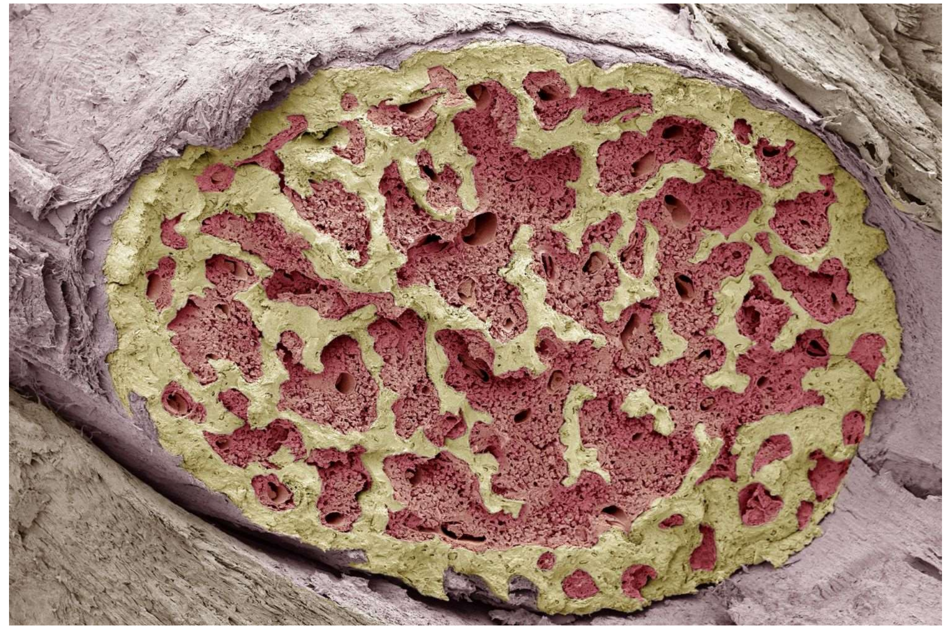
Bone Marrow

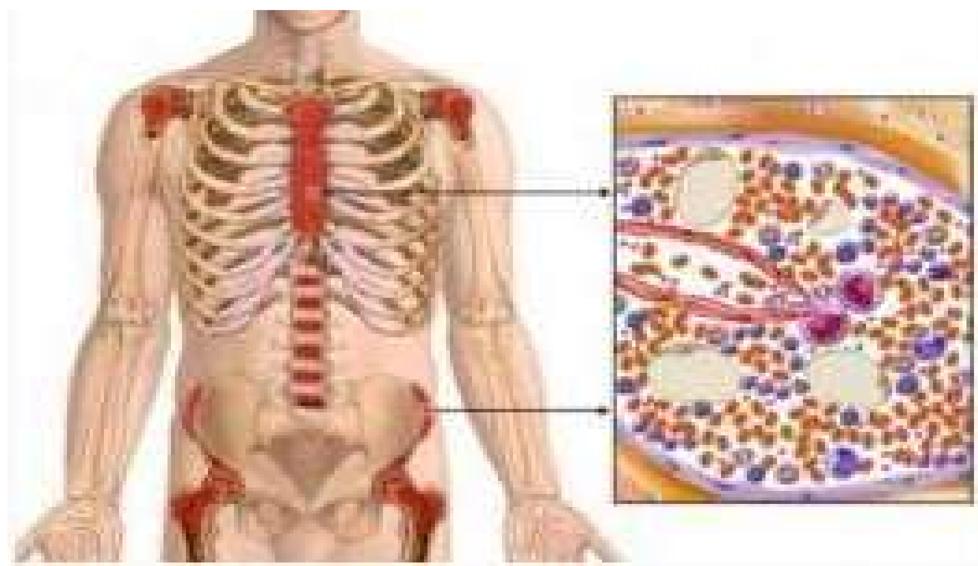
Assoc. Prof. Sinan Özkavukcu
Department of Histology and Embryology
Lab Director, Center for Assisted Reproduction, Dep. of Obstetrics and Gynecology

Bone Marrow

- Bone marrow is responsible for the production of the blood cells and contains many different cell types.



- Cylindrical cavities in the middle of the long bones
- Vertebral bones
- Ribs (costa)
- Sternum (breastbone)
- Pelvis (hip bones)
- Located in the spongy bone of the skull



Activity

- Active red bone marrow is present in all bones in the newborn
- At 4-5 years of age, number of blood-making cells decrease and the number of fat cells begins to increase
- Diaphyseal (middle) regions of long bones are completely surrounded by yellow bone marrow, rich in fat cells.
- In the adult, red bone marrow remains in the metaphyseal (tip) regions of the long bones, such as the femur and humerus, and in the axial flat bones.
- When needed, yellow bone marrow can turn into red bone marrow.

