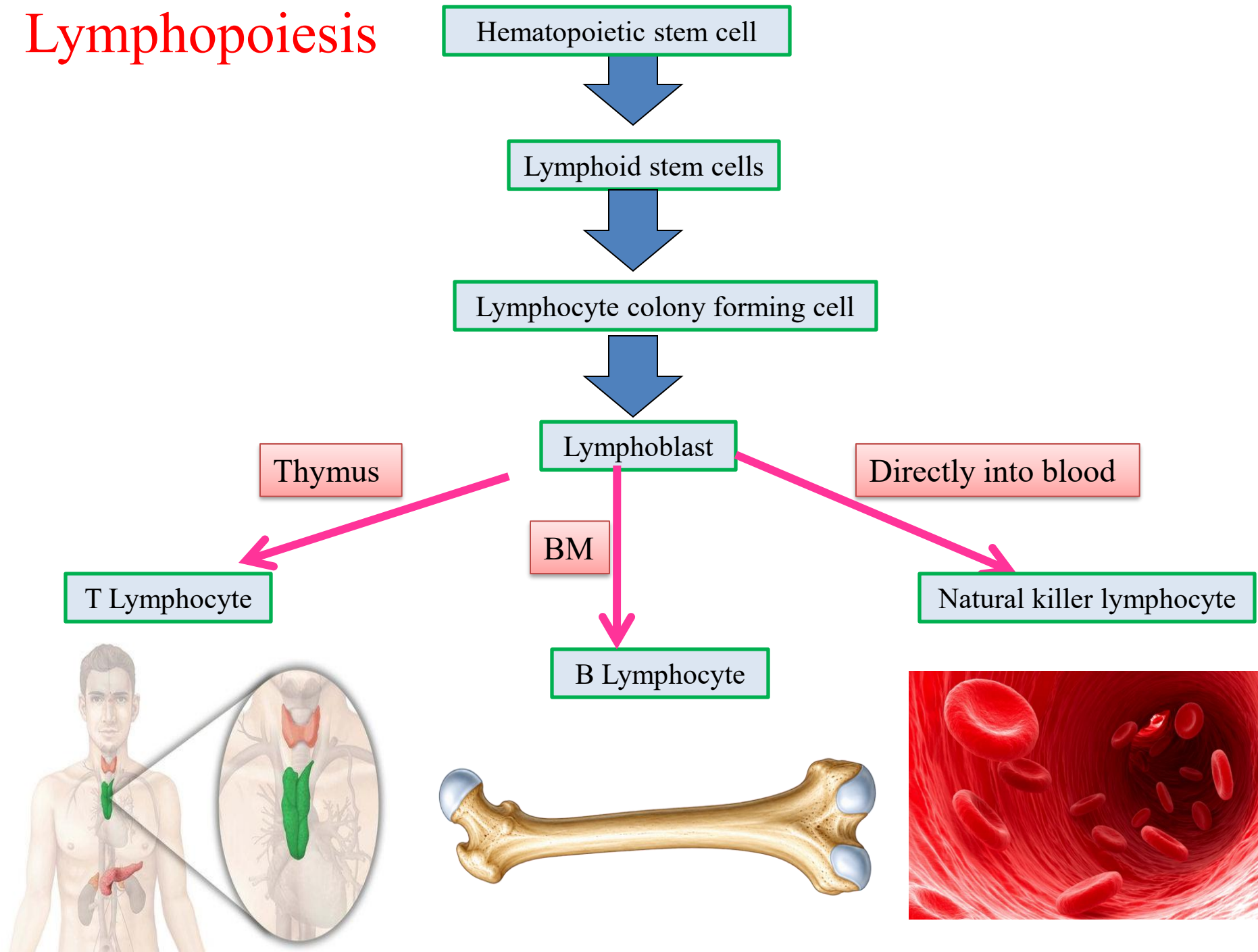
Thrombopoiesis

