Histology - HLS

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Hematopoiesis

(Part 2)

In this lecture we' re going to complete about HEMATOPOIESIS :

* Granulopoiesis
* Thrombopoiesis
* Lymphopoiesis
*Monocytopoiesis

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Granulopoiesis (Neutrophils, Eosinophils and Basophils formation) (granules formation)

Takes about 2 weeks

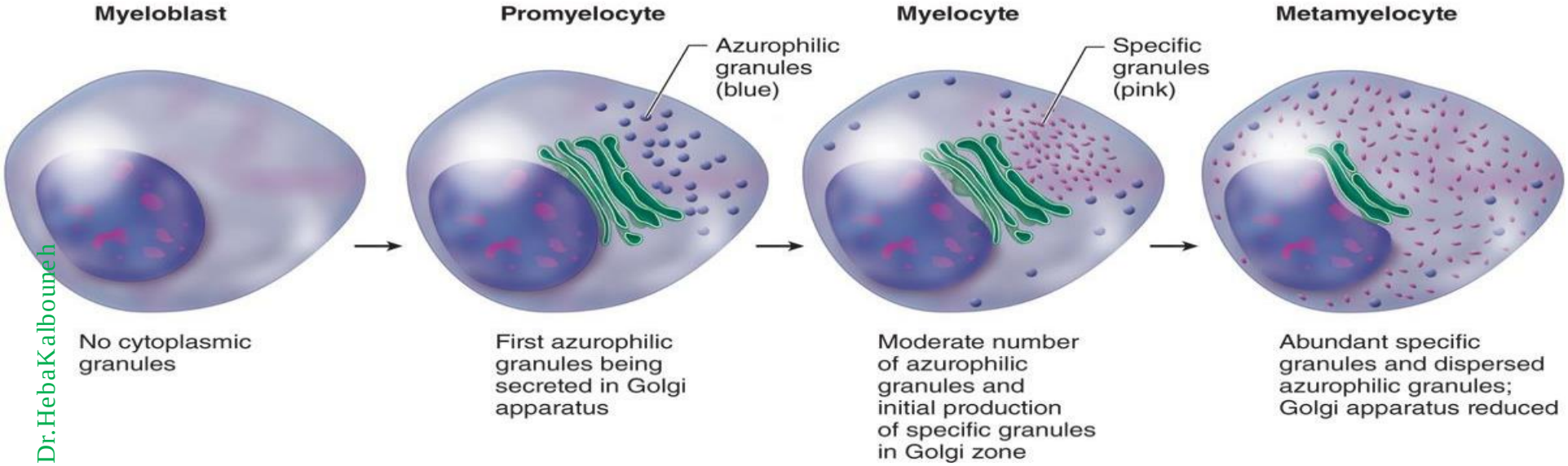
Stages of differentiation are characterized by:

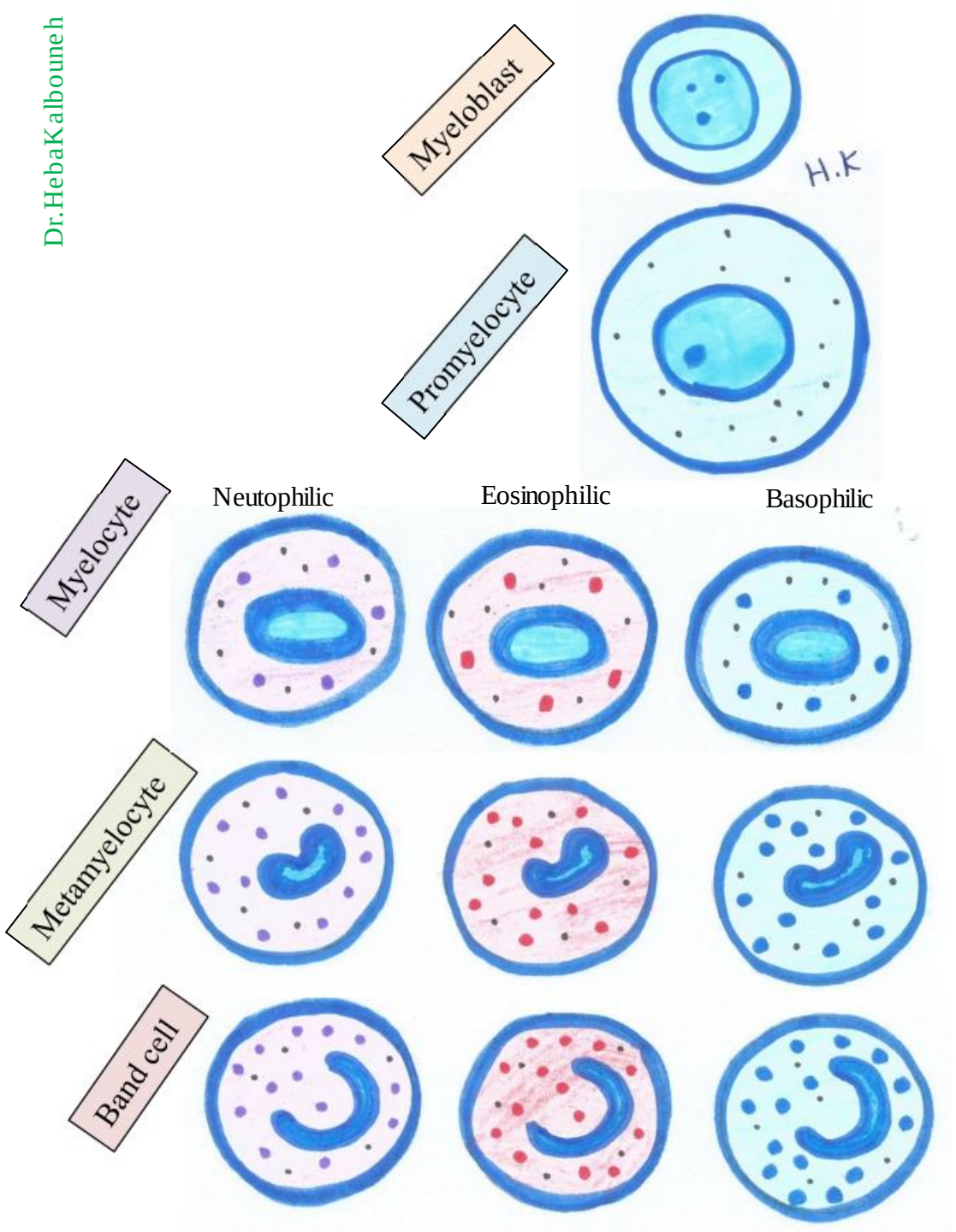
1- **Cytoplasmic changes** dominated by synthesis of azurophilic granules and specific granules.

