



# Hematopoiesis

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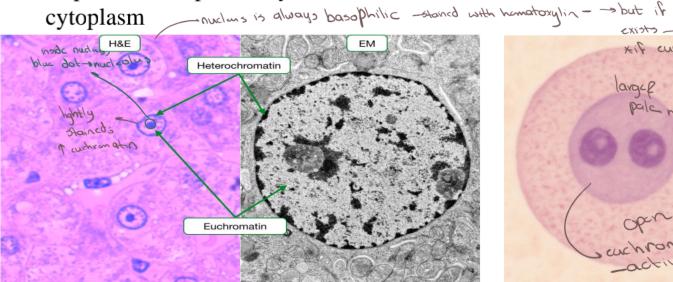
#### **Chromatin**

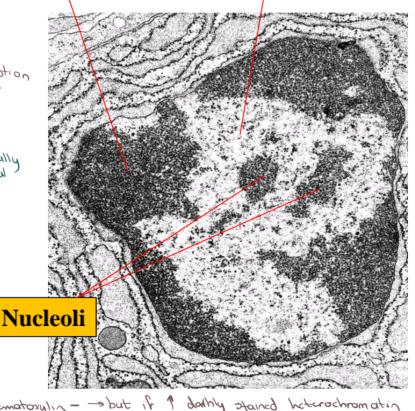
Formed of **DNA**.

- <u>2 Forms</u>:
  - <u>Euchromatin</u>: extended active → allows transcription chromatin (pale).
  - Heterochromatin: condensed inactive chromatin (dark) -clectron dense usually condensed at peripheral part of nucleus

#### **Nucleolus**

- It is a spherical dark basophilic mass not surrounded by a membrane.
- Usually one. prominant nucleolus indicates protein
   Synthetic activity of the cell
   Function: formation and assembly of
- <u>Function</u>: formation and assembly of ribosomal RNA (rRNA), which is responsible for protein synthesis in the





**Euchromatin** 

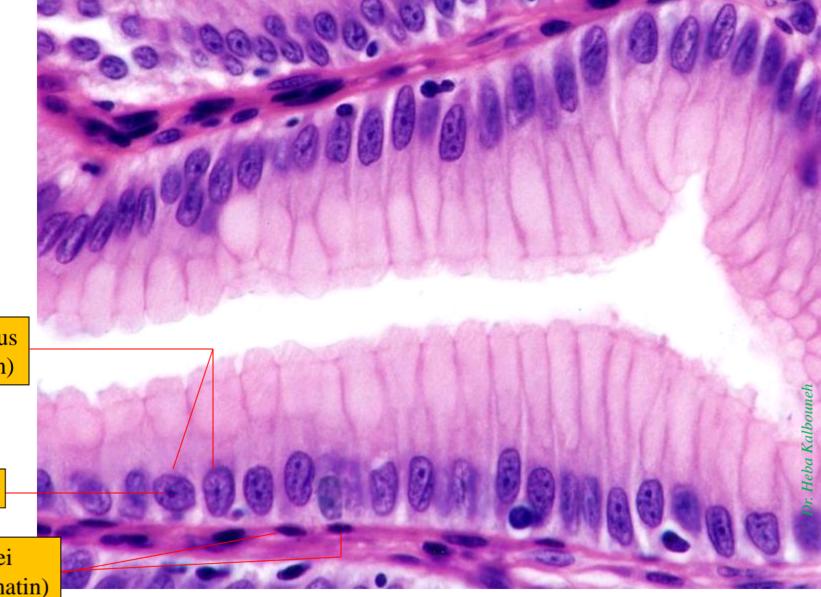
Heterochromatin



Note:

The nucleus stains blue (basophilic) using H&E

Lightly basophilic: active Deeply basophilic and small: inactive



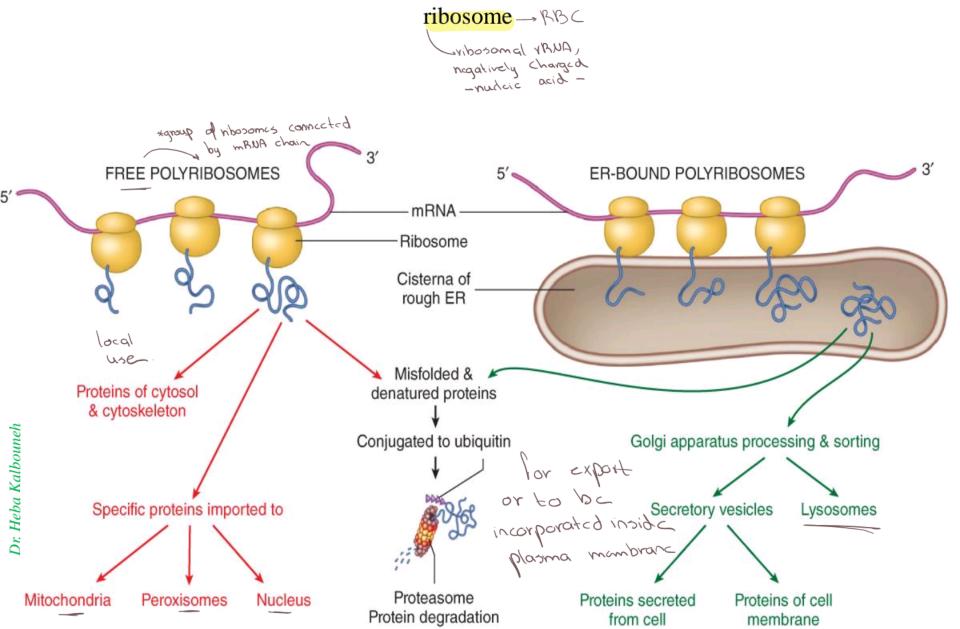
Active nucleus (Euchromatin)

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



## Dense irregular connective tissue

- ✓ Bundles of collagen fibers are randomly interwoven
  with no definite orientation
  - ✓ Provides resistance to stress from all directions
  - ✓ Dermis of skin (deeper layer), organ capsules,
    submucosa

    Submu

Connective fissue proper

Joose scells, Piber, ground substance
in same proportions

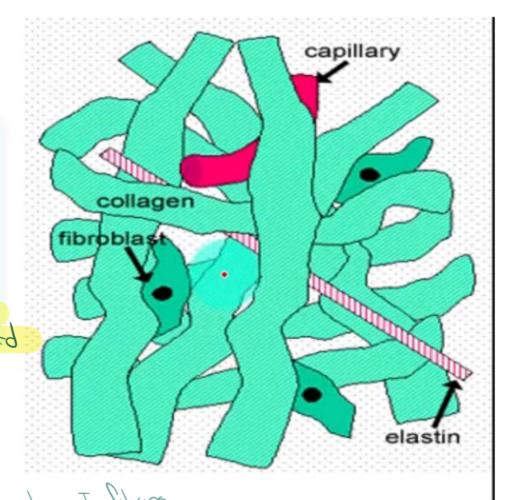
Jonse A collagen Type I Pibers

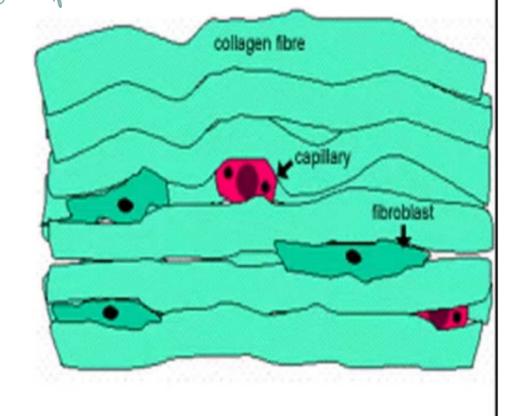
imagular libers > cells, ground substance

imagular based on orientation of collagen type I Pibers.



