Hematopoiesis

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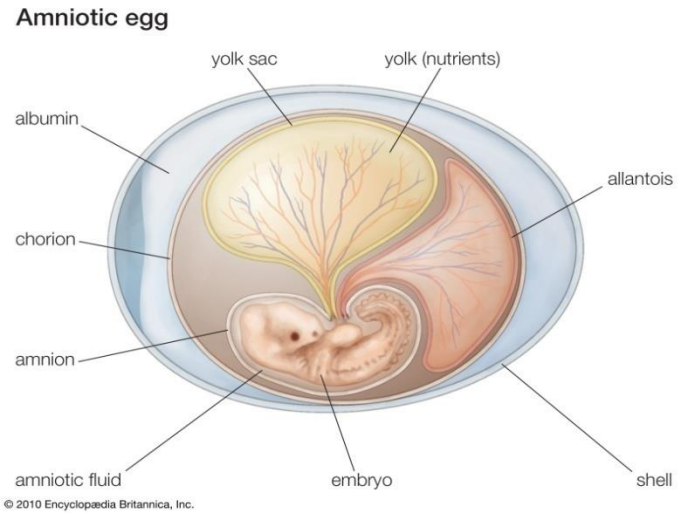
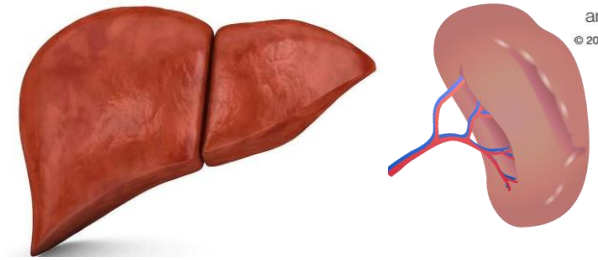
Blood Cell Formation (Hematopoiesis)

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

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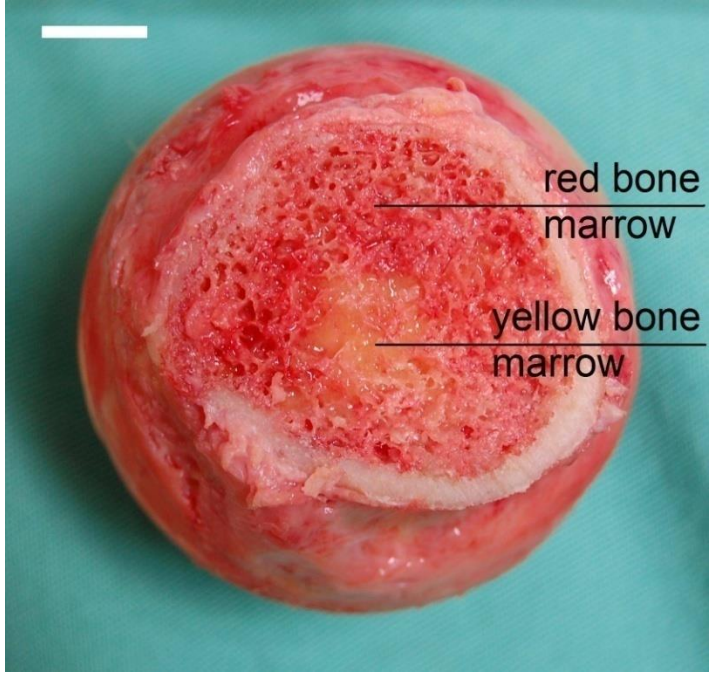
Bone marrow

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

It consists of:

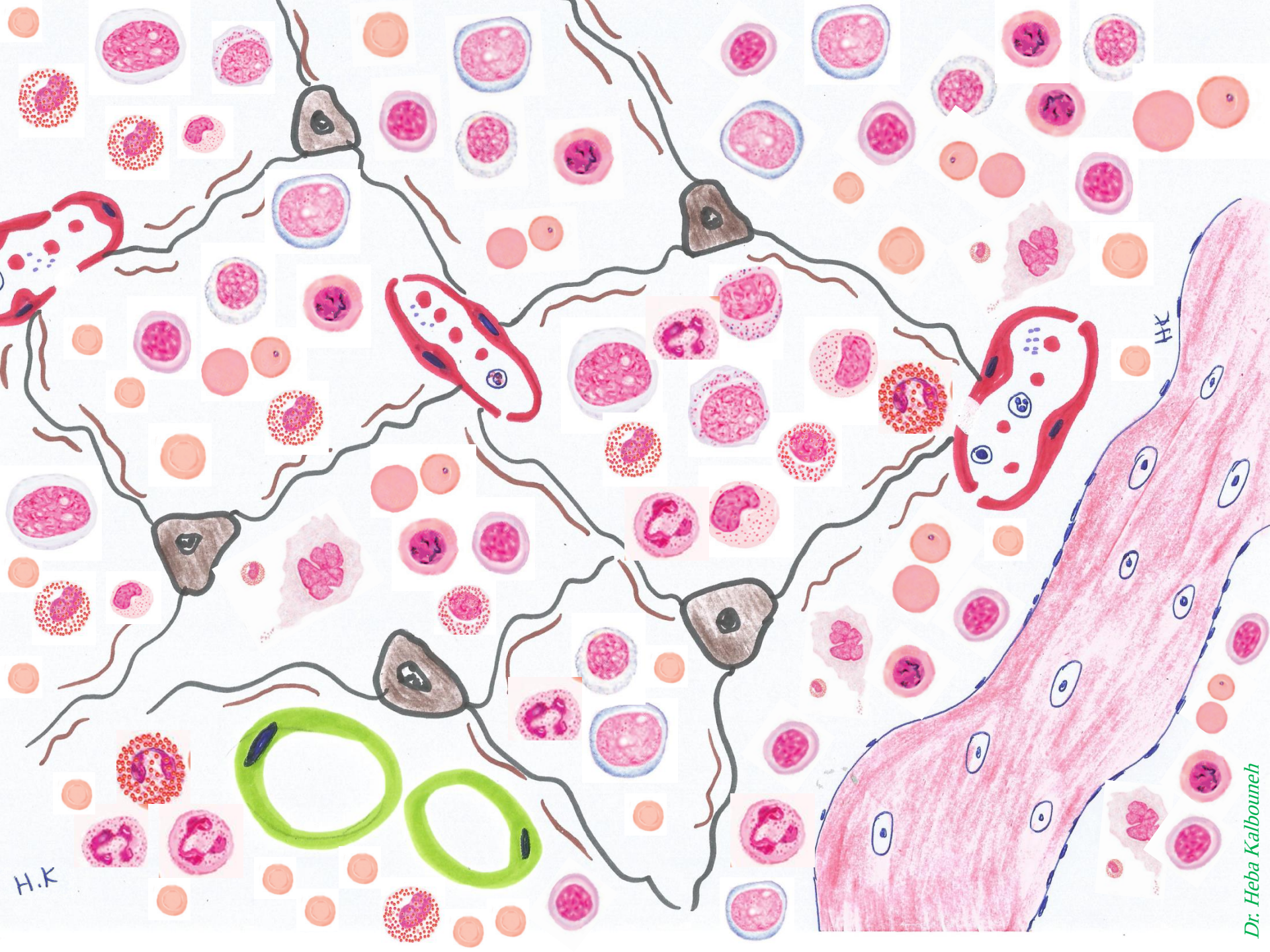
Hemopoietic stem cells (the origin of different blood cells) surrounded by numerous macrophages and sinusoidal capillaries and supported by a reticular tissue.



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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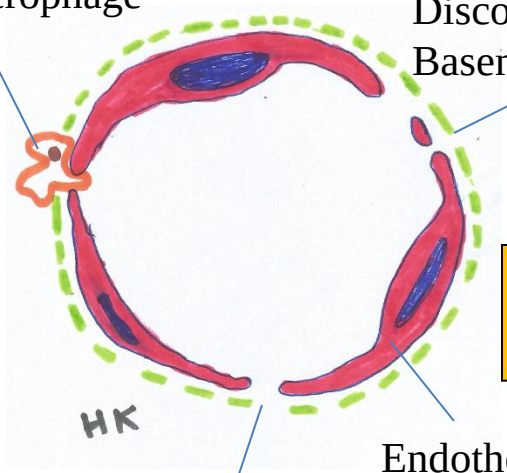
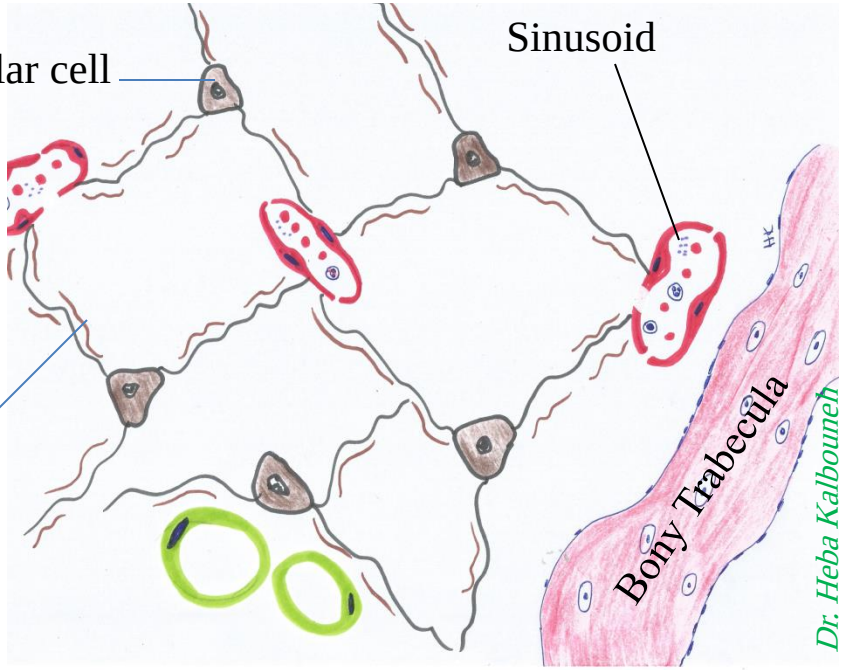