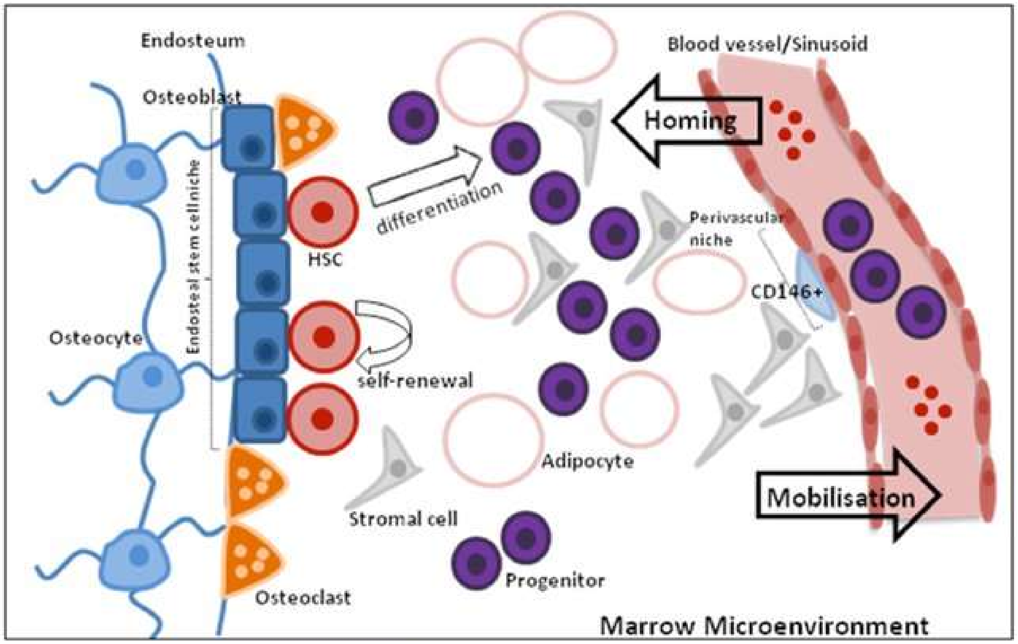
General structure

- Bone-bone marrow (macroenvironment)
- Bone marrow cells, stroma
- Matrix
- Stem cells

(microenvironment)