✓ Parallel Bundles of collagen fibers with few fibrocytes aligned with collagen and separated by very little ground substance





Stroma means bed

In all organs:
main function of

rougan

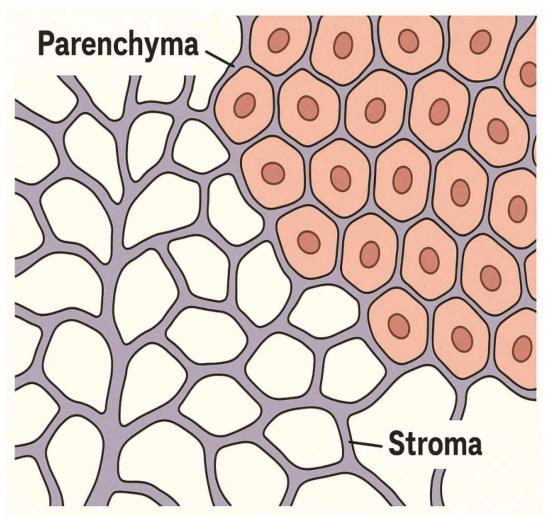
supporting tissue.

## 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 andans

(allagm

- Consists of reticular cells (modified fibroblasts) and 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

(Reticulo-Endothelial

organs)

wide spaces hill with blood or lymph lined with endotheliam of reticular bissuc

Reticular cell

**Reticular fibers** are thin and branching forming a network

spaces to permit movement of large molecules or even cells Dr. Heba Kalbouneh

Types of capillaries

## Continuous capillaries

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

- supported by continuous layer of BM

## Fenestrated capillaries

➤ Endothelium contains pores

(fenestrations) but BM continuous.

Found wherever active capillary

absorption or filtrate formation occurs

Found in endocrine glands, small

★ Basement membrane

Endothelial layer (tunica intima)

Intercellular clef

intestine, and kidney

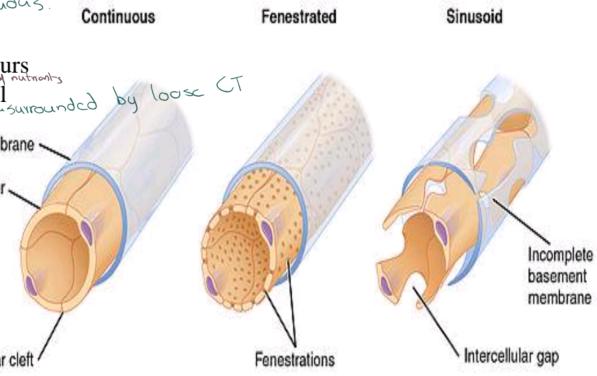
materials

Sinusoidal capillaries large lumen

> Exhibit wide diameters with wide gaps between endothelial cells

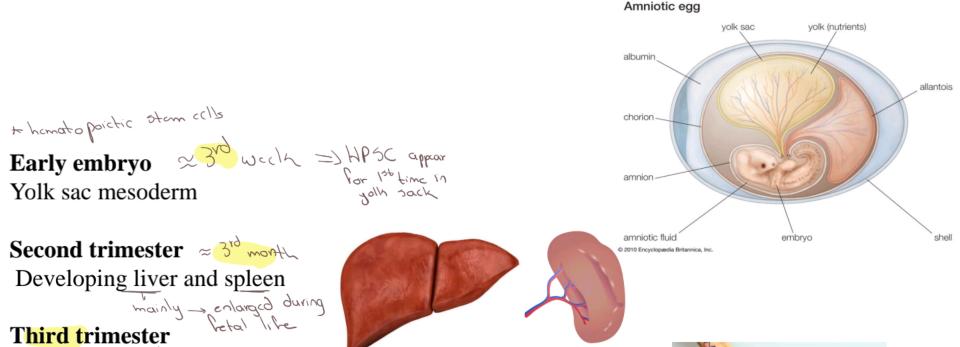
- ➤ Basement membrane incomplete or absent
- Allow large molecules (proteins and blood cells) to pass between the blood and surrounding tissues
- Found in liver, spleen, and bone marrow

large plasma



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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).



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

pour mamon

Bone marrow

outside BM:

cxtra-medullary BM = Sliver, splean,
yolk sack

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

It consists of:

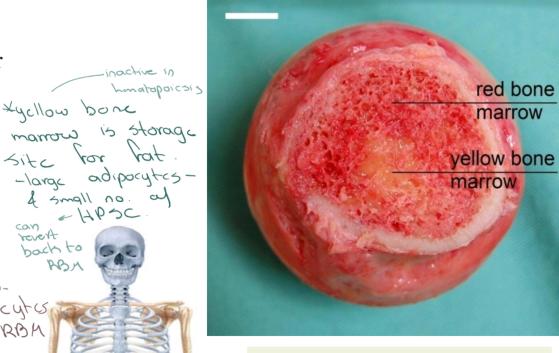
Hemopoietic stem cells(the origin of different blood cells)

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.

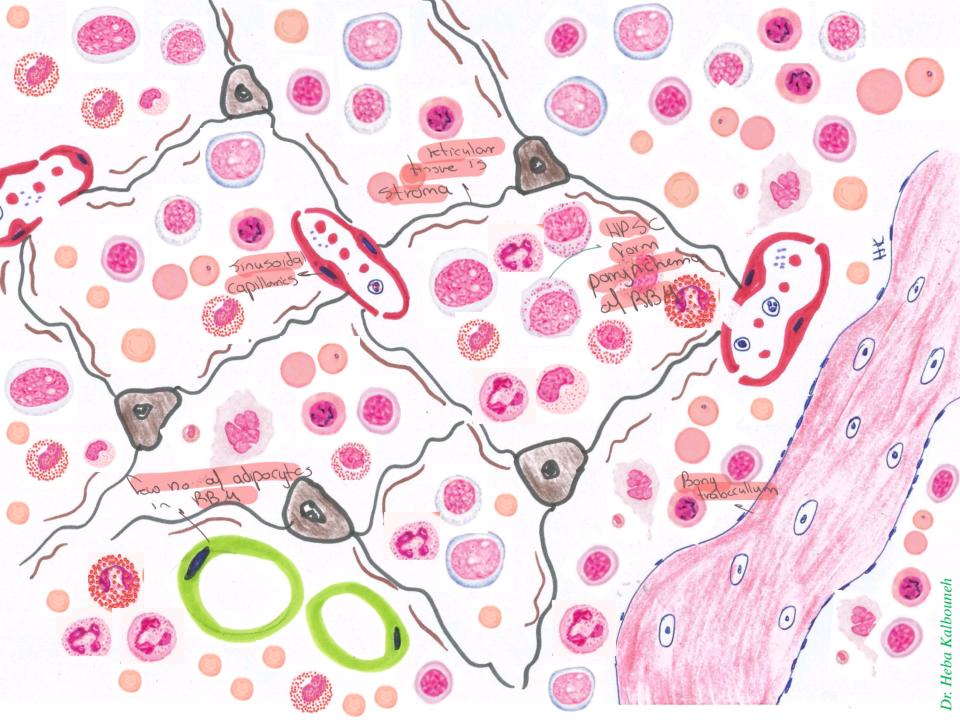
Consequently, they lose the hemopoietic functions.