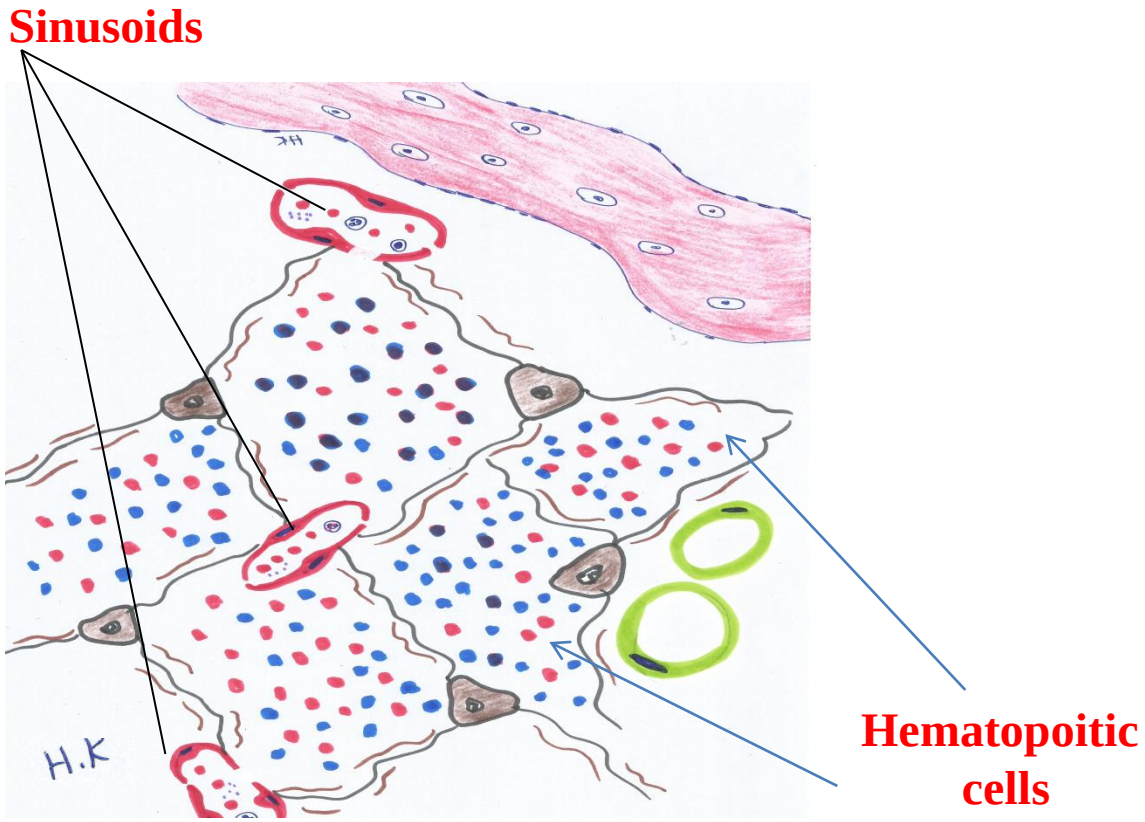
Sinusoidal capillary

Continuous capillary

Reticular tissue forming the stroma of the bone marrow

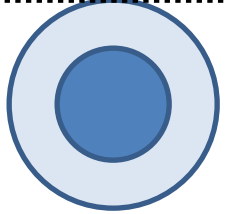


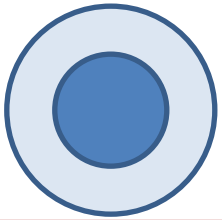
Between the hematopoitetic cells run the **sinusoids,** which have discontinuous endothelium, through which newly differentiated blood cells and platelets enter the circulation



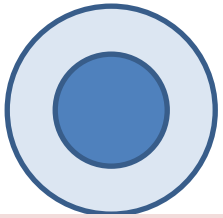
Red marrow is also a site where older, defective erythrocytes undergo phagocytosis by macrophages, which then reprocess heme-bound iron for delivery to the differentiating erythrocytes.

Hematopoietic stem cell
(Pluripotent)



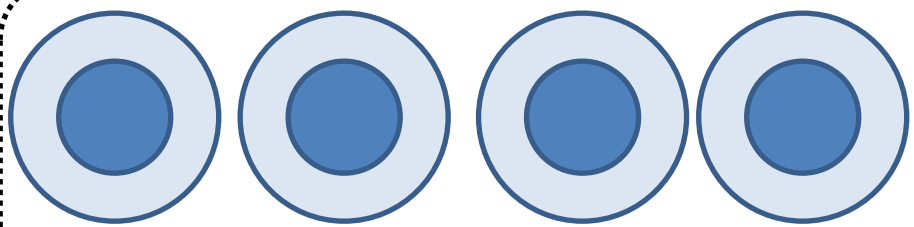


Stem cells



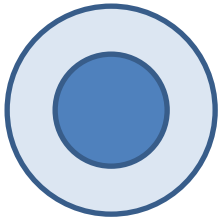
Myeloid stem cell
(Multipotent) **GEMM**

Lymphoid stem cell
(Multipotent)



Progenitor cells

(Commited, unipotent stem cells)



CFU-E

CFU-M

CFU-G

CFU-M

CFU-Ls

Erythroblast

Megakaryoblast

Myeloblast

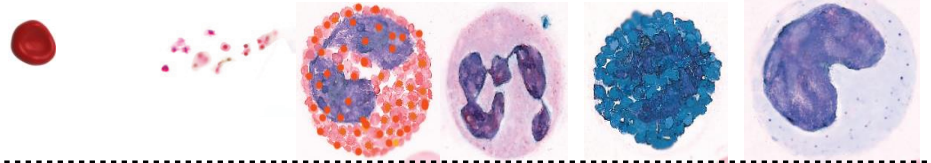
Monoblast

Precursor cells

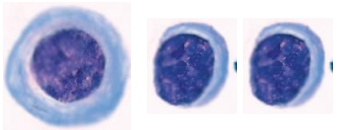
NK Lymphoblast

B Lymphoblast

T Lymphoblast

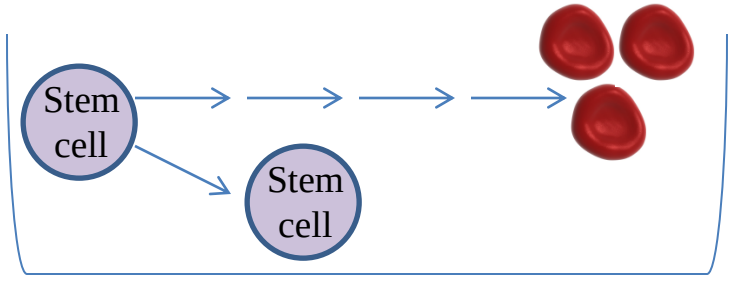


Mature cells



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

Stem cells can maintain the original population



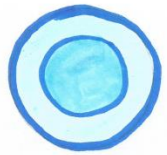
Every time the stem cell multiplies, it will give two cells, one differentiates into mature RBCs and the other cell adds to the original population

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

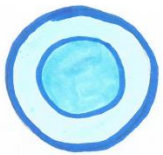
Hematopoietic pluripotent stem cells



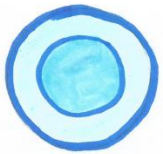
Note:

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

Myeloid stem cells

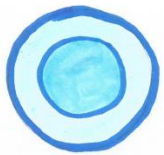


Lymphoid stem cells



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

Pluripotent hematopoietic stem cells

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

It proliferates and forms two major cell linages

Myeloid stem cells

Progenitor and precursor cells

Granulocytes
-Neutrophils
-Basophils
-Eosinophils
Erythrocytes
Megakaryocytes
Monocytes