First, formation of the **(non-specific)** azurophilic granules (similar in all three types of granulocytes) **(they contain lysosomal , hydrolytic enzymes)**

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

2- Condensation, indentation and segmentation **(lobulation)** of the nucleus **(nuclear changes)**





Myeloblast

The first recognizable precursor

Promyelocyte

The largest (20um)
Azurophilic granules start to appear(primary **granules)**

Myelocyte

3 types
The cell becomes smaller
The nucleus becomes smaller and Darker (**more condensed)**
Specific granules start to appear

Metamyelocyte

(meta means ما بعد)

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

Band cell (stab cell)

(the last stage of differentiation)

3 types
Nucleus becomes curved rod in shape
(c- shaped nuclei)

Explanation for previous slide

- ***Myeloblast*** :
- Has large active euchromatic nucleus
- Has prominent nuclei and that's an indication for ribosome synthesis inside this cell for (specific and nonspecific granules)
- cytoplasm is basophilic because of presence of ribosomes
- ***Promyelocyte*** :

It activates different genes to end up with 3 different myelocytes: Neutrophilic , Basophilic, Eosinophilic

- ***Myelocyte*** :

The nucleus becomes more condensed-------> nuclear condensation means : more Heterochromatin and less Euchromatin .

- ***Metamyelocyte :***

They only mature : they go morphological changes (change their shape to end up with the mature granulocyte and we called it metamorphosis)

Note :

Myeloblasts ,promyeloblasts and myelocytes are mitotic cells (they divide) ,but metamyelocytes are not .

For example:

If you culture one promyelocyte and you supply it with factors necessary to promote its differentiation and mitosis, this cell will produce many granulocytes at the end of differentiation. And if you culture a single neutrophilic myelocyte , we are going to have many neutrophils and so on.....

. But if you culture a single neutrophilic metamyelocyte, it will end up with only one neutrophil (it does not divide)---- this property is called metamorphosis .

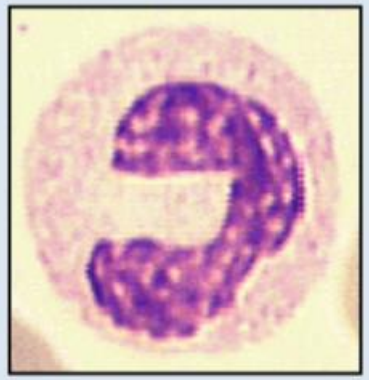
Neutrophilic band cells (important)

Their percentage does not exceed 5% in peripheral blood

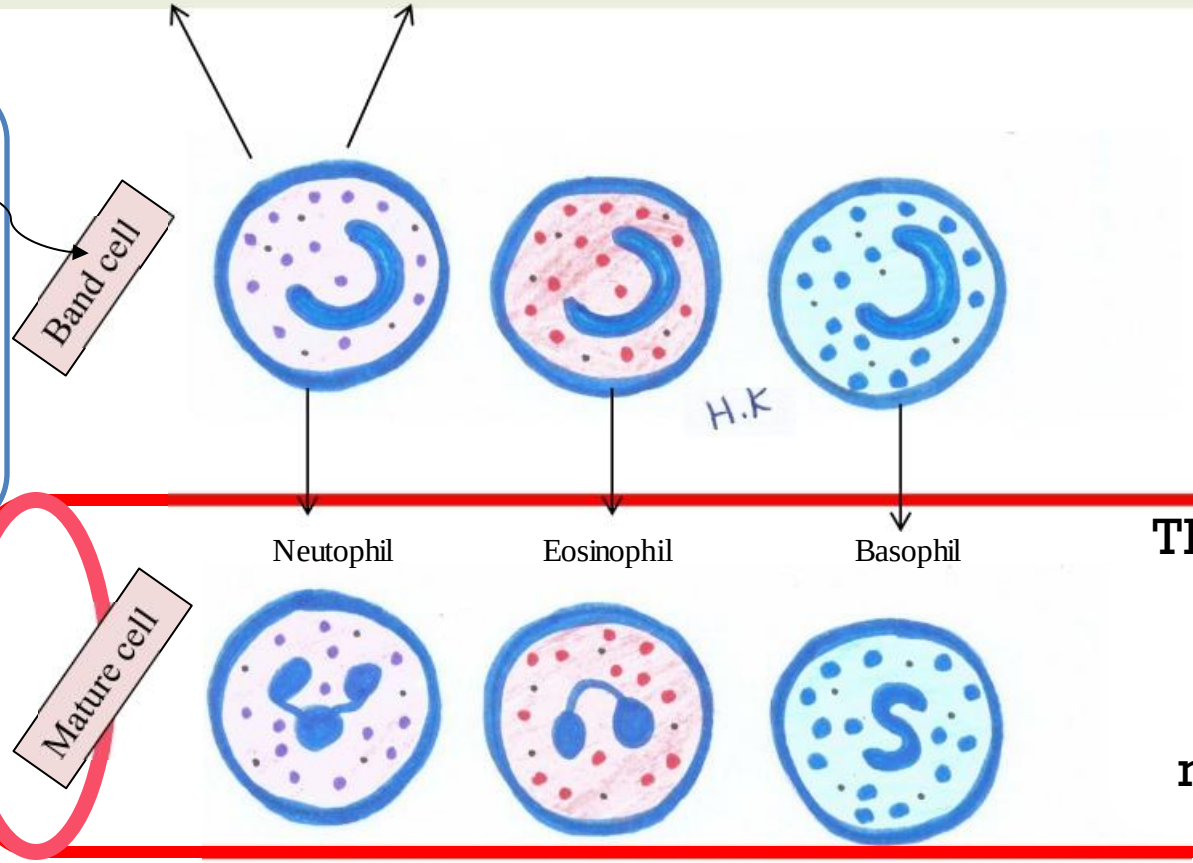
The appearance of large numbers of immature neutrophils (band cells) in the blood, sometimes called a "shift to the left," is clinically significant, usually indicating **a bacterial infection**.