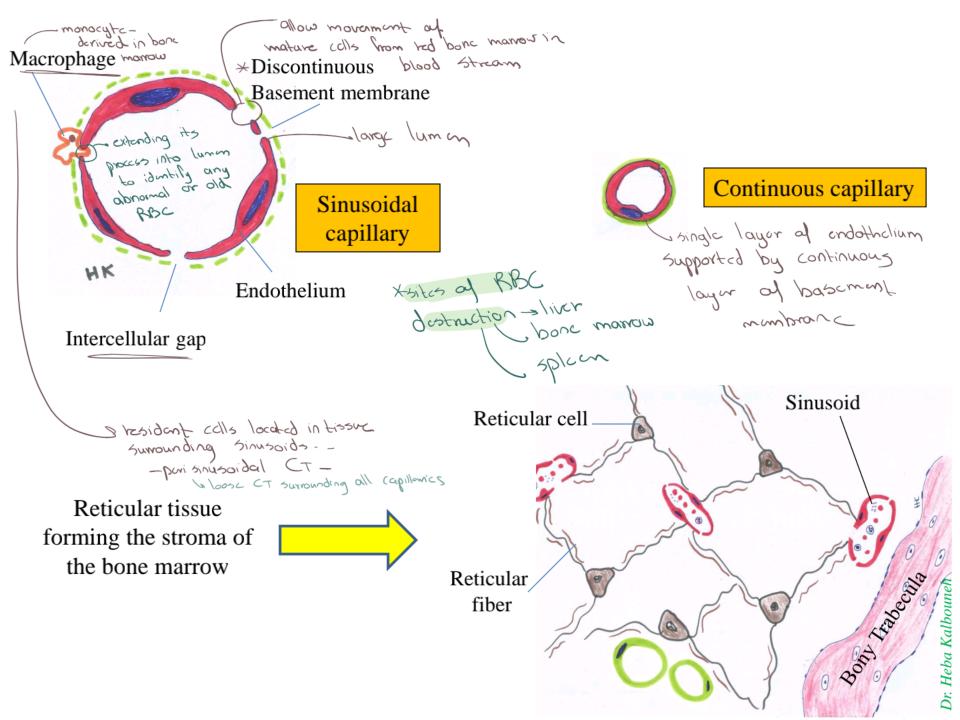


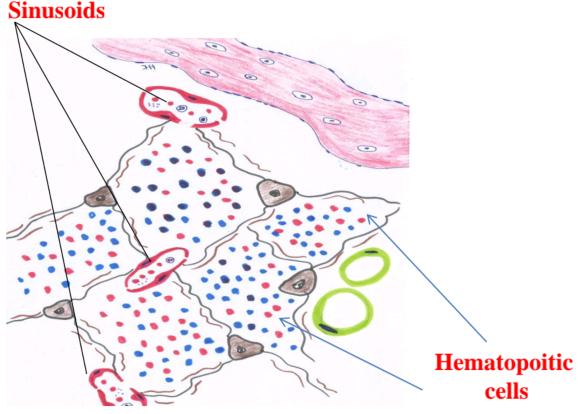
Extramedullary
hematopoiesis refers to the
hematopoiesis that occurs in
organs other than bone
marrow.

(fetal development, normal immune responses, and pathological circumstances)