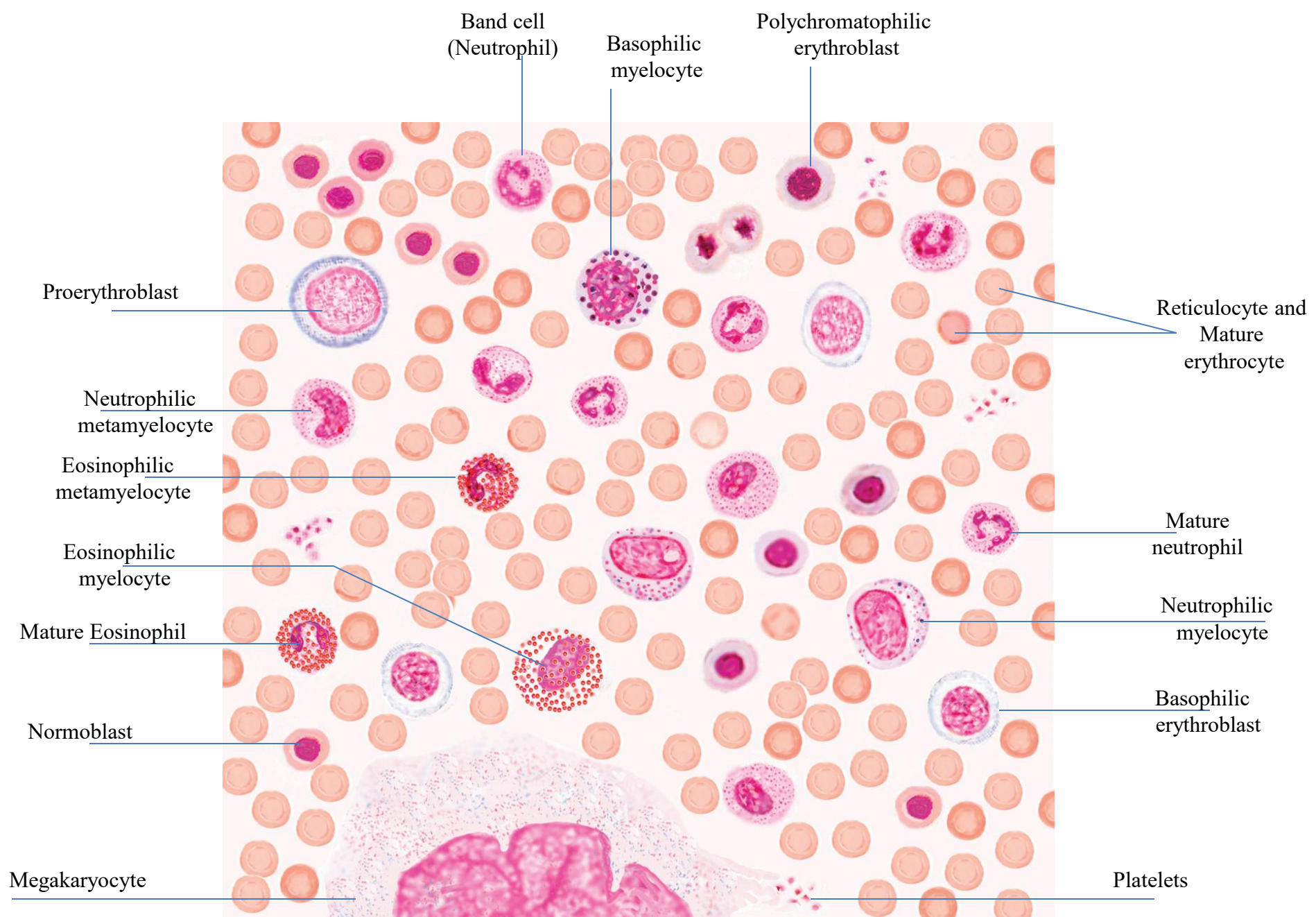


Monocytopoiesis

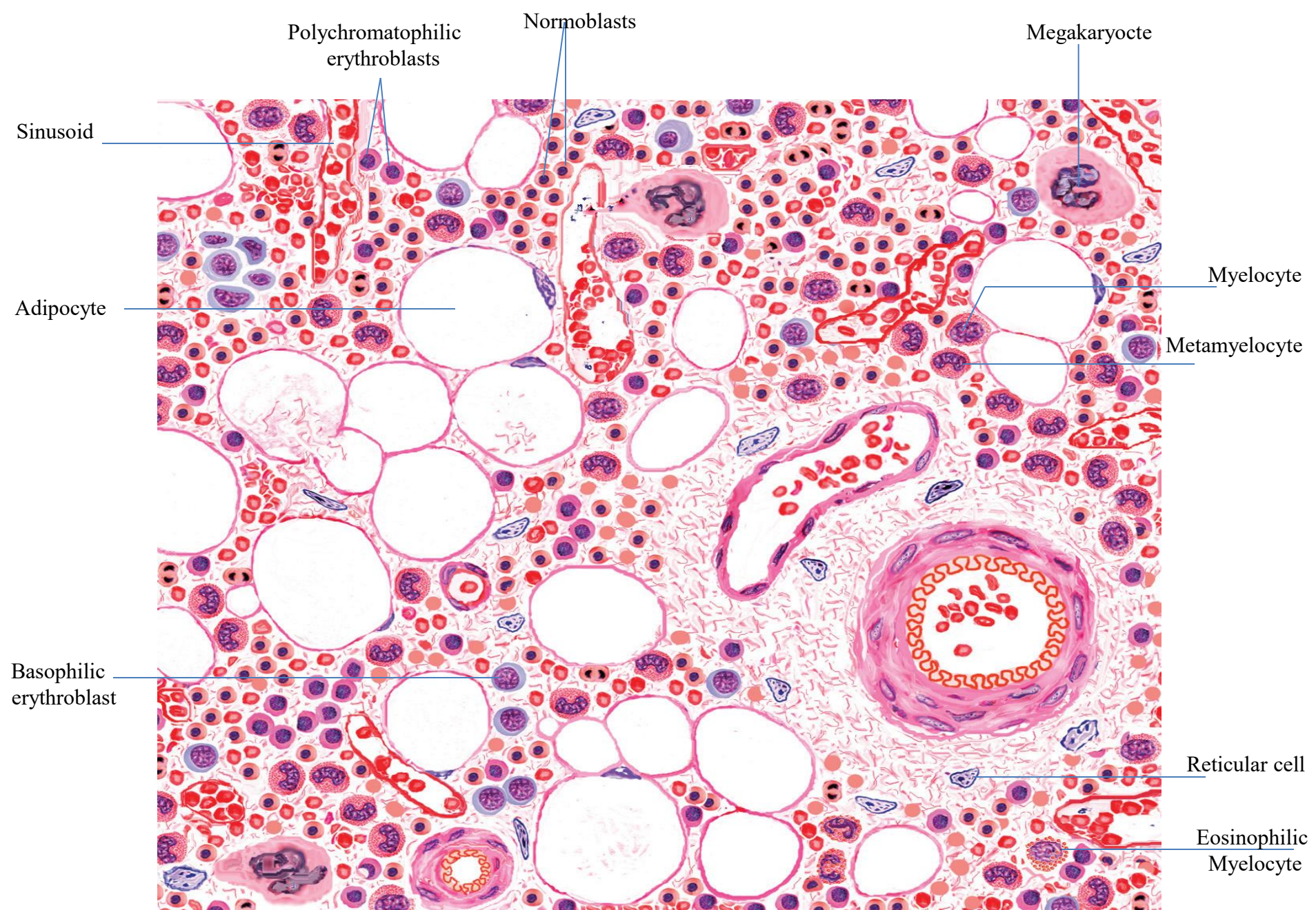


Lymphopoiesis





Bone marrow (Giemsa stain)