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

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

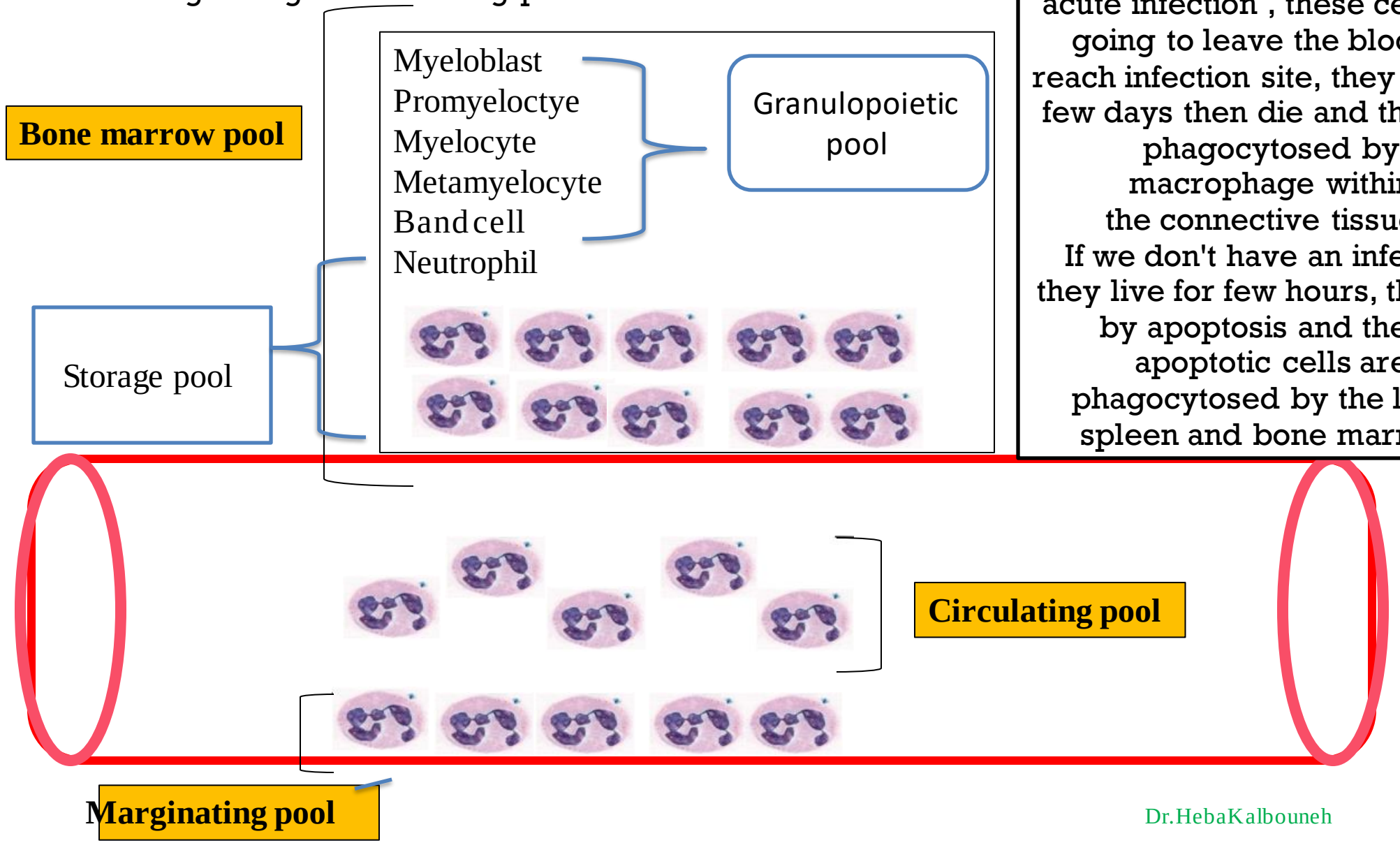


Nucleus are C- shaped , they don't have segmentation , these cells are immature .



These band cells can be released into blood stream to complete their nuclear maturation inside blood.

* neutrophilia can happen due to
- increased production from the bone marrow (granulopoiesis)
- movement of **mature** neutrophils from the storage pool to the circulating pool
- movement from the marginating to circulating pool



Remember :

When neutrophils released into blood stream , they circulate for few hours and if you have an acute infection , these cells are going to leave the blood to reach infection site, they live for few days then die and they are phagocytosed by macrophage within the connective tissue .

If we don't have an infection they live for few hours, then die by apoptosis and these apoptotic cells are phagocytosed by the liver, spleen and bone marrow.

Explanation for the previous slide

- We classify neutrophils according to their locations into 4 different pools:
- ***Circulating pool:*** flowing with blood flow.

- ***Marginating pool :*** loosely attached to endothelium. they are located inside the blood, but they are not truly circulating inside the blood, but also not necessarily leaving the bloodstream and entering the tissue.
- they are in continuous movement with marginating pool & circulating pool (neutrophils from marginating pool supply the circulating pool and vice versa.)

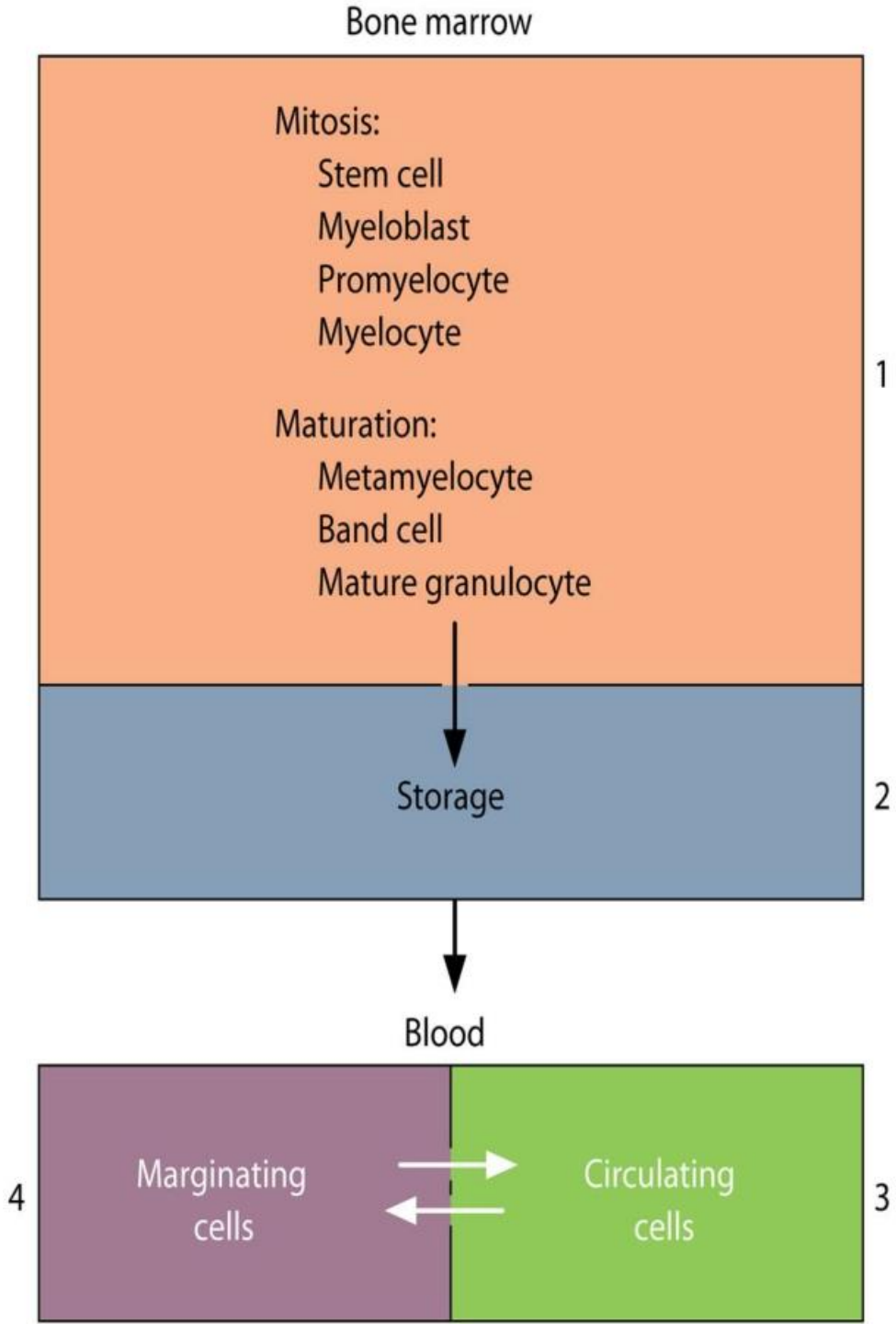
- ***Bone marrow pool :***
- We divide this pool into 2 pools :
- 1- Dividing & differentiating cells -----> ***Granulopoietic pool.***
- 2- Stored mature neutrophil stored inside the bone marrow waiting for their release into the blood stream -----> ***Storage pool***

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.