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

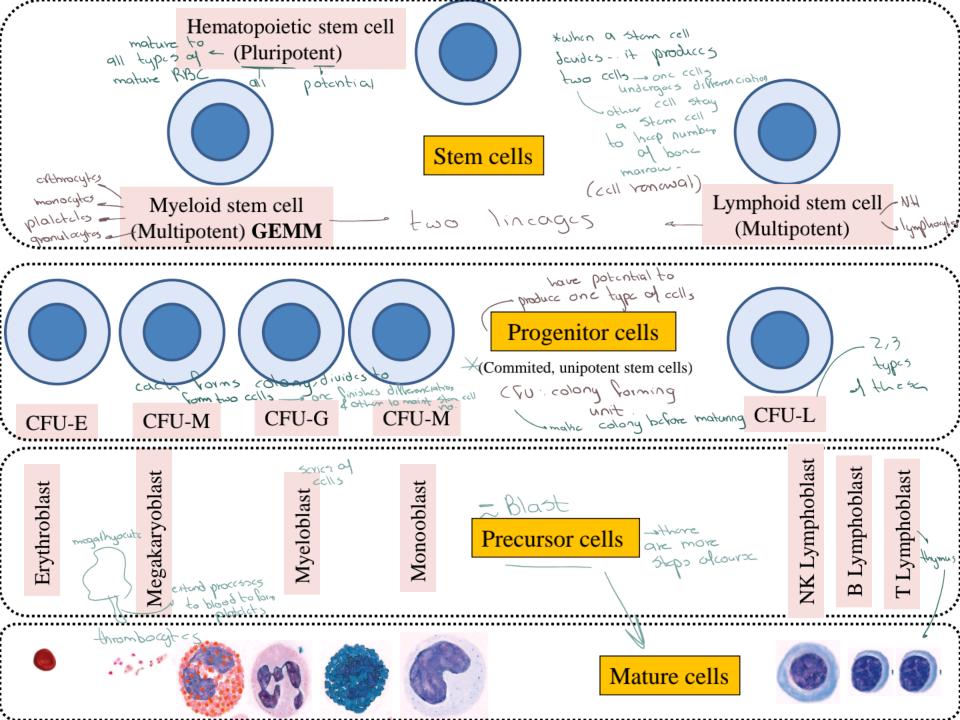


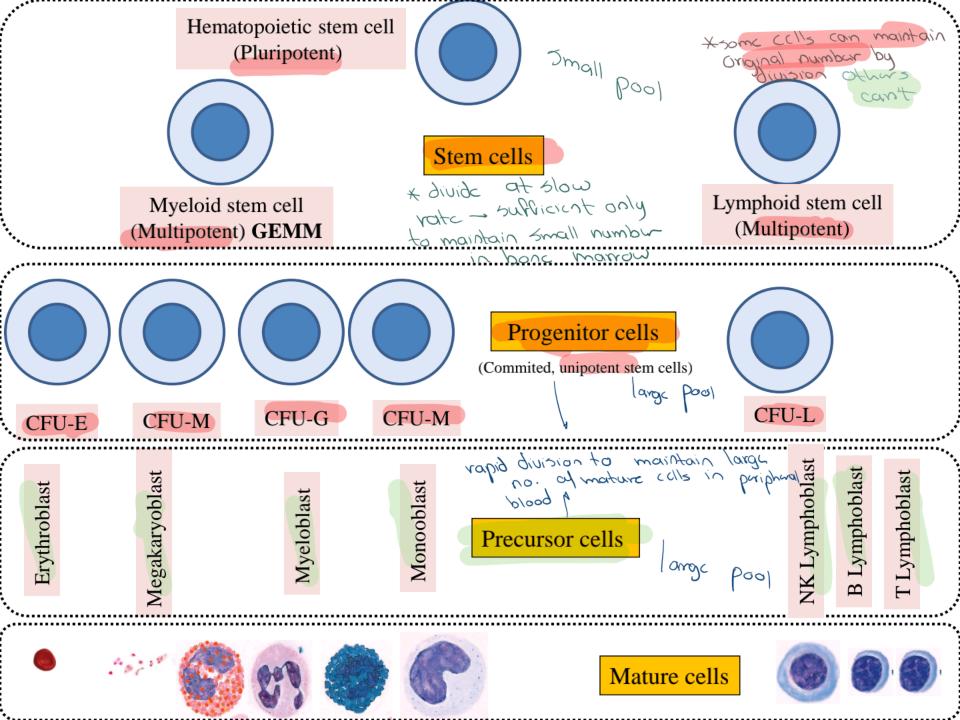




circulation

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.

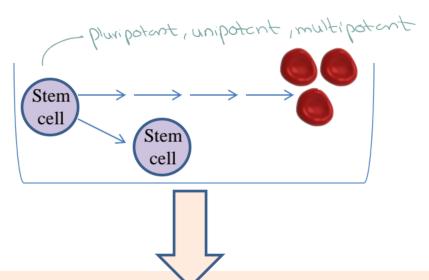




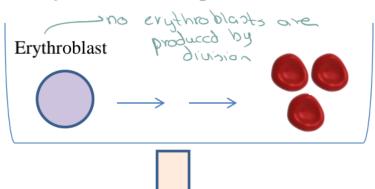
# **Stem cells** are capable of asymmetric division and self-renewal.

**Stem cells** can maintain the original population

**Precursor cells** produce only mature blood cells



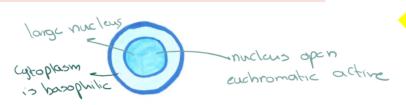
Every time the stem cell multiplies, it will give two cells, one differentiate into mature RBCs and the other cell add to the original population Erythroblasts are precursor cells



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

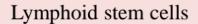
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Hematopoietic pluripotent stem cells



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

Myeloid stem cells





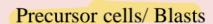


Rate of cell division:
Slow in Stem cells
Rapid in progenitor and precursor cells

Progenitor cells/ CFUs



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

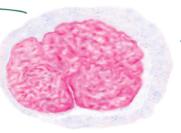




Selected precursors of different blood cells







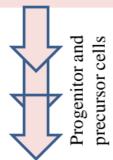
Precursor cells gradually assume the morphologic characteristics of the mature, functional cell types they will become

## 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



Granulocytes

- -Neutrophils
- -Basophils
- -Eosinophils

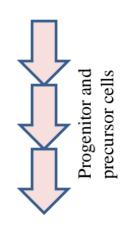
Erythrocytes

Megakaryocytes

Monocytes

## Lymphoid stem cells

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

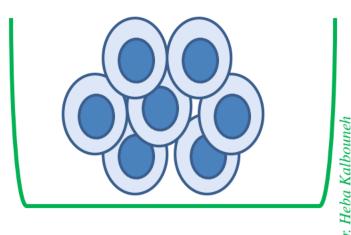


T lymphocyte B lymphocyte Natural killer cells

## Pluripotent hematopoietic stem cells

## Lymphoid stem cells Myeloid stem cells CFU Erythrocyte **CFU-E** Progenitor cells/ CFUs CFU Lymphocyte **CFU Monocyte** CFU-L CFU Granulocyte-**CFU-M** Monocyte CFU Granulocyte **CFU-GM CFU-G** CFU Megakaryocyte **CFU-M**

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

In the Imphopoiesis occurs in the Imphopoiesis occurs in the Imphoid and in the Imphoid marrow and in the Imphoid organs to which precursor organs to which precursor migrate from marrow.

## Proerythroblast

- nucl cated cell -baso Philic Cytoplasm - langur



Basophilic erythroblast



Polychromatophilic erythroblast



Normoblast



Reticulocyte

- acidophilic cytoplasm

Erythrocyte

Erythropoiesis (red cell formation)

-synthesis of Hb inside cytoplasm of cell inon AA ✓ Takes about 1 week

✓ Rate is controlled by the hormone erythropoietin (secreted by the kidney cells) and the availability of iron, folic acid, vitamen B12, protein precursors

\* becomes a cidophilic due to Hb - basic protein-

Stages of differentiation are characterized by:

1- Decreasing cell size

2- Progressive loss of organelles

Presence of free ribosomes at early stages

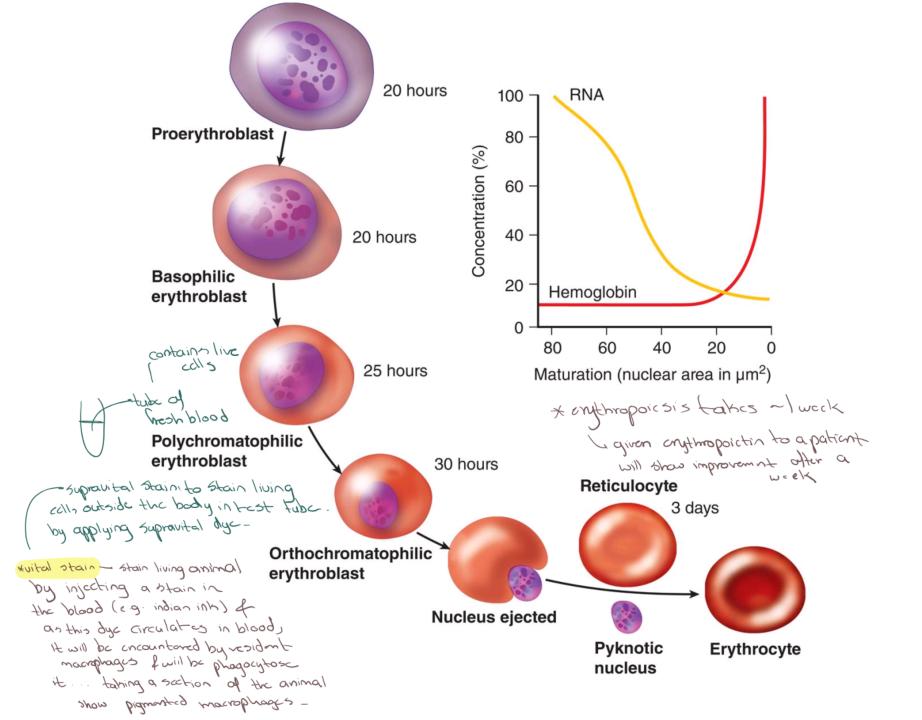


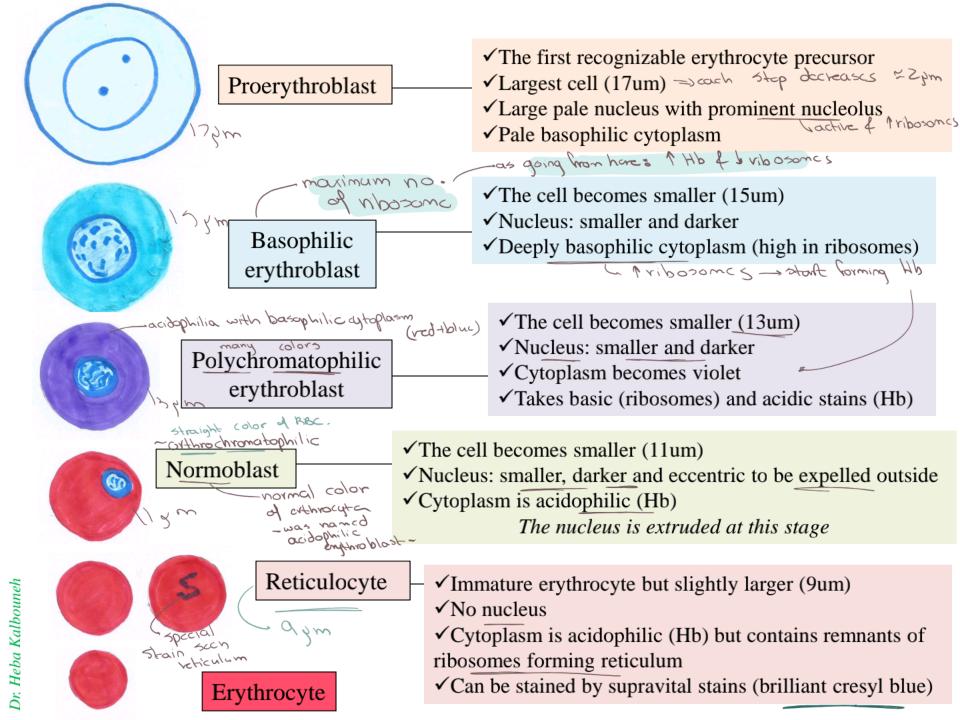
Accounts for the marked cytoplasmic basophilia (blue)

3- Progressive increase in hemoglobin content



Accounts for increasing eosinophilia (pink/red)

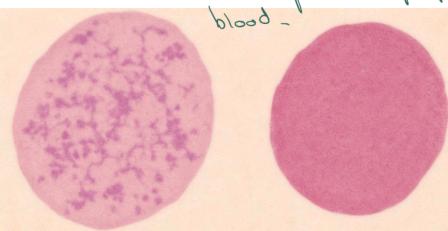




## Reticulocytes

- ➤ 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 <u>1-2 days before</u> developing into mature red blood cells
- An increase in reticulocytes ---- blood loss (hemorrhage) overactivate bone marrow -

Primature product in paripheral

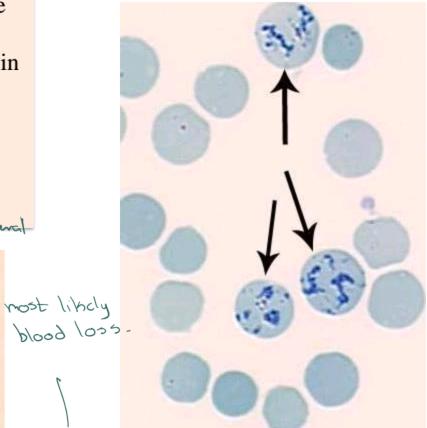


Reticulocyte

Mature Erythrocyte







xir you take a Cilm & notice

#### **Granulopoiesis (Neutrophils, Eosinophils and Basophils formation)**

✓ Takes about 2 weeks

Stages of differentiation are characterized by:

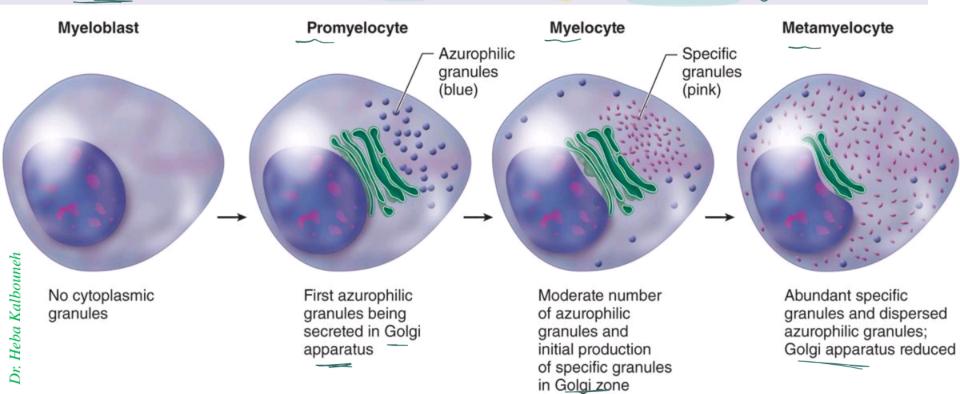
scondan 1- Cytoplasmic changes dominated by synthesis of azurophilic granules and specific granules.