Bone marrow (H&E)

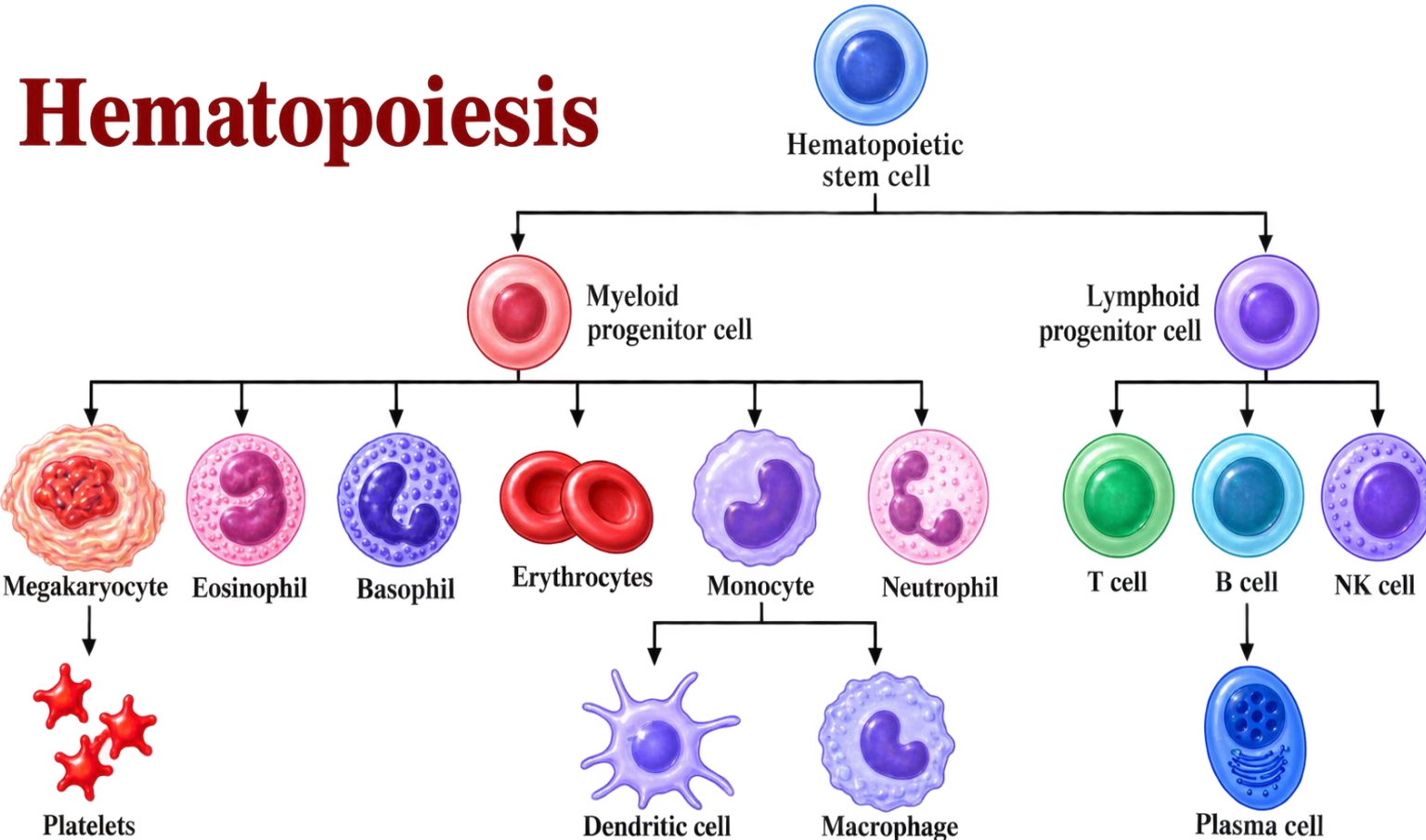
Hematopoietic Growth Factors

Hematopoietic growth factors are mainly glycoproteins that regulate hematopoiesis by stimulating the survival, proliferation, differentiation, and maturation of hematopoietic progenitor and precursor cells along specific blood cell lineages.