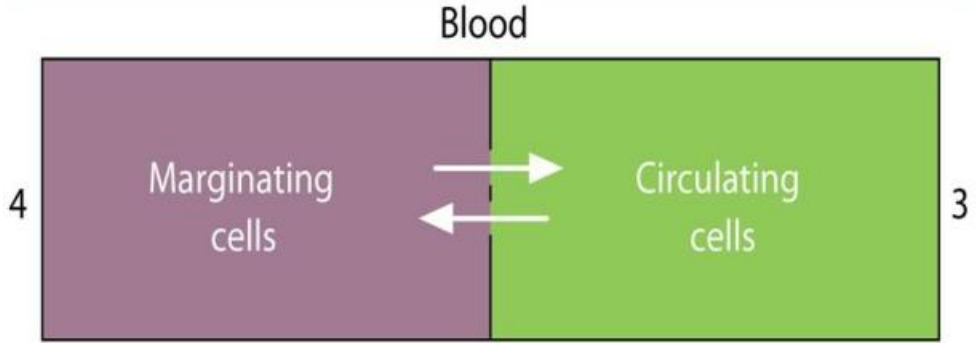
At sites of injury or infection, neutrophils and other granulocytes enter the connective tissues by migrating through intercellular junctions between endothelial cells of postcapillary venules in diapedesis.

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 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

The number of RBCs in peripheral blood is much more the number of WBCs BUT, the lifespan for RBCs is 120 days, while granulocytes live for only a few hours or days. Because of that, we need more precursor cells inside BM to produce high number of these cells So, the ratio is (Myeloid 3:Erythroid 1)

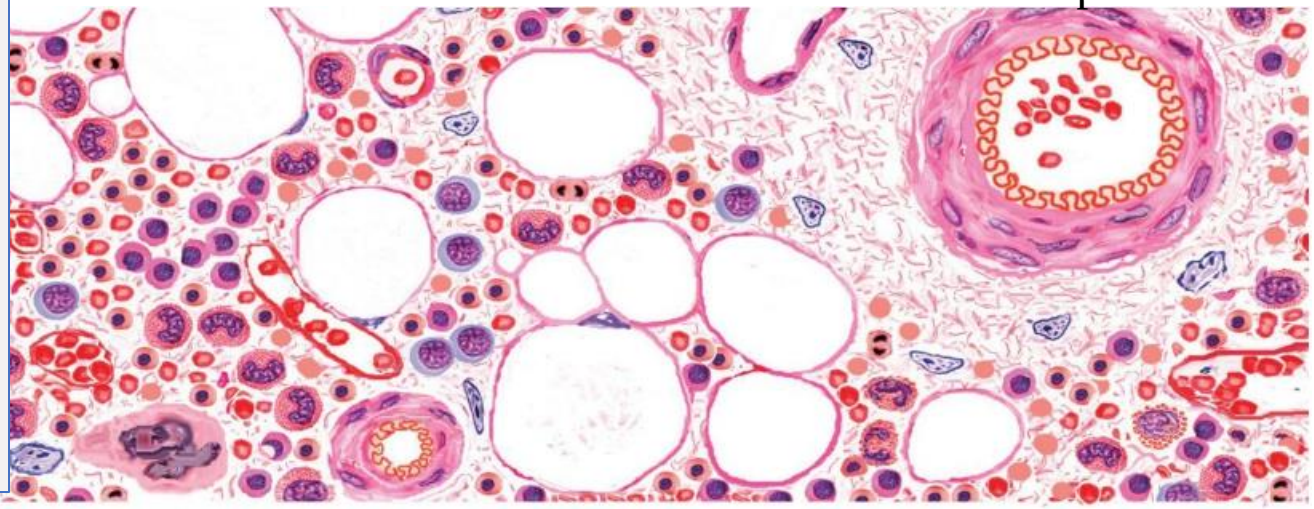
But in the bone marrow (myeloid tissue)!!!

Because most of cells in the bone marrow are precursor cells for granulocytes

Myeloid: Erythroid

3:1

Remember the life span!!!!!

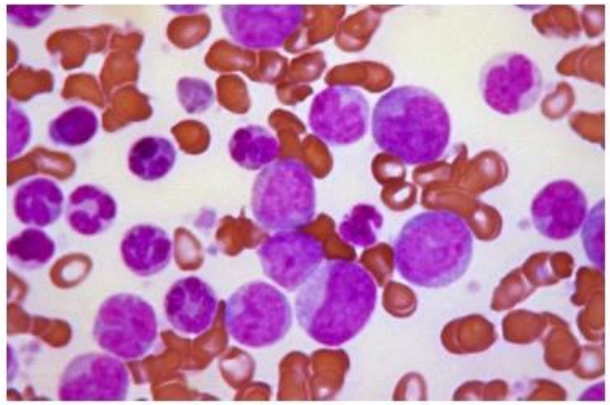


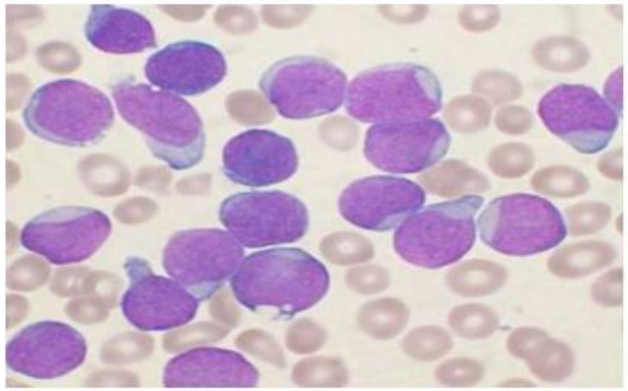
White blood cell abnormalities

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 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)

** this explanation is not in original slides but in recorded video.

Inside the BM we have stem, progenitor, precursor cells that should not be seen in peripheral blood except for reticulocytes and band cells in a certain percentage.

* these 3 types of cells can be destroyed by radiation, chemotherapy, autoimmune disease resulting in suppression in the activity of these cells which a condition that called hypoplasia in the BM (hypoproliferation or underdevelopment)

So, cells cannot devide at enough speed to maintain the number of different types of blood cells.

We name the condition that is caused by the hypoplastic bone marrow Aplastic Anemia - that's a misnomer, it should be called pancytopenia- because we have a reduction in all types of blood cells not only RBCs

-another condition is when we have malignant proliferation of these 3 cells inside the BM, they show neoplastic changes, and this condition is called leukemia.