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

Lymphoid stem cells

Progenitor and precursor cells

T lymphocyte
B lymphocyte
Natural killer cells

Pluripotent hematopoietic stem cells

Myeloid stem cells

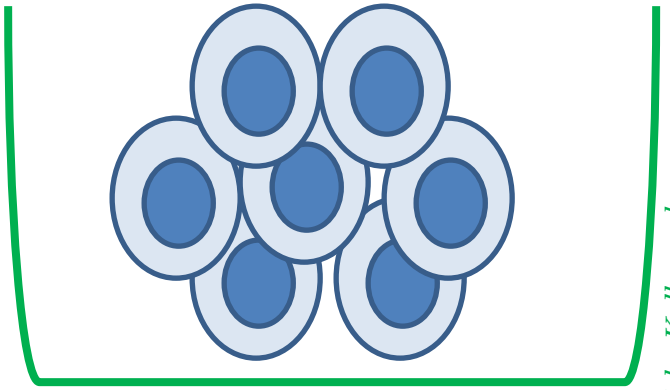
Progenitor cells/ CFUs

- CFU Erythrocyte **CFU-E**
- CFU Granulocyte-Monocyte **CFU-GM**
  - CFU Monocyte **CFU-M**
  - CFU Granulocyte **CFU-G**
- CFU Megakaryocyte **CFU-M**

Lymphoid stem cells

- CFU Lymphocytes **CFU-Ls**

The progenitor cells for blood cells are often called **colony-forming units** (CFUs), because they give rise to colonies of only one cell type when cultured in vitro or injected into a spleen.



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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

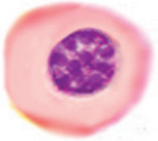
Erythropoiesis: the process which produces erythrocytes
Granulopoiesis: the process which produces granulocytes
Thrombopoiesis: the process which produces thrombocytes
Lymphopoiesis: the process which produces lymphocytes
Monocytopoiesis: the process which produces monocytes

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

Proerythroblast

Basophilic erythroblast

Polychromatophilic erythroblast



Normoblast

Reticulocyte

Erythrocyte

Nuclear maturation

Cytoplasmic maturation

Erythropoiesis (red cell formation)

✓ Takes about 1 week

✓ Rate is controled by the hormone erythropoietin (secreted by the kidney cells) and the availability of iron, folic acid, vitamen 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

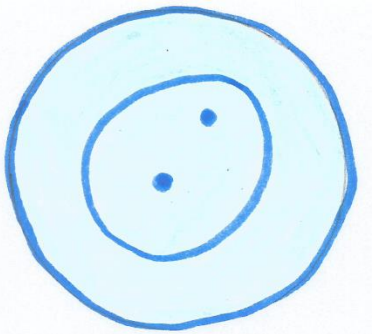
⇩

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

3- Progressive increase in hemoglobin content

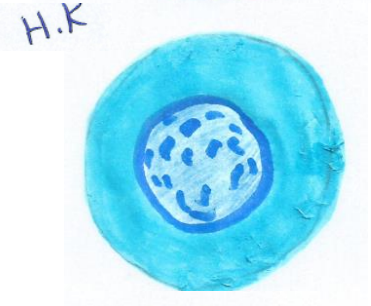
⇩

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 (Acidophilic erythroblast!!!)

- ✓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

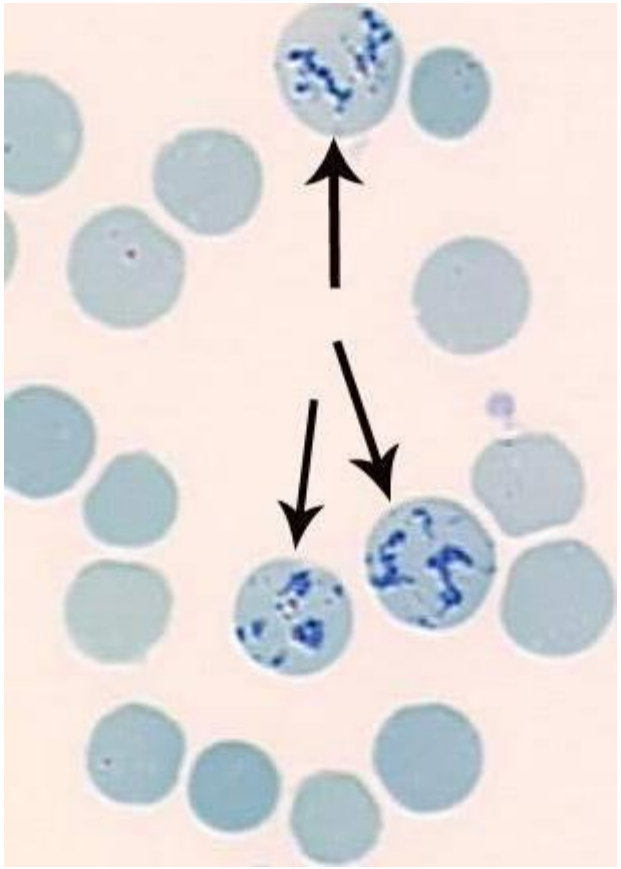
- ✓Immature erythrocyte but slightly larger (9um)
- ✓No nucleus
- ✓Cytoplasm is acidophilic (Hb) but contains remnants of ribosomes forming reticulum
- ✓Can be stained by supravital stains (brilliant cresyl blue)

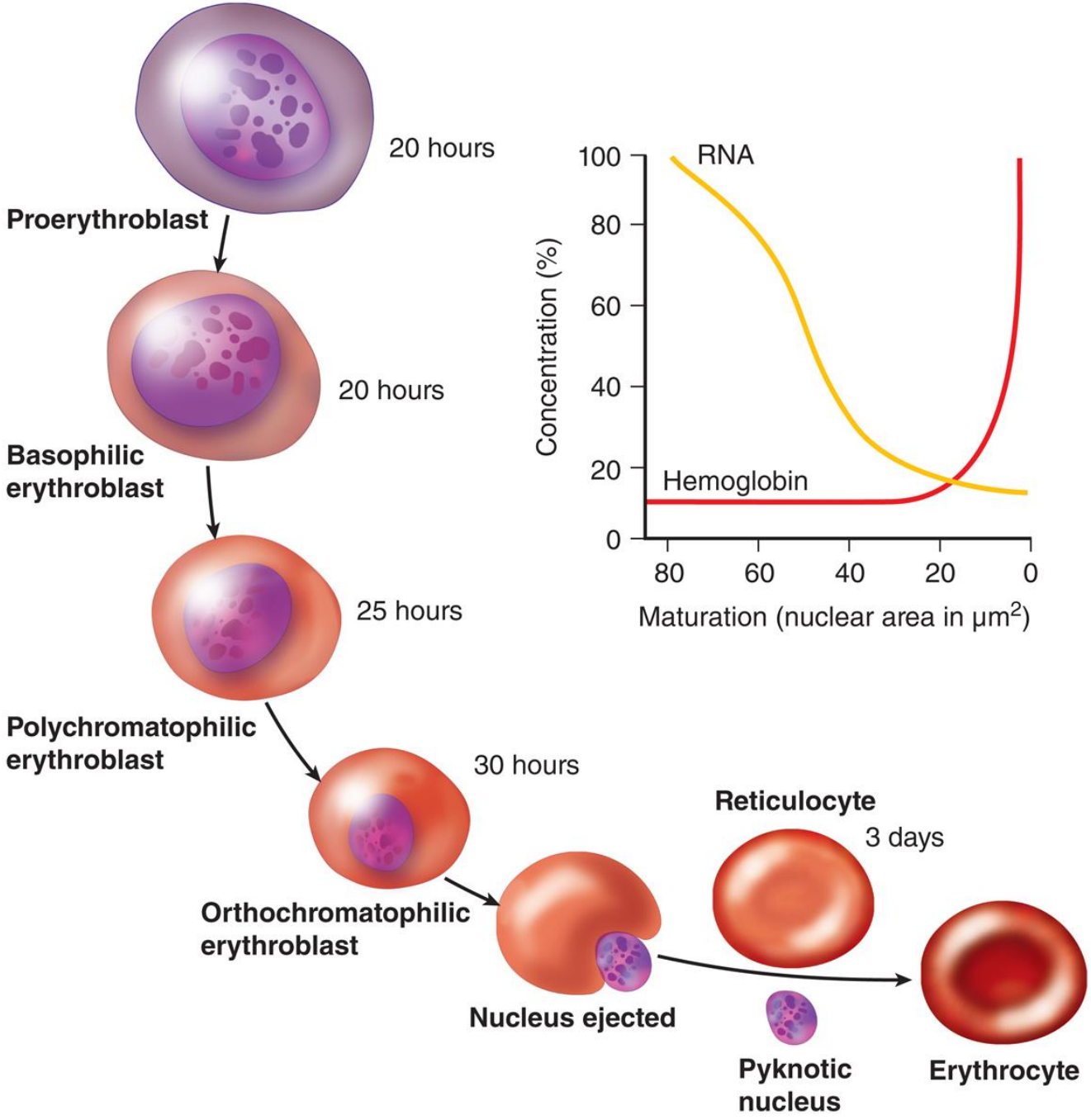
Erythrocyte

Reticulocytes

- Are immature red blood cells (last stage)
- The cell has extruded its nucleus, but is still capable of producing hemoglobin
- 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)