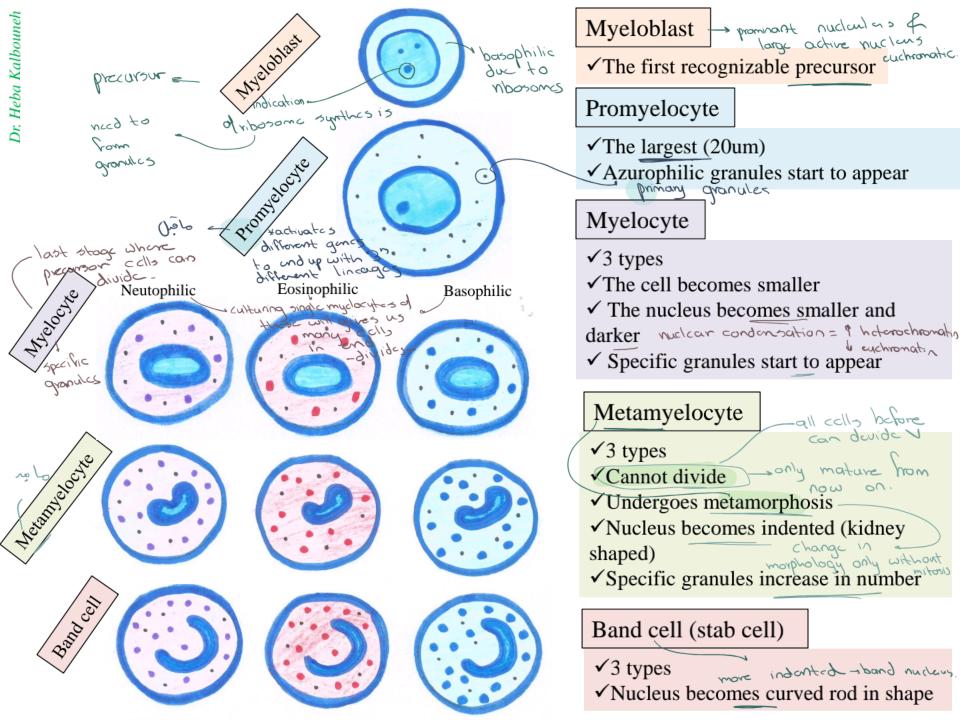
usame in all

**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)

\*start with cuchromatic open nucleus

2- Condensation, indentation and segmentation of the nucleus nucleur charges



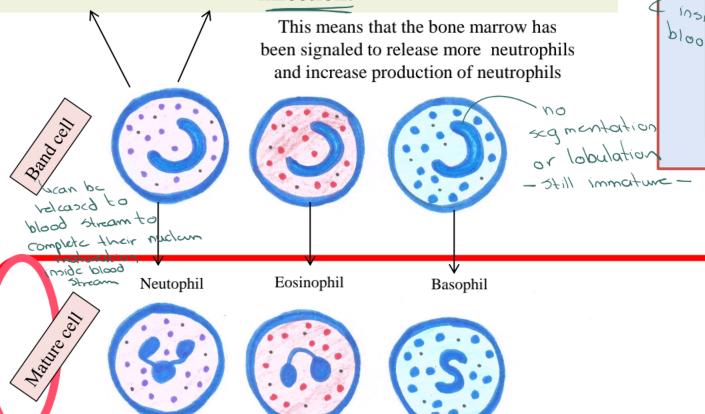


#### Neutrophilic band cells (important CLINICALLY)

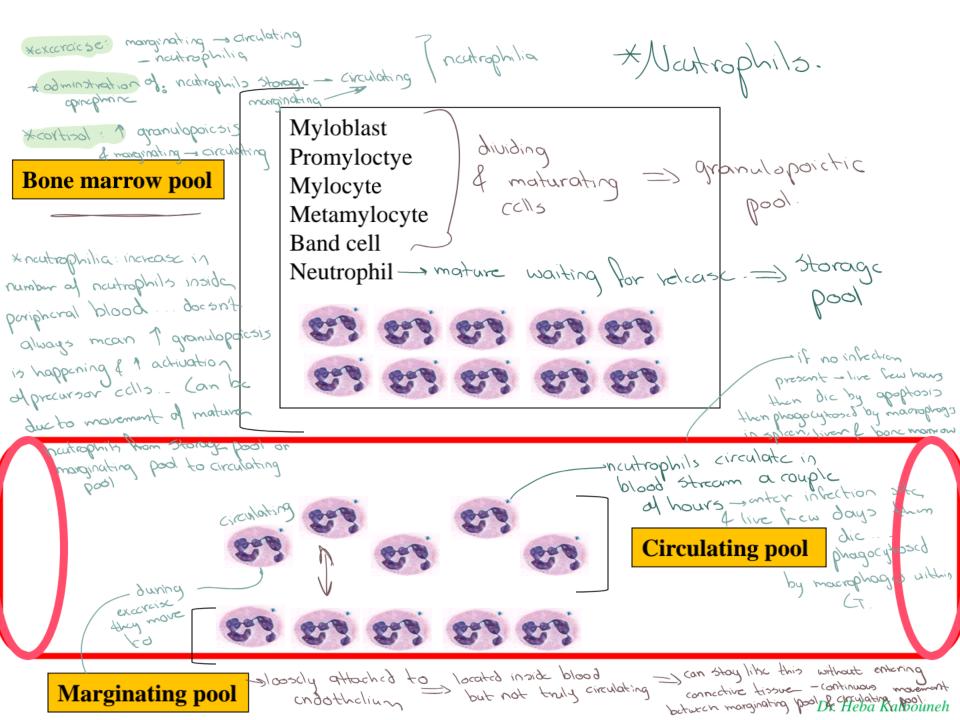
Their percentage does not exceed 5% in peripheral blood



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.



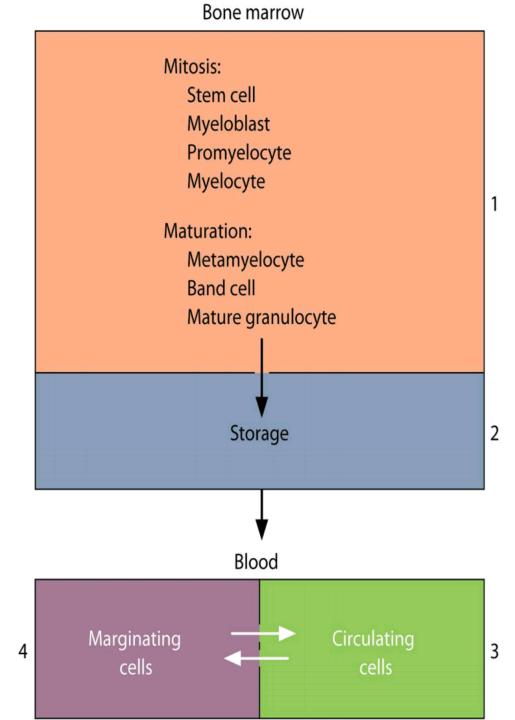
Band cell is almost a mature neutrophil, just doesn't have a segmented nucleus yet



- (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.



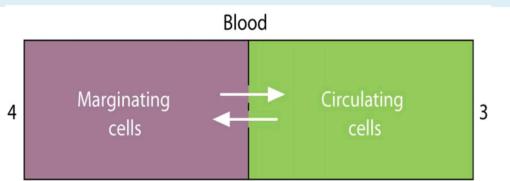
Inflamed connective tissues thus form a fifth terminal compartment for neutrophils, where the cells reside for a few days and then die by apoptosis, regardless of whether they have performed their major function of bacterial phagocytosis.

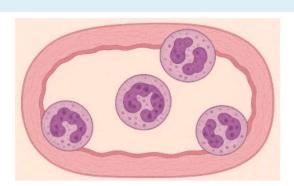
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Changes in the number of neutrophils in the blood must be evaluated by taking all their compartments into consideration.

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.