-ex:
If you take a blood film and you observe reduction in all types of blood cells or you see abnormal neoplastic precursor cells in the peripheral blood, in this case you have to take bone marrow Aspirate or Biobsy

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

BM Aspirate:

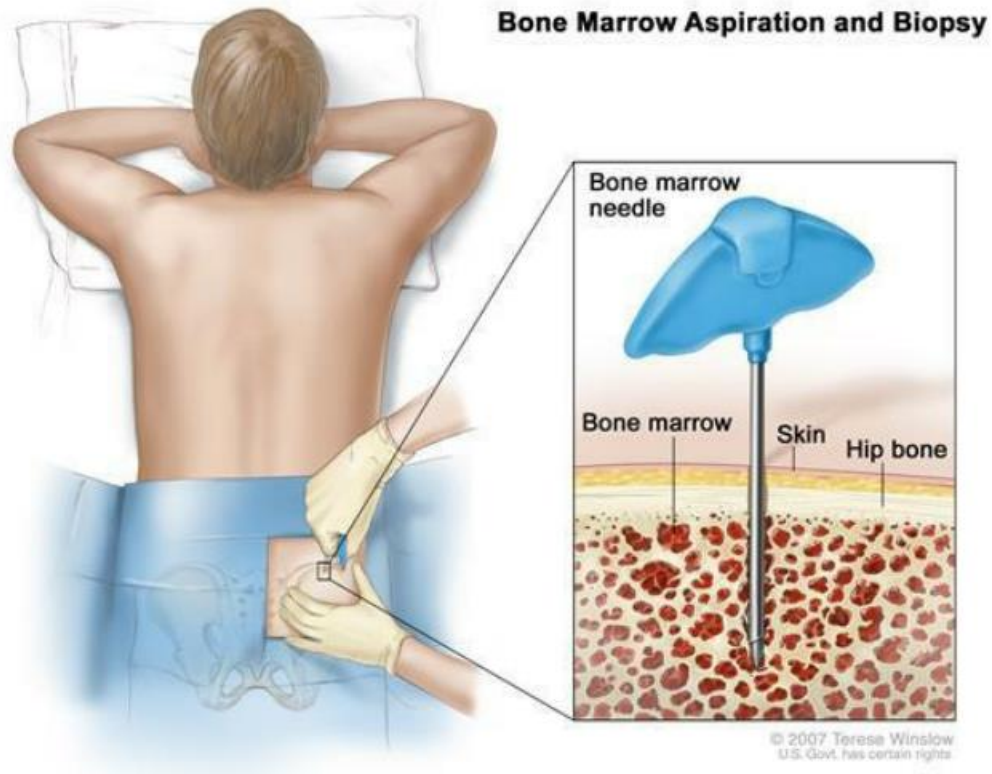
You place a needle to take sample from the red bone marrow of iliac crest or sternum, then you place the red bone marrow over a glass slide and stain it to diagnose leukemia or a plastic anemia

BM biobsy:

Taking a red bone marrow with the surrounding bone

BM transplantation :

We take hematopoitic stem cells from a donor and inject the patient with these stem cells that going to circulate in the blood until they settle down inside the bone marrow then they devide and proliferate to produce normal cells (they go to the BM because of the specific adhesion molecules on the reticular cells that act as homing-in property of hematopoitic stem cells



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

The names of cells are not required

Hematopoietic pluripotent stem cell

↓

Myeloid stem cell

↓

Colony forming unit- megakaryocyte

↓

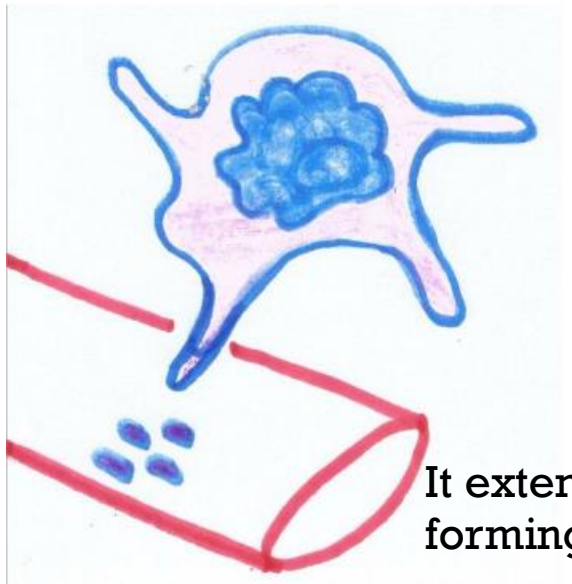
Megakaryoblast

↓

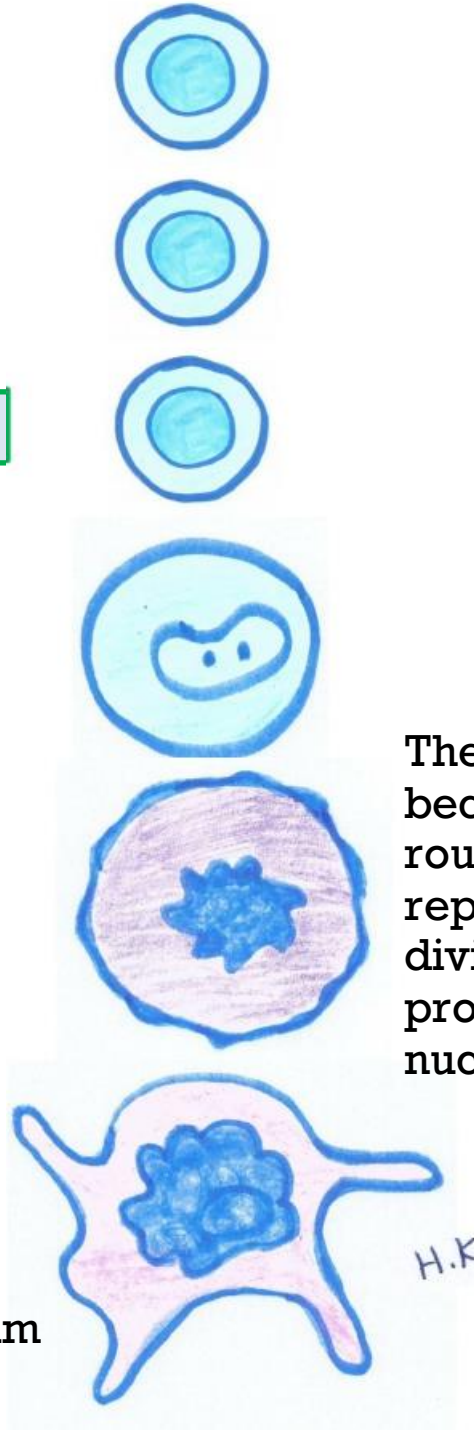
Promegakaryocyte

↓

Megakaryocyte



It extends its processes into the blood stream forming platelets with the blood flow



The nucleus is large because it goes many rounds of DNA replication without division of the nucleus producing polyploid nucleus

Monocytopoiesis

Hematopoietic pluripotent stem cell

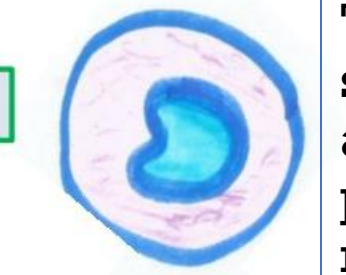
Myeloid stem cell

Colony forming unit- monocyte

Monoblast

Promonocyte

Monocyte



A lot of ribosomes producing basophilia and these ribosomes are going to synthesis the primary azurophilic granules inside the cytoplasm.

The nucleus gets smaller in size, more condensed and indentation in the nucleus preparing for the c shaped nucleus.