Very important




20 hours
Proerythroblast
20 hours
Basophilic erythroblast
25 hours
Polychromatophilic erythroblast
30 hours
Orthochromatophilic erythroblast
Nucleus ejected
Reticulocyte
3 days
Pyknotic nucleus
Erythrocyte
RNA
Hemoglobin
Concentration (%)
100
80
60
40
20
0
80
60
40
20
0
Maturation (nuclear area in μm²)

Granulopoiesis (Neutrophils, Eosinophils and Basophils formation)

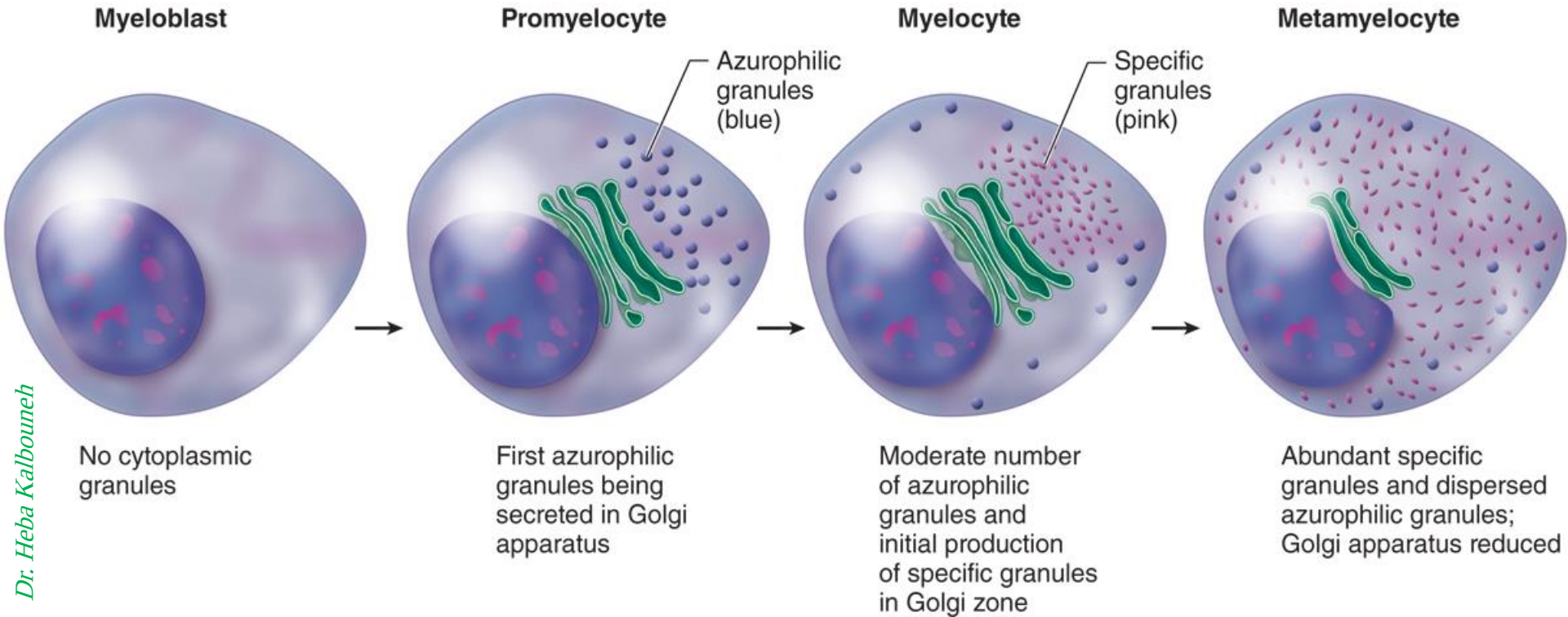
✓ Takes about 2 weeks

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



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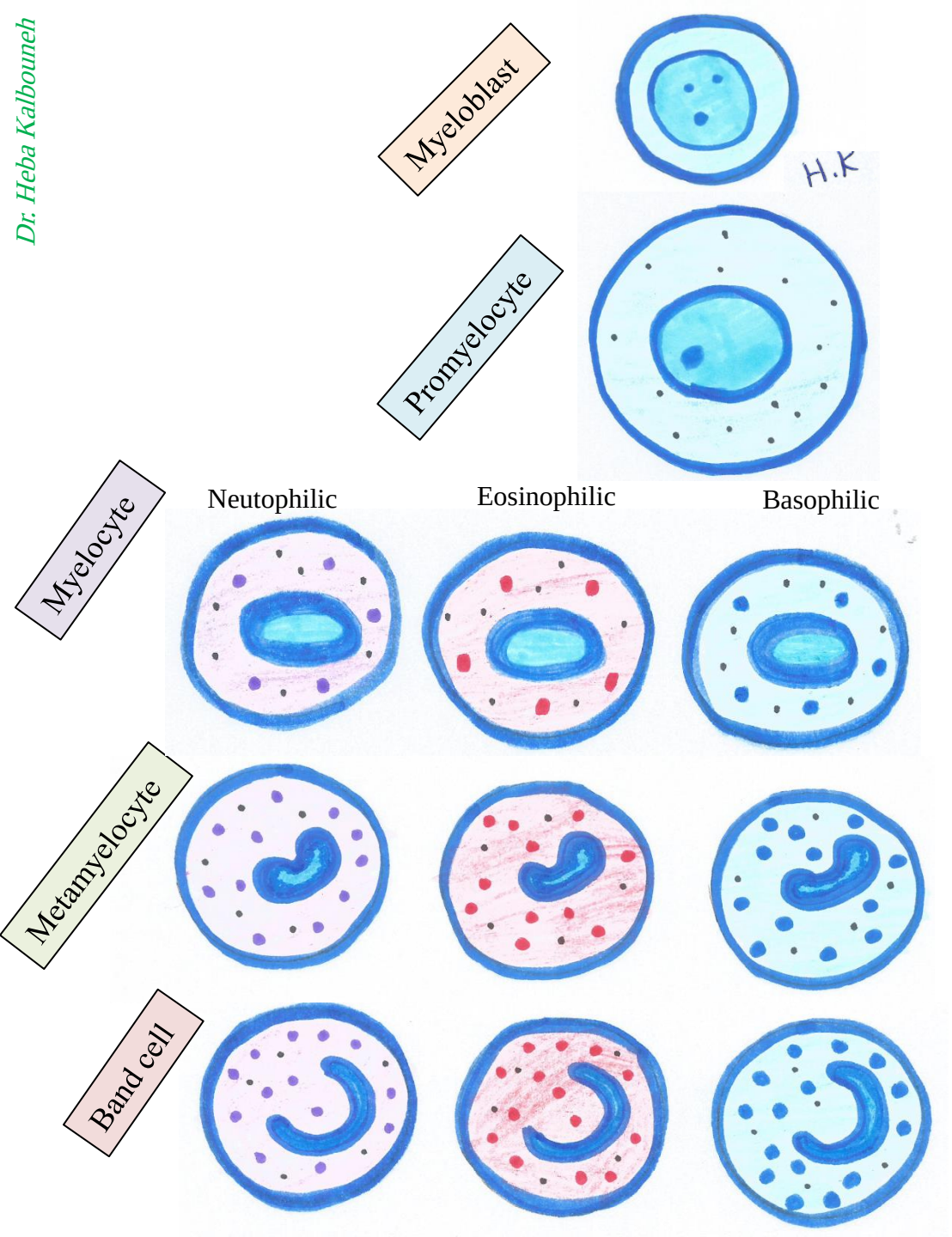


Myeloblast

✓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)