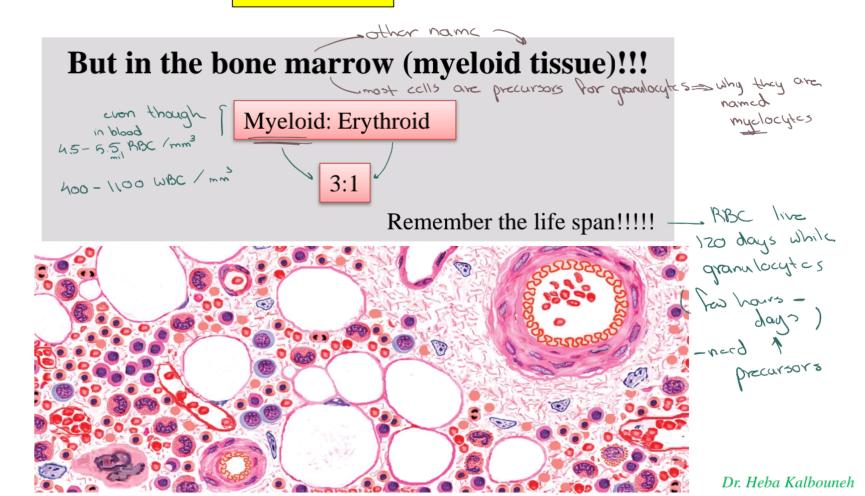


## How many RBCs are in 1 ul of peripheral blood?

5 million/ul

## How many WBCs are in 1 ul of peripheral blood?

4500-11000/ul

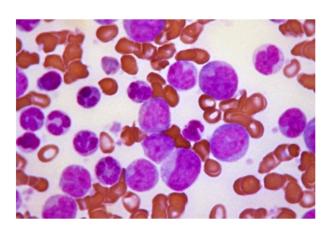


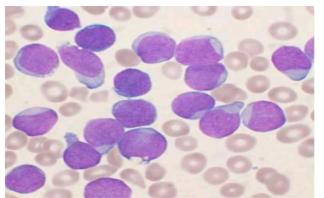
#### White blood cell abnormalities

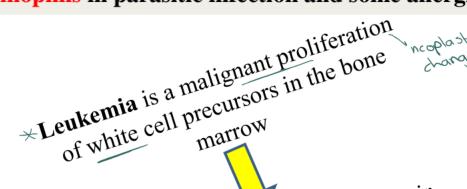
Increased numbers of white cells appear in the peripheral blood in a variety of disorders and provide a useful clue to the underlying disease.

A considerable and sustained increase of circulating neutrophils in bacterial infection

An increase of circulating eosinophils in parasitic infection and some allergies







Vast number of white cells and their

Vast number of white cells and their

precursors (many of which spell over

into the blood)

into the blood)

into the blood)

into the cell according to the

cell line involved (granulocytic,

monocytic, lymphocytic)

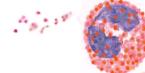
monocytic, lymphocytic)

100 plood except for band colls & reticulocytes at a contain %

Stem cells **Bone marrow** Progenitor cells Precursor cells

those colls can be destroyed by radiation/ chamathorapy) autoimmune diseases which causes hypoplasia inside bone marrow (or even a plastic)

Peripheral blood









in activity of flucte colls.

recent divide to



mentain number of cells





should take something called bone aspirate or bone if you observe reduction in all piopsytupes of cells on see abnormal precursor **Blood film/smear** 4

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

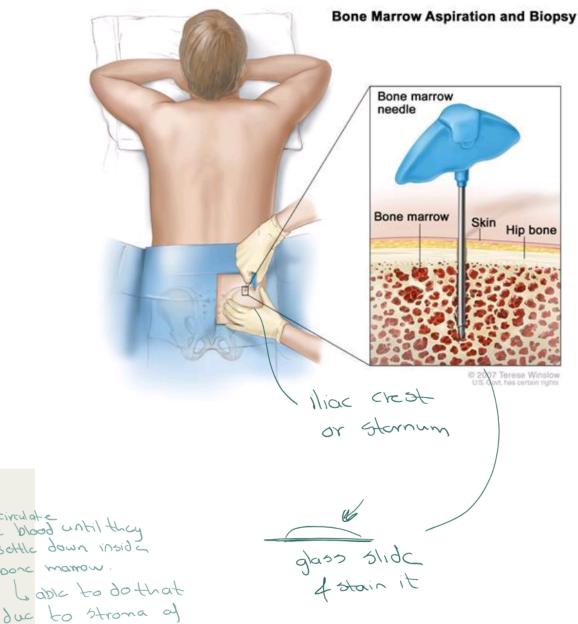
by hypoplastic
bone manow

\* aroming here is misnomets:

Should be called—spaneytopenia

due to reduction in all types

of blood cells not only RBCs.