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

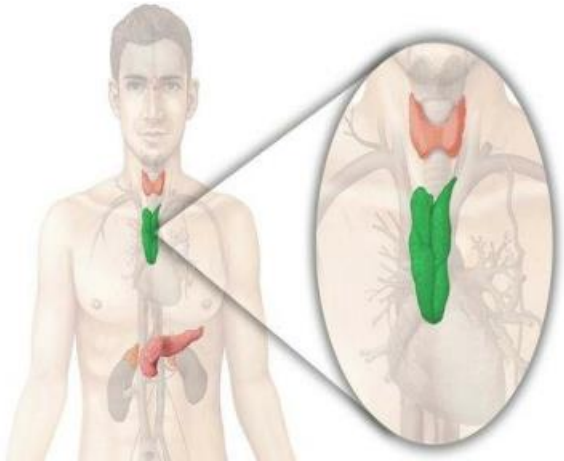
Directly into blood

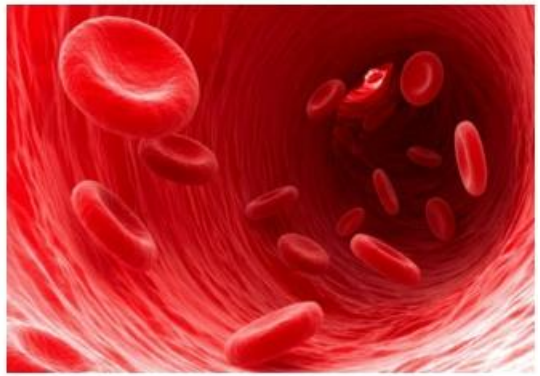
T Lymphocyte

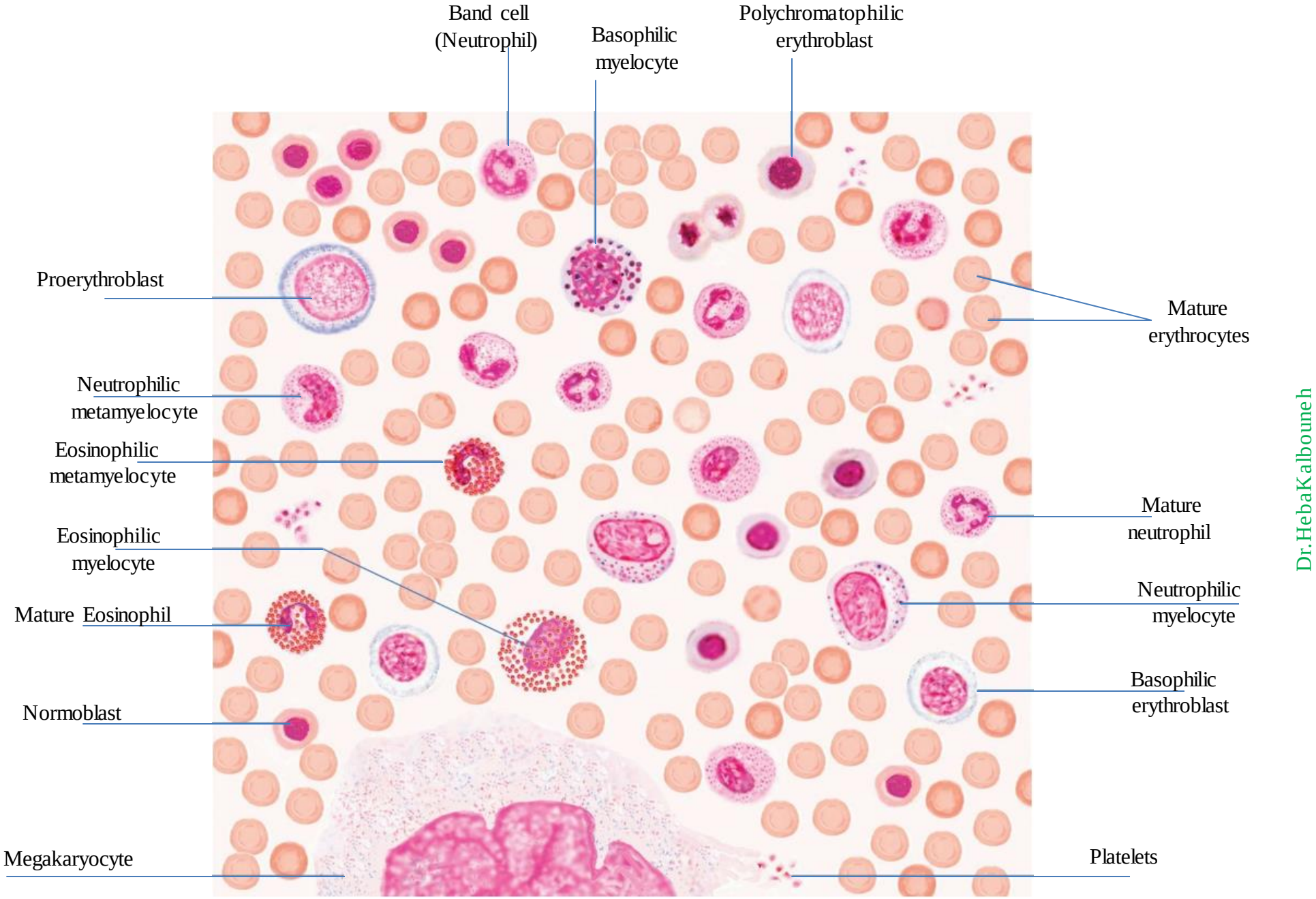
BM

Natural killer lymphocyte

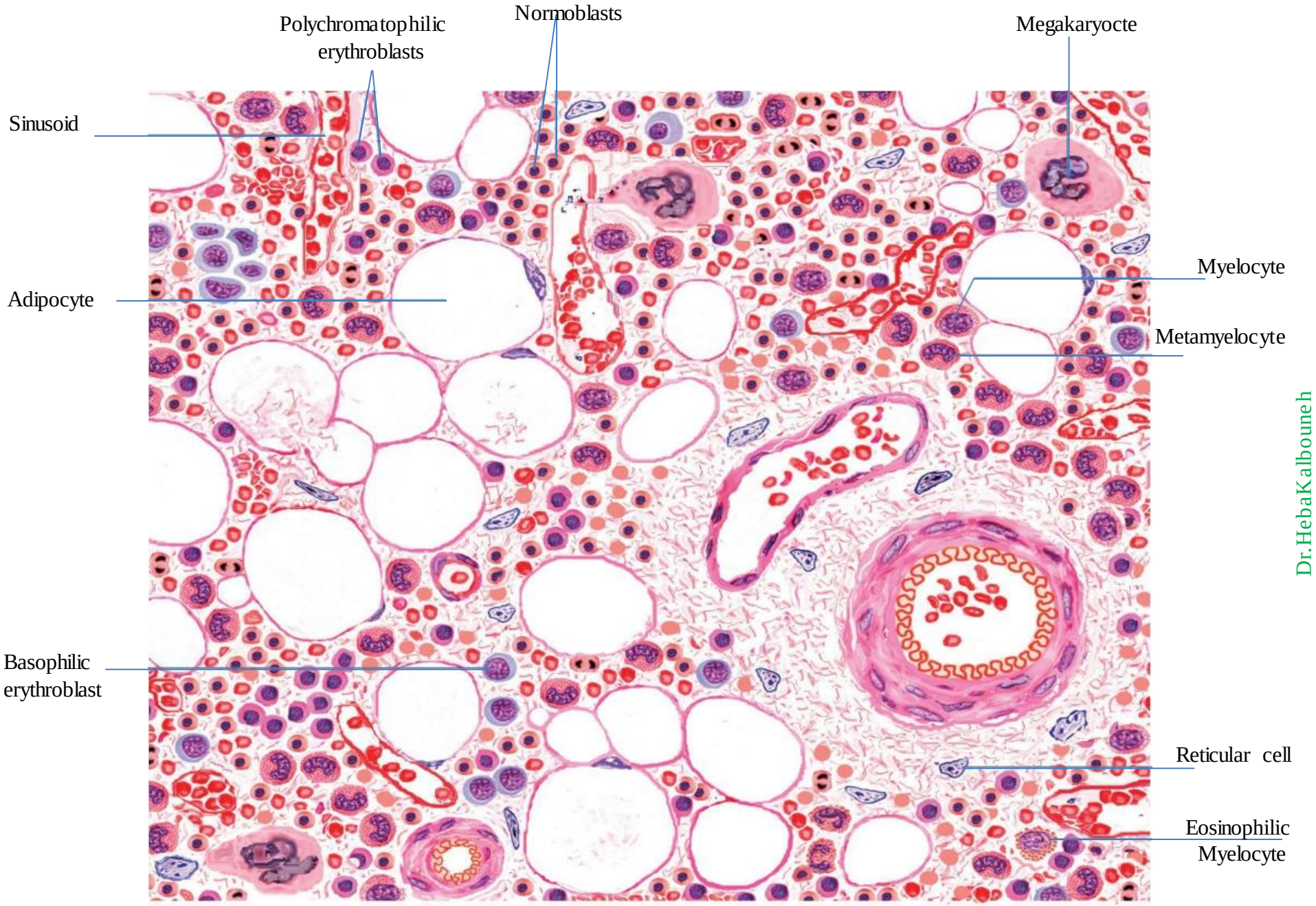
B Lymphocyte







Bone marrow (Giemsa stain)



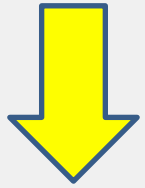
Bone marrow (H&E)