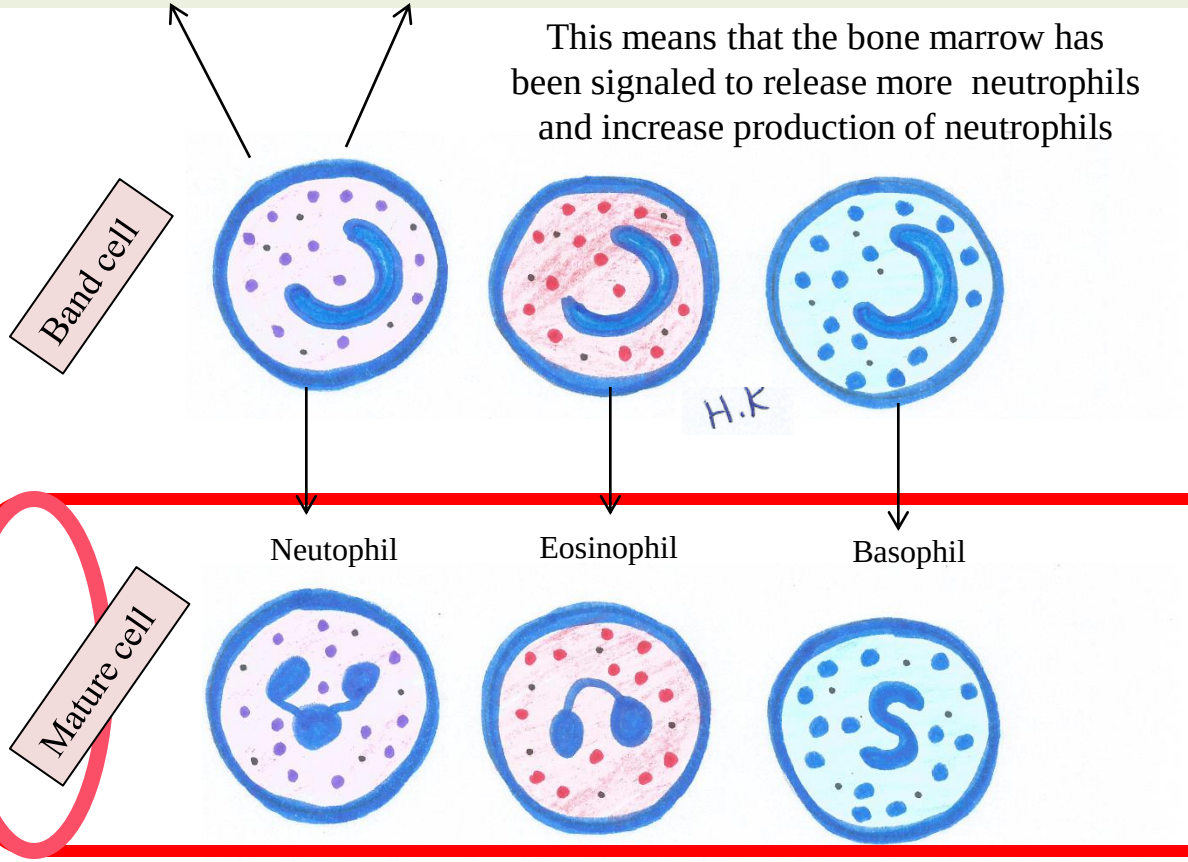
✓3 types
✓Nucleus becomes curved rod in shape

Neutrophilic band cells (important)

Their percentage does not exceed 5% in peripheral blood

The appearance of large numbers of immature neutrophils (band cells) in the blood, sometimes called a "shift to the left," is clinically significant, usually indicating **a bacterial infection**.

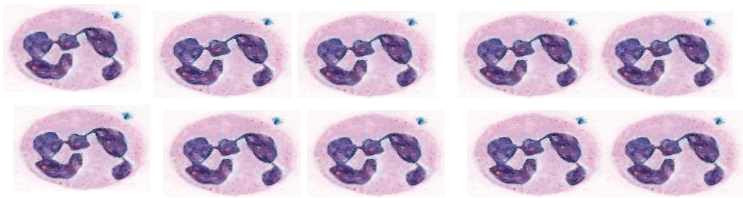
This means that the bone marrow has been signaled to release more neutrophils and increase production of neutrophils

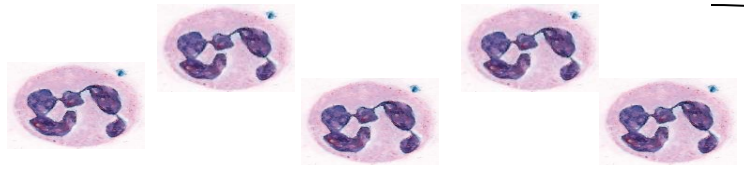


Band cell is almost a mature neutrophil, just doesn't have a segmented nucleus yet

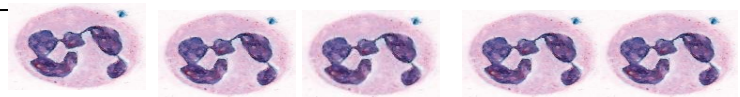
Bone marrow pool

Myeloblast
Promyeloctye
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.

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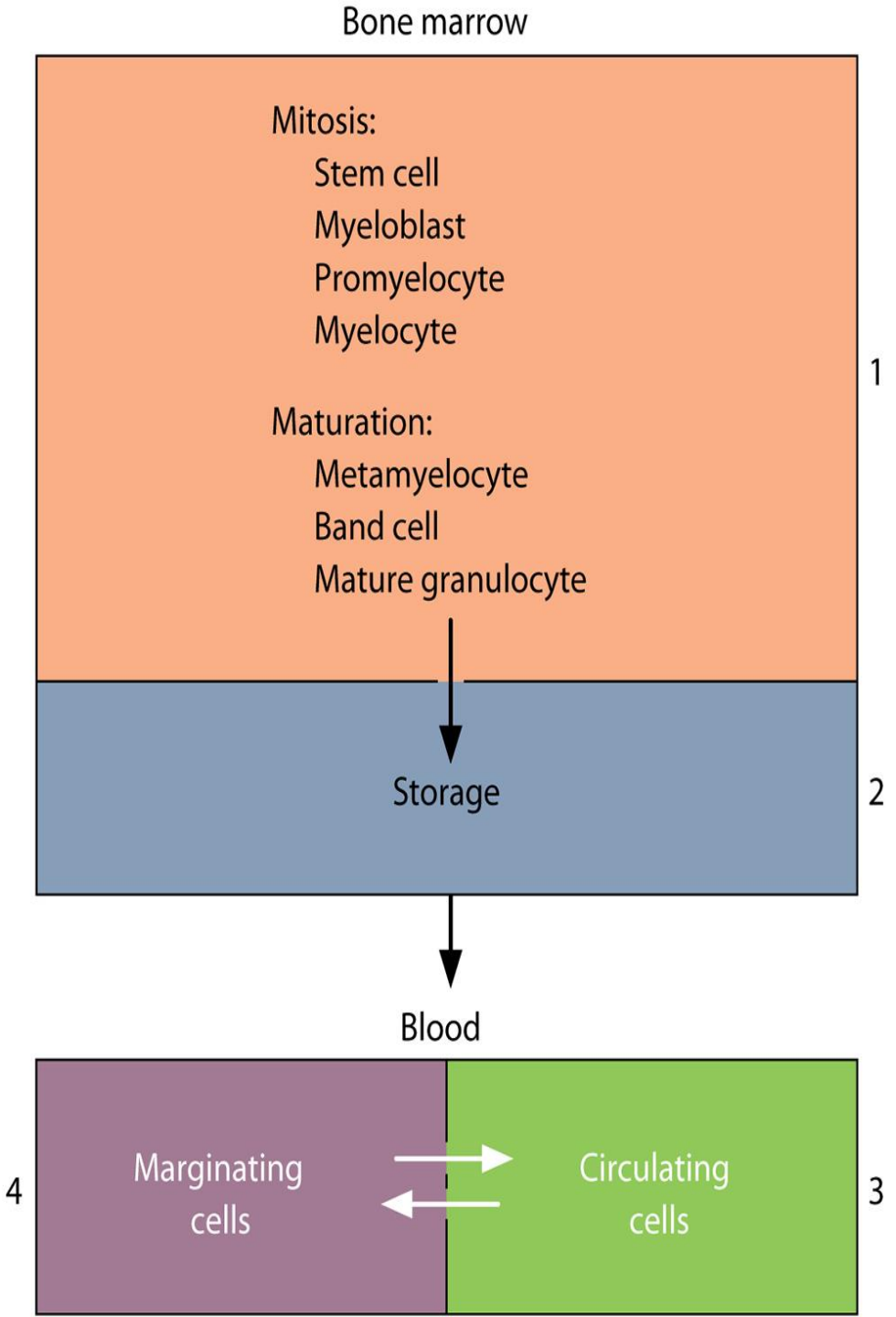


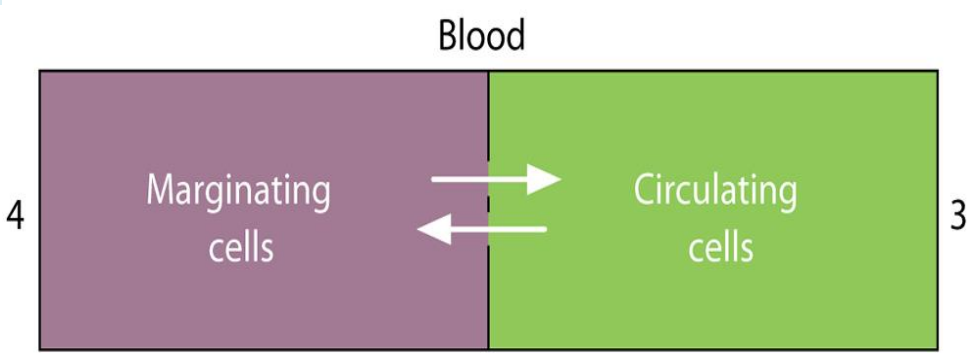
At sites of injury or infection, neutrophils and other granulocytes enter the connective tissues by migrating through intercellular junctions between endothelial cells of postcapillary venules in diapedesis.