Important examples include:

- **Erythropoietin (EPO)** → promotes the erythroid lineage → **RBC production**
- **Thrombopoietin (TPO)** → promotes megakaryocyte development → **platelet production**
- **Granulocyte colony-stimulating factor (G-CSF)** → promotes neutrophil progenitor proliferation and differentiation → **neutrophil production**

Clinical Importance
Cloning the genes encoding hematopoietic growth factors has enabled their recombinant production for clinical use.



In which of the following cells involved in erythropoiesis does hemoglobin synthesis begin?

- a. Orthochromatic erythroblast
- b. Polychromatophilic erythroblast
- c. Reticulocyte
- d. Basophilic erythroblast

In which stage does hemoglobin accumulation become morphologically evident?

- a. Orthochromatic erythroblast
- b. Polychromatophilic erythroblast
- c. Reticulocyte
- d. Basophilic erythroblast
- e. Proerythroblast

Which of the following can be used to describe megakaryocytes?

- a. Multinucleated
- b. Formed by fusion of haploid cells
- c. Precursors to bone marrow macrophages
- d. A minor but normal formed element found in the circulation
- e. Possess dynamic cell projections from which one type of formed element is released

Which cytoplasmic components are the main constituents of the dark precipitate that forms in reticulocytes upon staining with the dye cresyl blue?

- a. Golgi complexes
- b. Hemoglobin
- c. Nucleoli
- d. Nuclear fragments
- e. Polyribosomes

Which process occurs during granulopoiesis but not during erythropoiesis?

- a. Cells lose their capacity for mitosis
- b. Euchromatin content increases
- c. Nucleus becomes increasingly lobulated
- d. Overall cell diameter decreases
- e. Overall nuclear diameter decreases

**What fate often awaits granulocytes that have entered the
marginating compartment?**

- a. Undergo mitosis
- b. Crossing the wall of a venule to enter connective tissue
- c. Cannot reenter the circulation
- d. Differentiate into functional macrophages
- e. Begin to release platelets

What is the earliest stage at which specific granulocyte types can be distinguished from one another?

- a. Myelocyte
- b. Band form
- c. Reticulocyte
- d. Metamyelocyte
- e. Promyelocyte

Which cell type is capable of further mitosis after leaving the hemopoietic organ in which it is formed?

- a. Basophil
- b. Eosinophil
- c. Reticulocyte
- d. Lymphocyte
- e. Neutrophil

Shortly after her birth a baby is diagnosed with a mutation in the erythropoietin receptor gene which leads to familial erythrocytosis (familial polycythemia). During the seventh to ninth months of fetal development, the primary effect on her red blood cell production was in which of the following?

- a. Liver
- b. Yolk sac
- c. Spleen
- d. Thymus
- e. Bone marrow

A 54-year-old man presents with recurrent breathlessness and chronic fatigue. After routine tests followed by a bone marrow biopsy he is diagnosed with lymphocytic leukemia.

Chemotherapy is administered to remove the cancerous cells, which also destroys the precursor cells of erythrocytes. To reestablish the erythrocytic lineage, which of the following cells should be transplanted?

- A. Reticulocytes
- B. Orthochromatophilic erythroblasts
- C. Megakaryoblasts
- D. Basophilic erythroblasts
- E. Metamyelocytes
- F. Hematopoietic stem cells

A smear of blood from a 70-year-old leukemia patient reveals a larger than normal population of cells that have large, round nuclei with 1 or 2 nucleoli. The cytoplasm of these cells shows azurophilic granules. Which of the following forms of leukemia would you suspect?

- a. Promyelocytic leukemia
- b. Basophilic leukemia
- c. Lymphoblastic leukemia
- d. Stem cell leukemia
- e. Eosinophilic leukemia