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 imp for Erythropoiesis

Thrombopoietin imp for Thrombopoiesis

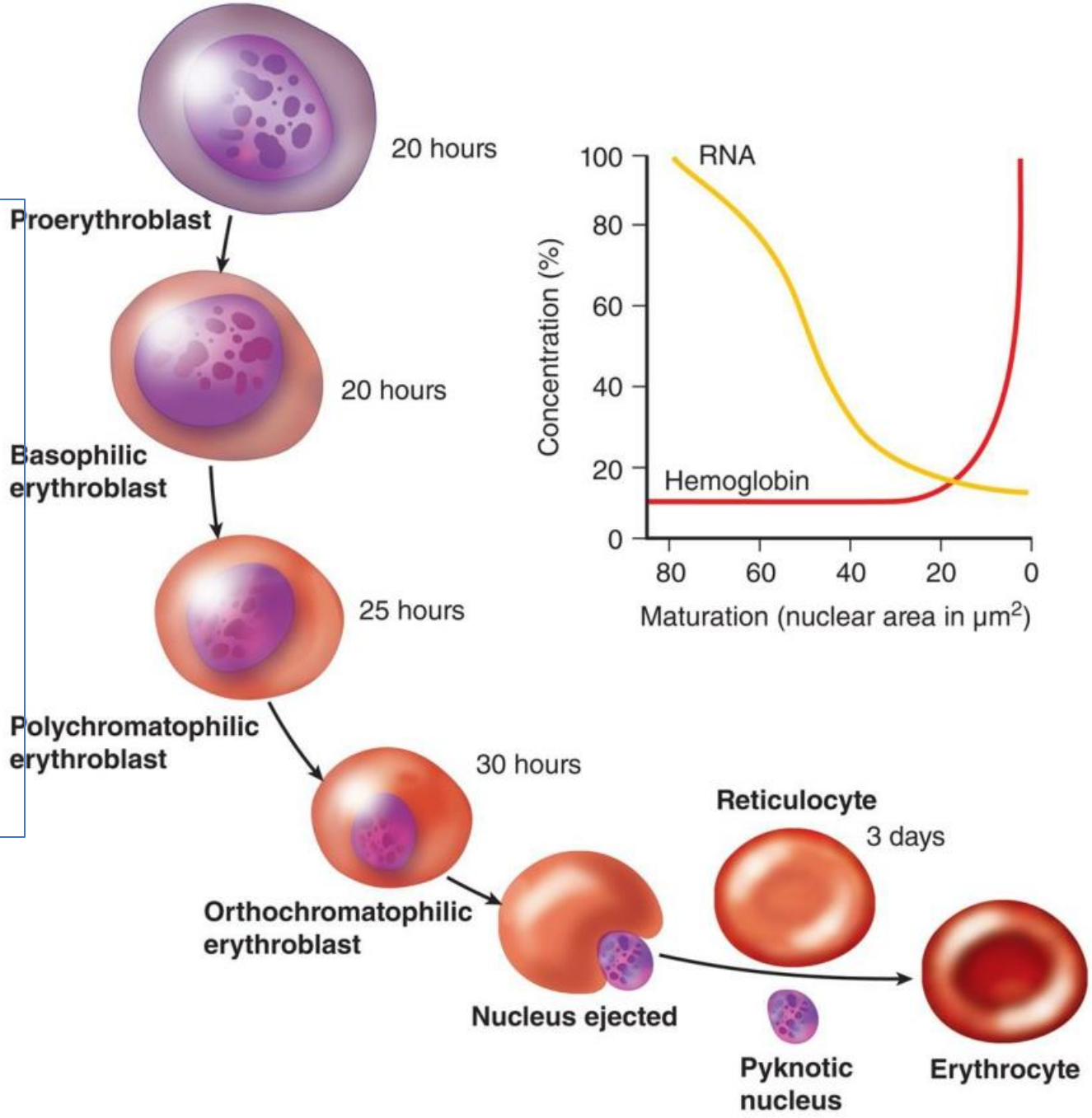
CSF-G imp for granulopoiesis

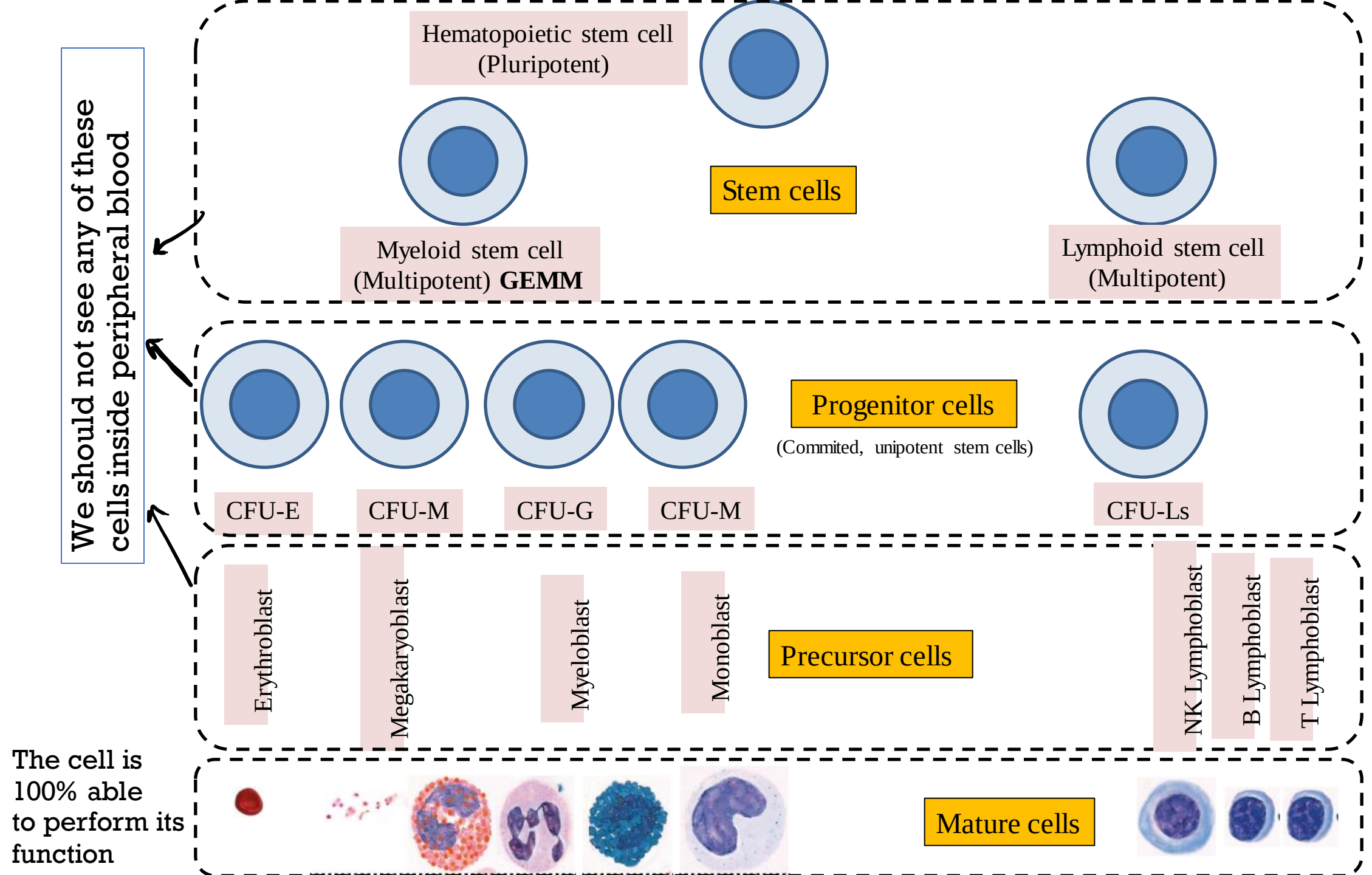


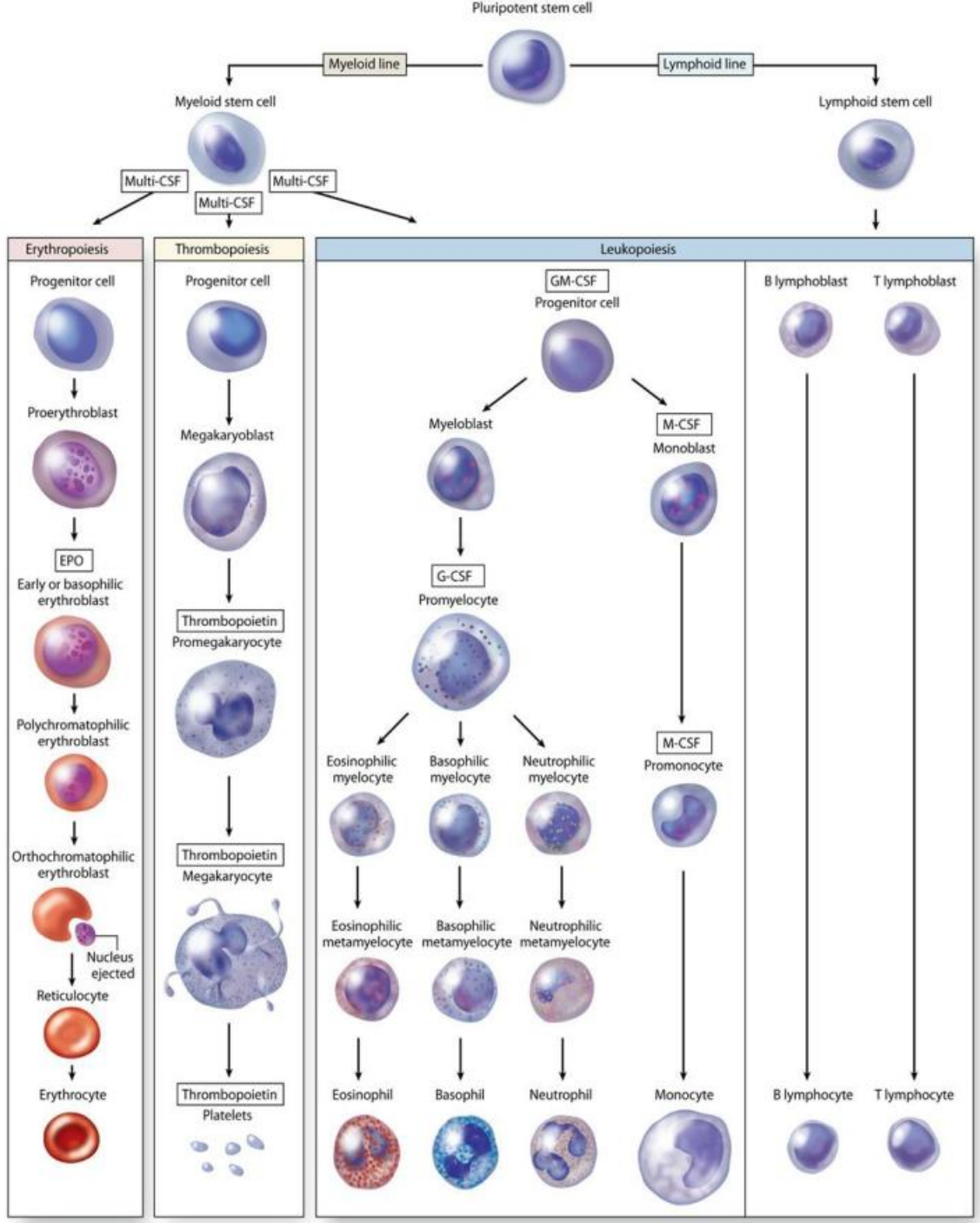
Cloning of the genes for several important hematopoietic growth factors has significantly advanced study of blood formation and permitted the production of clinically useful factors for patients with hemopoietic disorders.

Patients with renal failure (Erythropoieten deficiency), you should give him erythropoieten to stimulate the production of RBCs in BM

Erythropoiesis needs about 1 week to form mature erythrocytes, so if you give a patient erythropoieten to stimulate RBCs production you have to wait at least 1 week to see a significant increase in the number of RBCs in peripheral blood




We should not see any of these cells inside peripheral blood
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
The cell is 100% able to perform its function


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
Eosinophilic myelocyte
Basophilic myelocyte
Neutrophilic myelocyte
M-CSF
Promonocyte
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

Click to add text

d

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

B

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

d

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

d

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

∀