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 compartment to move into the circulating compartment, producing neutrophilia even though granulopoiesis has not increased. However, glucocorticoids (adrenal hormones) such as cortisone increase the mitotic activity of neutrophil precursors and this also increases the blood count of neutrophils.



How many RBCs are in 1 ul of peripheral blood?

5 million/ul

How many WBCs are in 1 ul of peripheral blood?

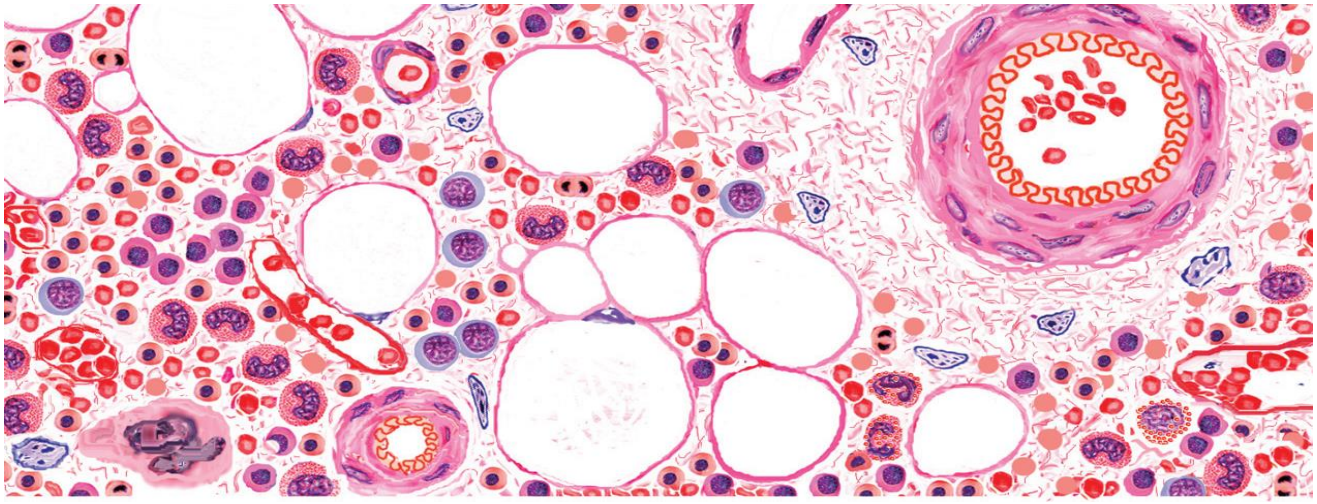
4500-11000/ul

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

Myeloid: Erythroid

3:1

Remember the life span!!!!!



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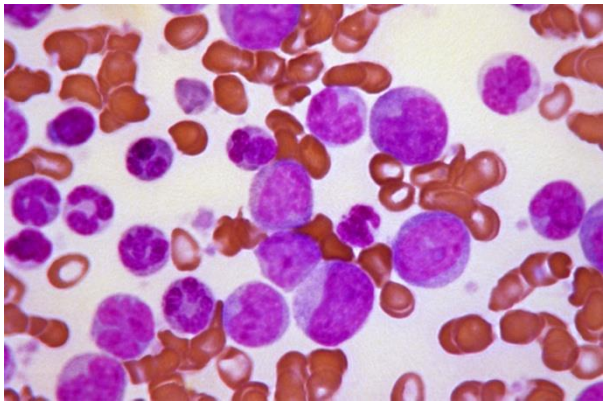
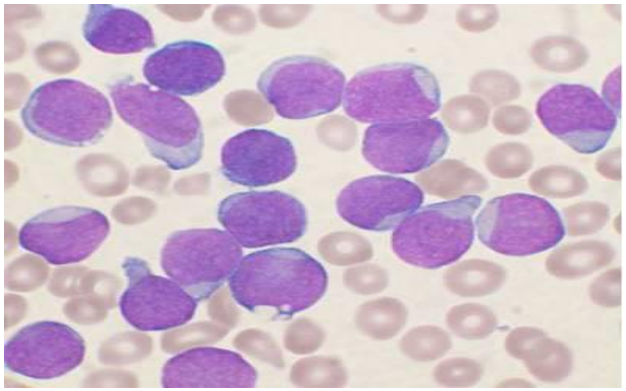
White blood cell abnormalities

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 proliferation of white cell precursors in the bone marrow

Vast number of white cells and their precursors (many of which spell over into the blood)

Leukemia is classified according to the cell line involved (granulocytic, monocytic, lymphocytic)

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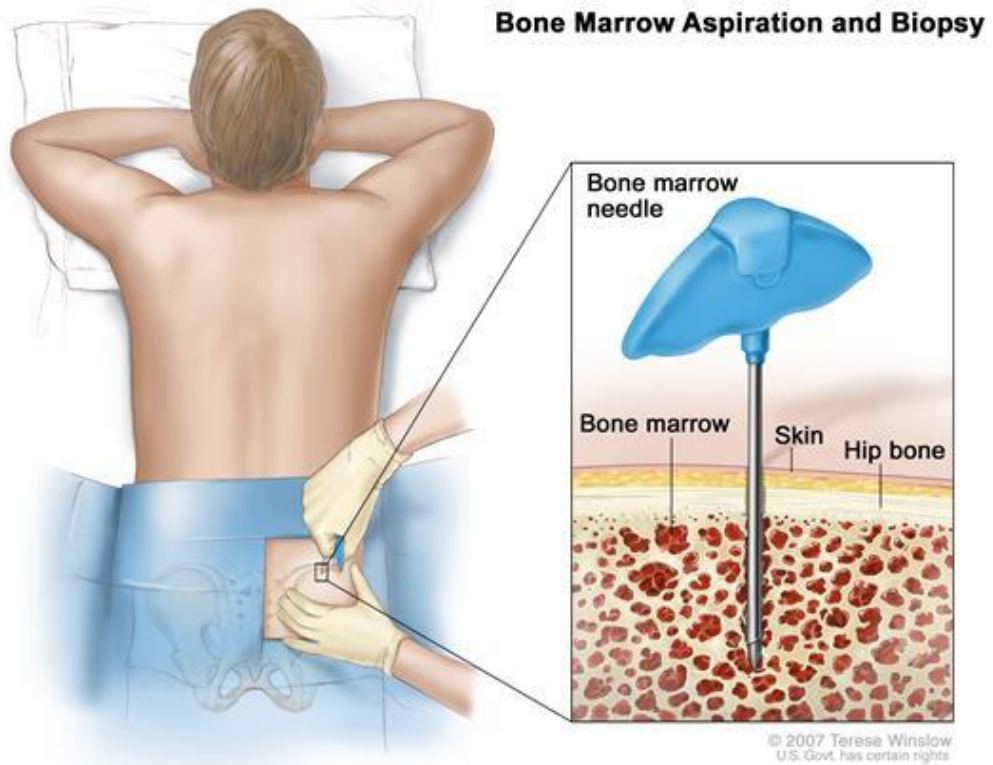
Bone marrow Apirate or biobsy
Needed to diagnose disorders like aplastic anemia or leukemia



Bone marrow transplantation
In bone marrow diseases like leukemia, hematopoietic stem cells taken from a donor are infused into the same or another person