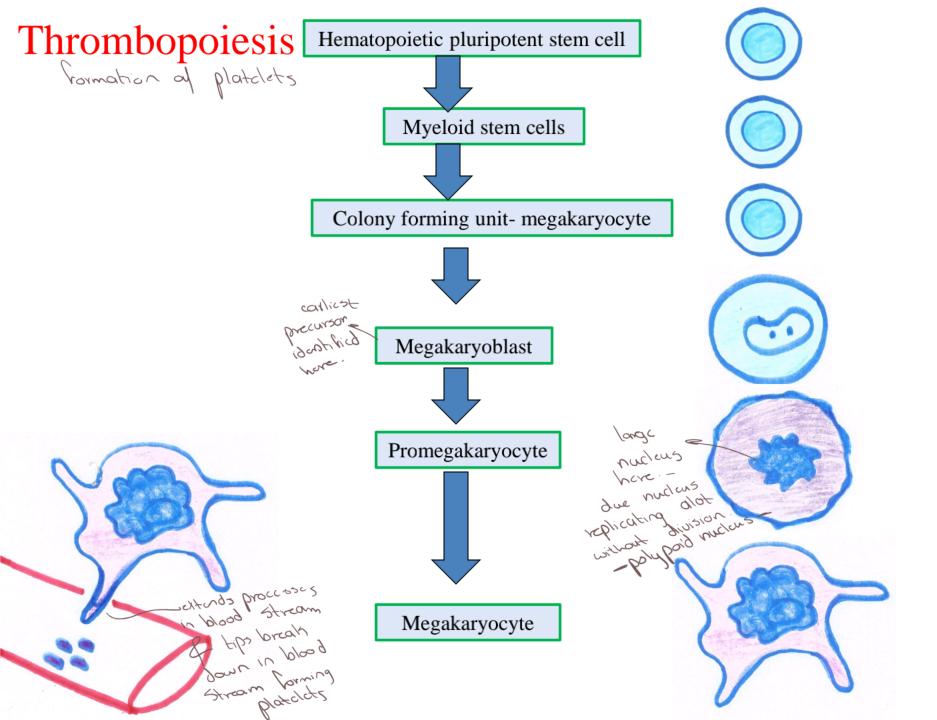


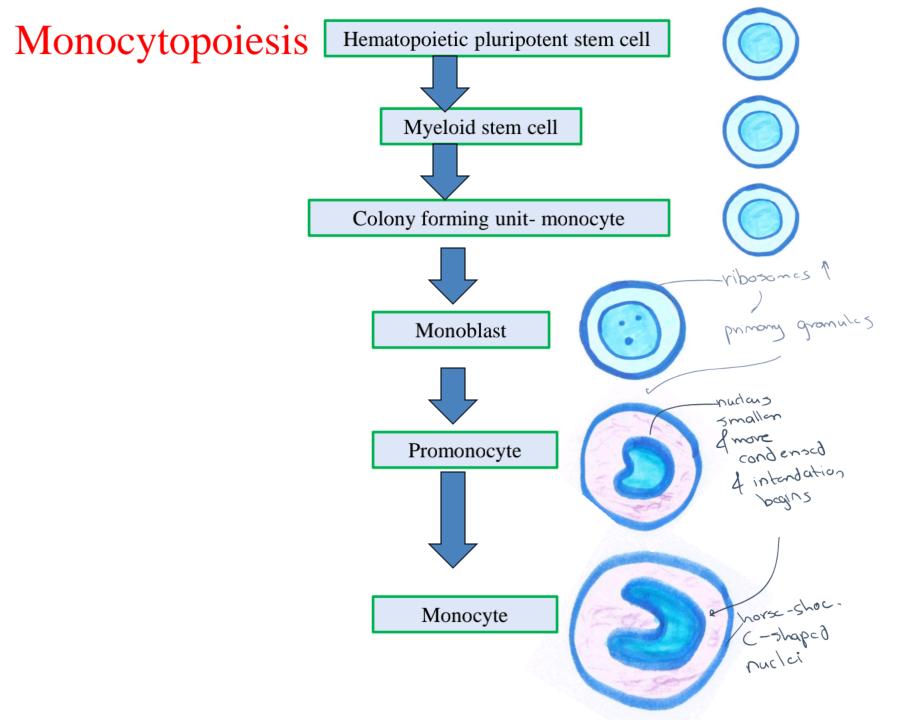
## **Bone marrow transplantation**

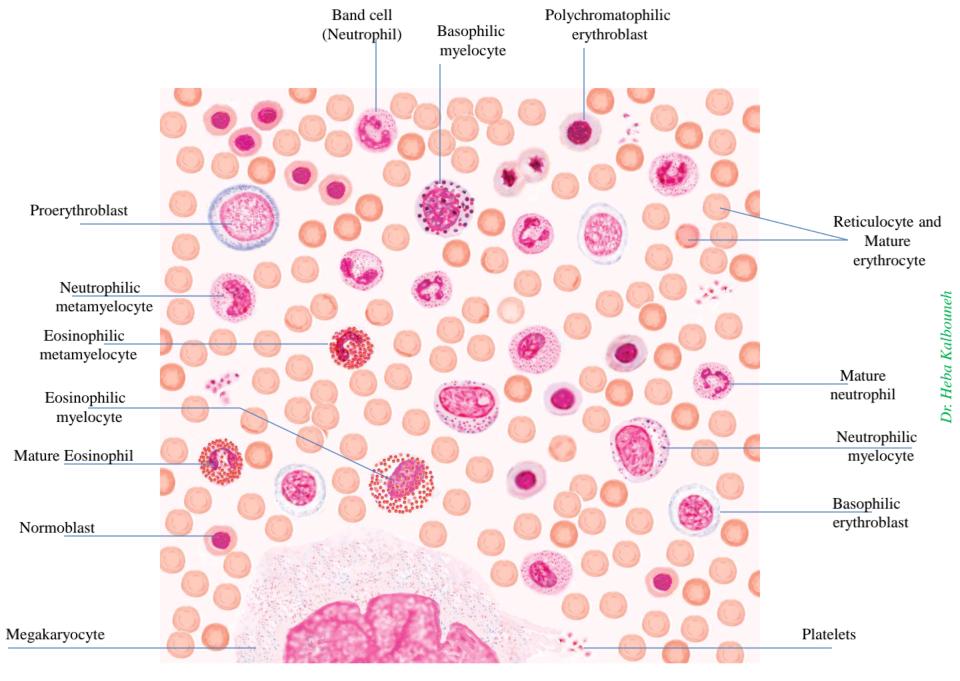
In bone marrow diseases like will circulate with they leukemia, hematopoietic stem cells settle down inside taken from a donor are infused into lone marrow.

the same or another person

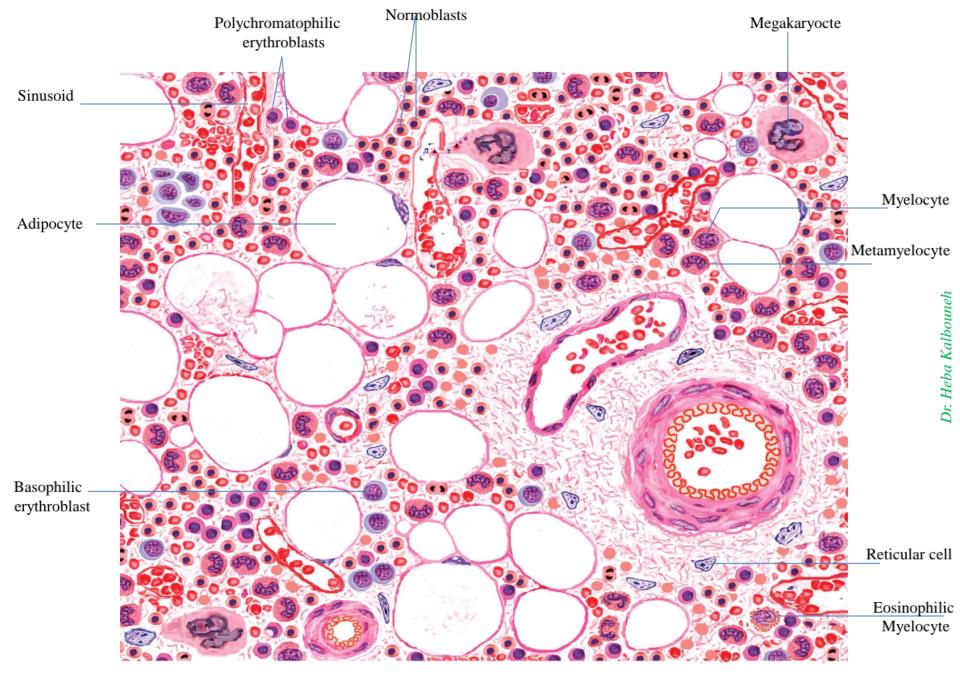
bone marrow—s reticular
cells have specific adhesions
that act as homing-in teceptor





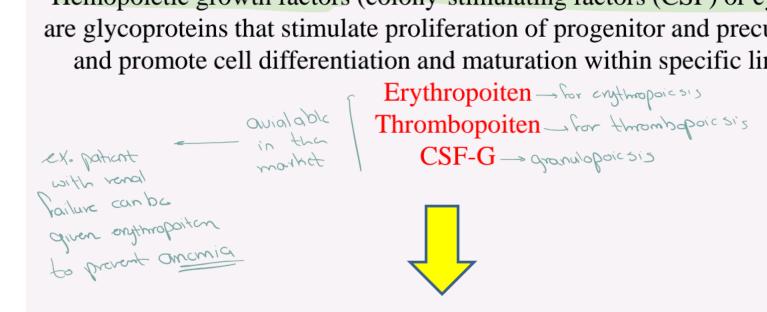


**Bone marrow (Giemsa stain)** 



Bone marrow (H&E)

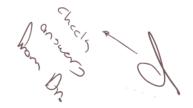
Hemopoietic growth factors (colony-stimulating factors (CSF) or cytokines) are glycoproteins that stimulate proliferation of progenitor and precursor cells and promote cell differentiation and maturation within specific lineages.



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.

## 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