Thrombopoiesis

Hematopoietic pluripotent stem cell

↓

Myeloid stem cell

↓

Colony forming unit- megakaryocyte

↓

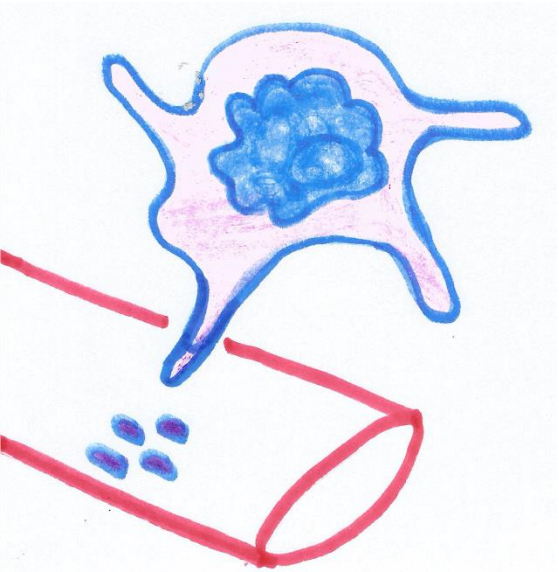
Megakaryoblast

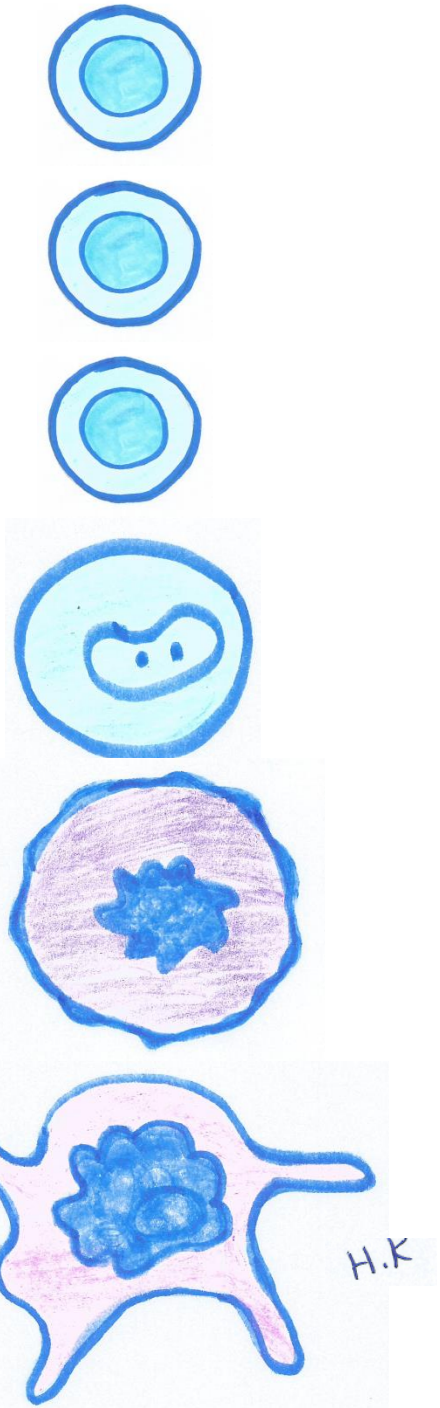
↓

Promegakaryocyte

↓

Megakaryocyte





Monocytopoiesis

Hematopoietic pluripotent stem cell

↓

Myeloid stem cell

↓

Colony forming unit- monocyte

↓

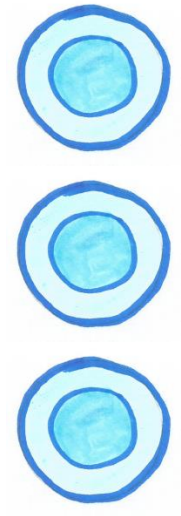
Monoblast

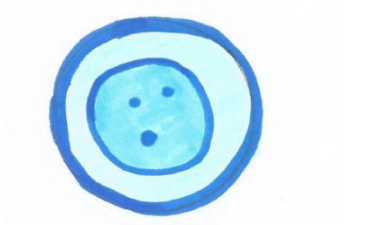
↓

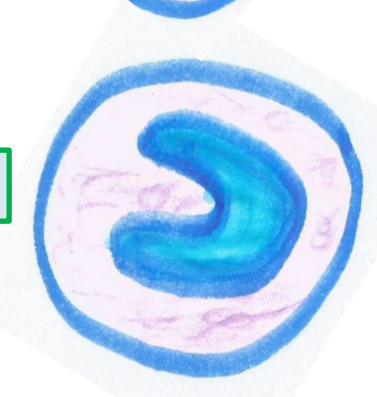
Promonocyte

↓

Monocyte







Lymphopoiesis

Hematopoietic pluripotent stem cell

Lymphoid stem cell

Extra note: some consider this progenitor cell as multipotent While some consider that we have 2 or 3 different progenitor cells

Lymphocyte colony forming cell

NK Lymphoblast
T Lymphoblast
B Lymphoblast

Thymus

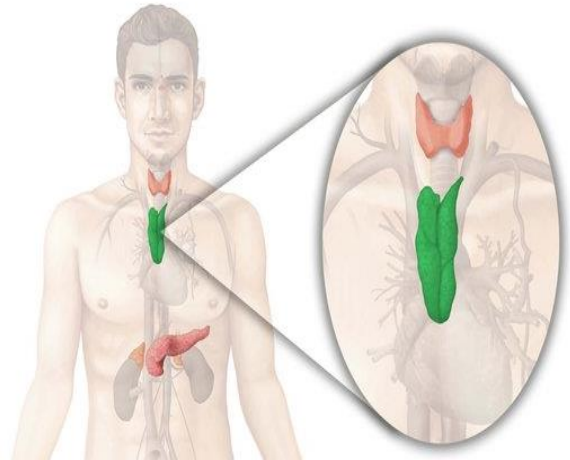
Directly into blood

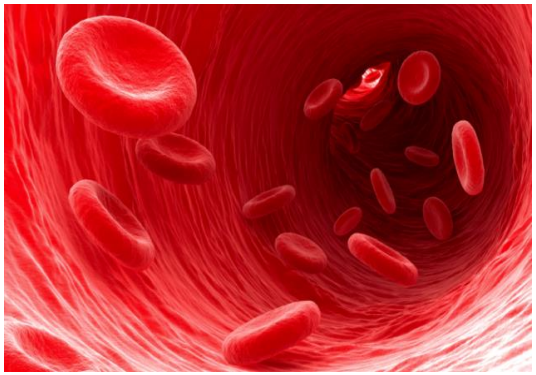
T Lymphocyte

BM

Natural killer lymphocyte

B Lymphocyte





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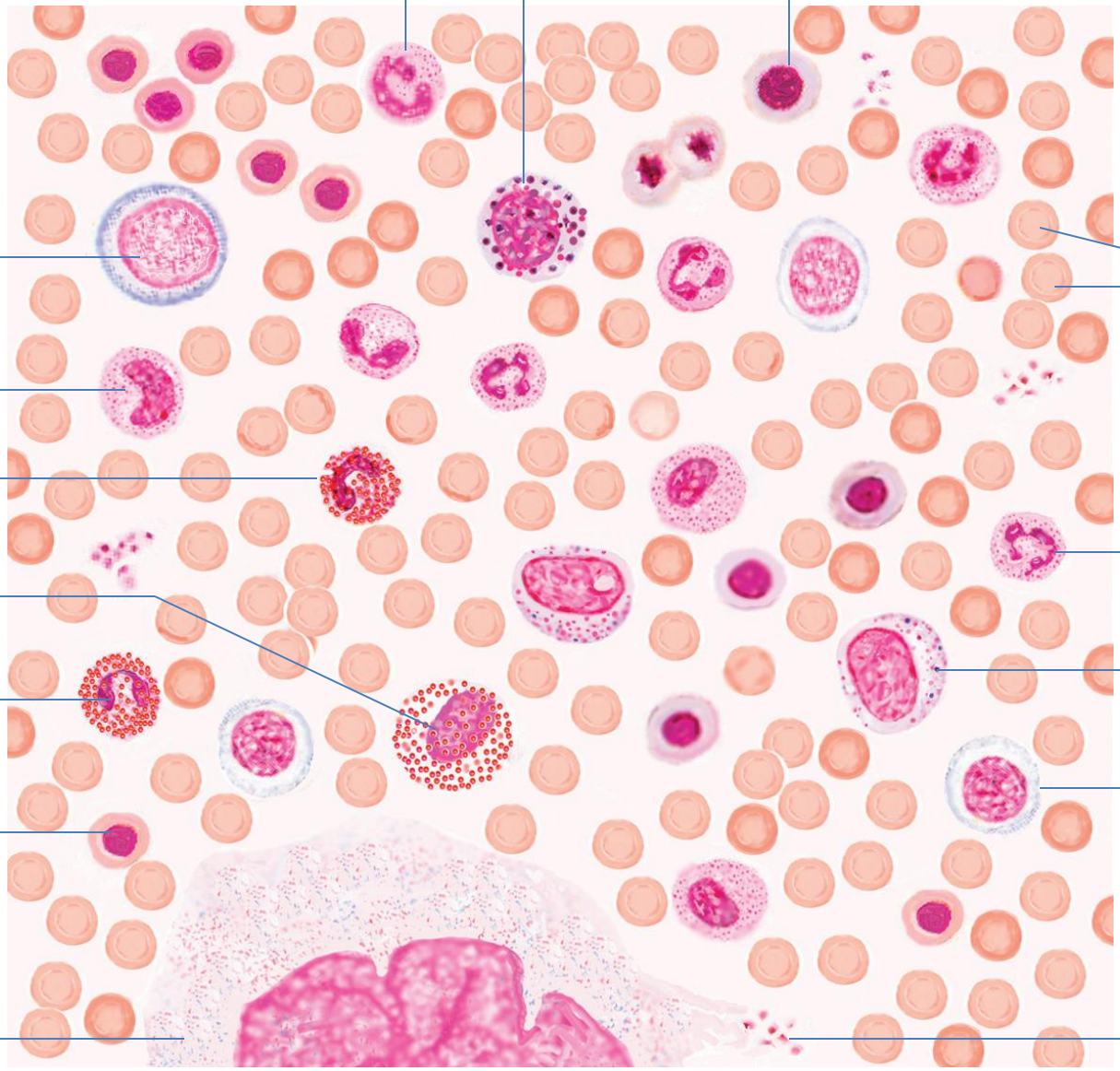
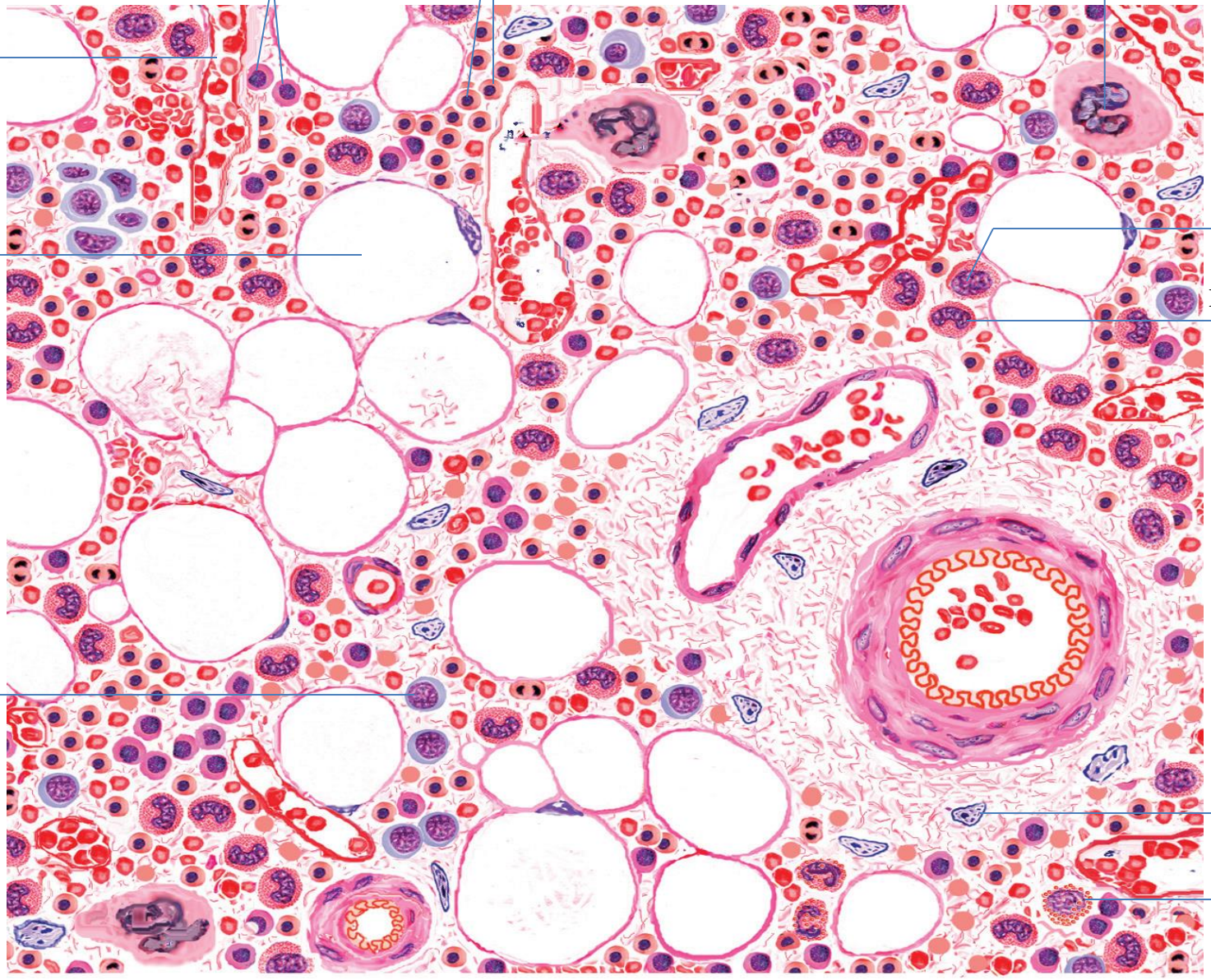


Bone marrow (Giemsa stain)



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Bone marrow (H&E)

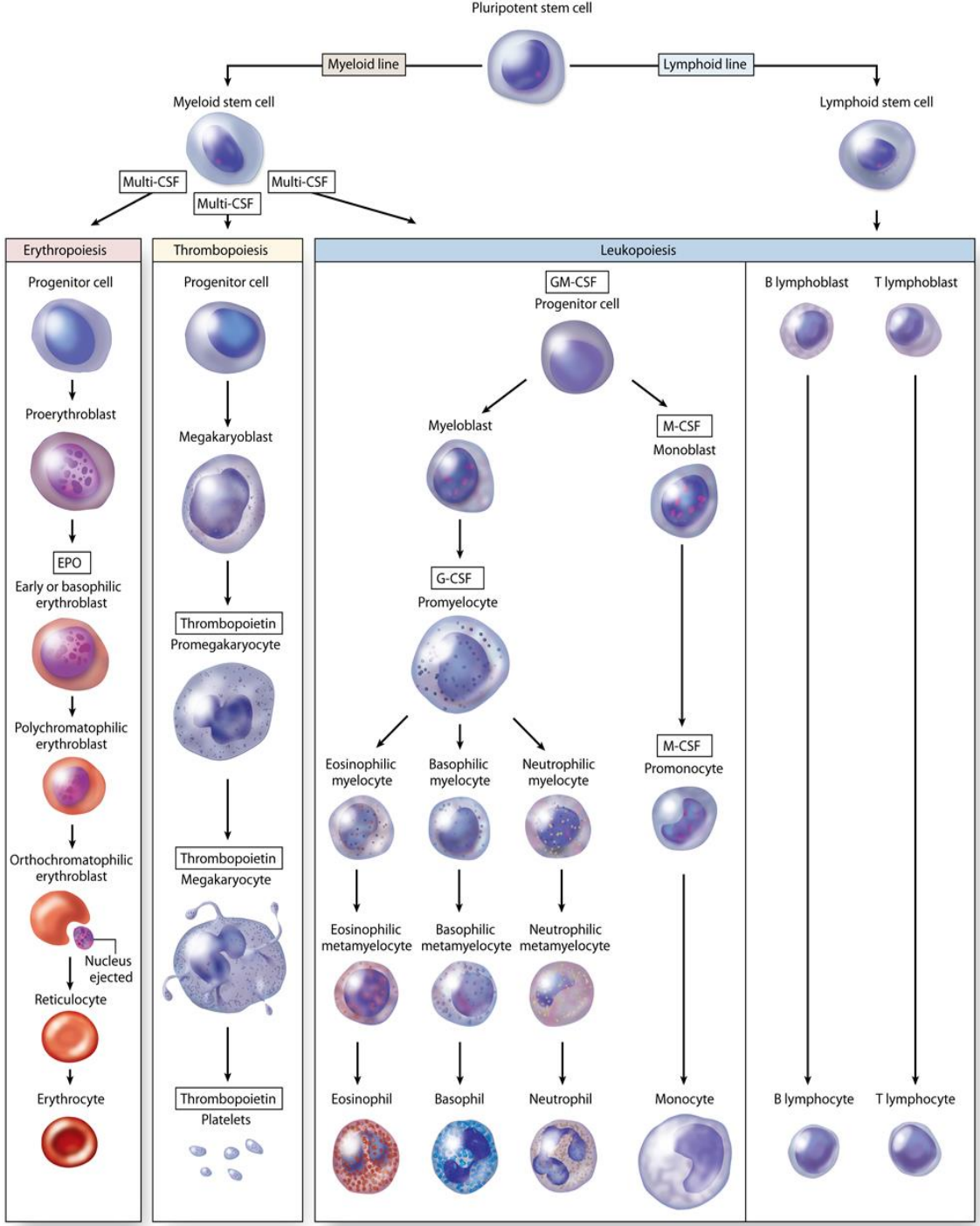
Hemopoietic growth factors (colony-stimulating factors (CSF) or cytokines) are glycoproteins that stimulate proliferation of progenitor and precursor cells and promote cell differentiation and maturation within specific lineages.

Erythropoietin

Thrombopoietin

CSF-G

Cloning of the genes for several important hematopoietic growth factors has significantly advanced study of blood formation and permitted the production of clinically useful factors for patients with hemopoietic disorders.


Pluripotent stem cell
Myeloid line
Lymphoid line
Myeloid stem cell
Lymphoid stem cell
Multi-CSF
Multi-CSF
Multi-CSF
Erythropoiesis
Thrombopoiesis
Leukopoiesis
Progenitor cell
Proerythroblast
EPO
Early or basophilic erythroblast
Polychromatophilic erythroblast
Orthochromatophilic erythroblast
Nucleus ejected
Reticulocyte
Erythrocyte
Progenitor cell
Megakaryoblast
Thrombopoietin
Promegakaryocyte
Thrombopoietin
Megakaryocyte
Thrombopoietin
Platelets
GM-CSF
Progenitor cell
Myeloblast
M-CSF
Monoblast
G-CSF
Promyelocyte
M-CSF
Promonocyte
Eosinophilic myelocyte
Basophilic myelocyte
Neutrophilic myelocyte
Eosinophilic metamyelocyte
Basophilic metamyelocyte
Neutrophilic metamyelocyte
Eosinophil
Basophil
Neutrophil
Monocyte
B lymphoblast
T lymphoblast
B lymphocyte
T lymphocyte

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

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

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