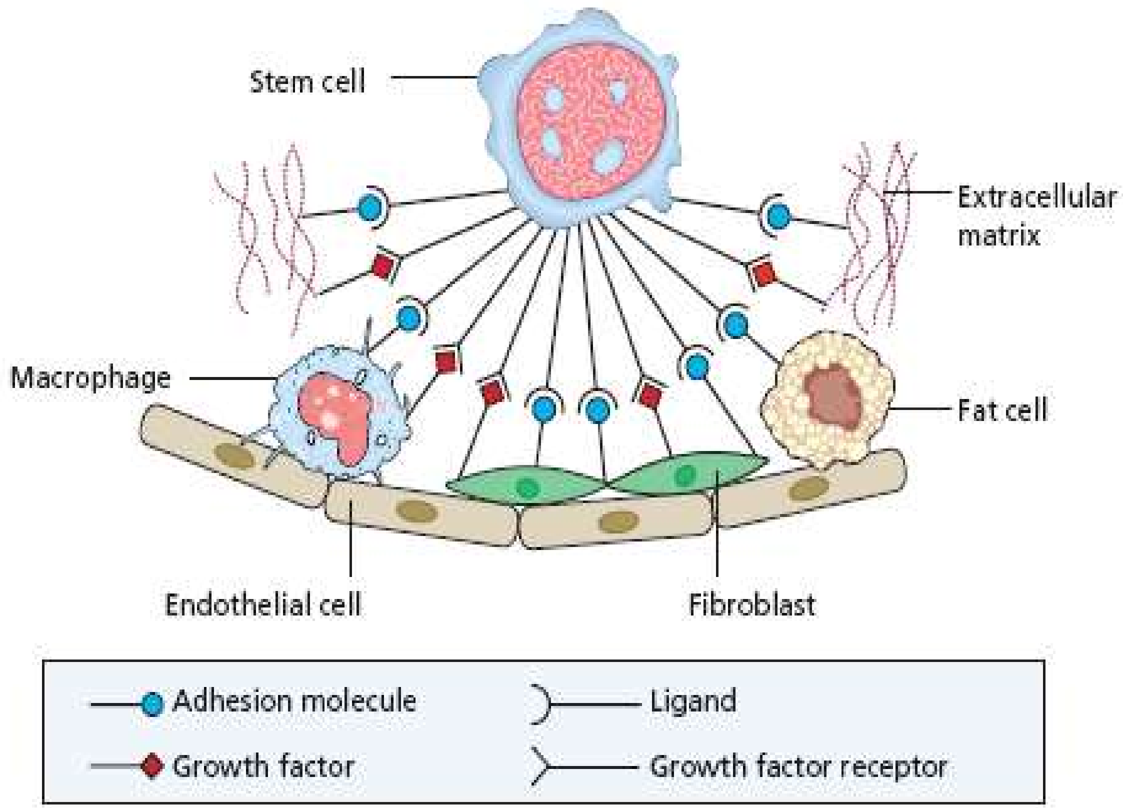
Blood forming unit

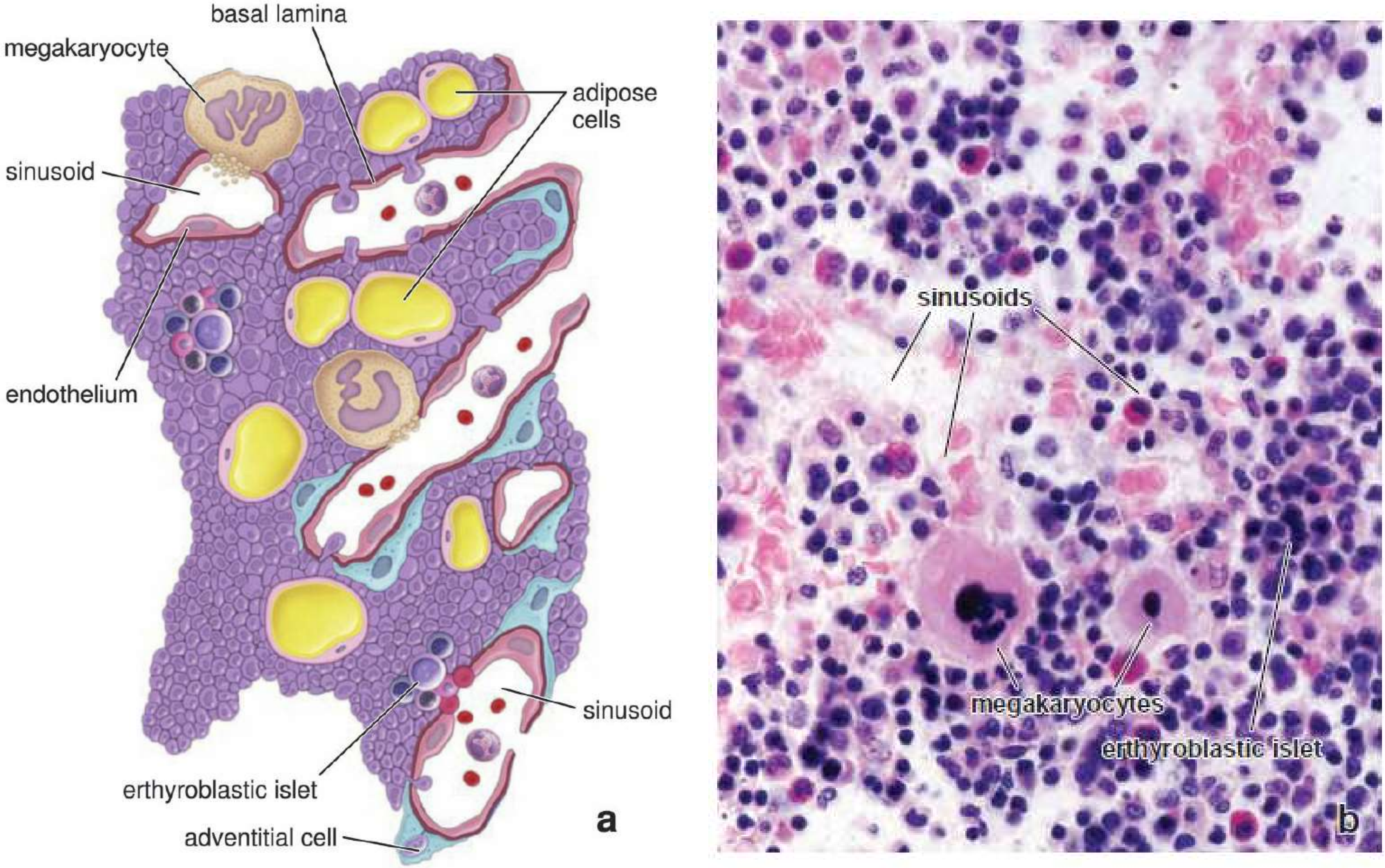
- Hosts hematopoietic stem cells
- These cells are irregularly located in the bone marrow, among which «venous sinus networks» or sinusoids perforate the tissue.
- The sinusoid wall consists of an endothelial lining, a discontinuous basement membrane, and an incomplete covering of adventitial cells.
- The endothelium is a simple squamous epithelium.



General structure

- Skeleton of the tissue has **reticular cell network**
- Network of **reticular fibers**
- **Fat cells**
- **Macrophages**





Sinusoids are special vascular structures. Lined with endothelium, there are intermittent adventitial (reticular) cells outside the basement membrane.

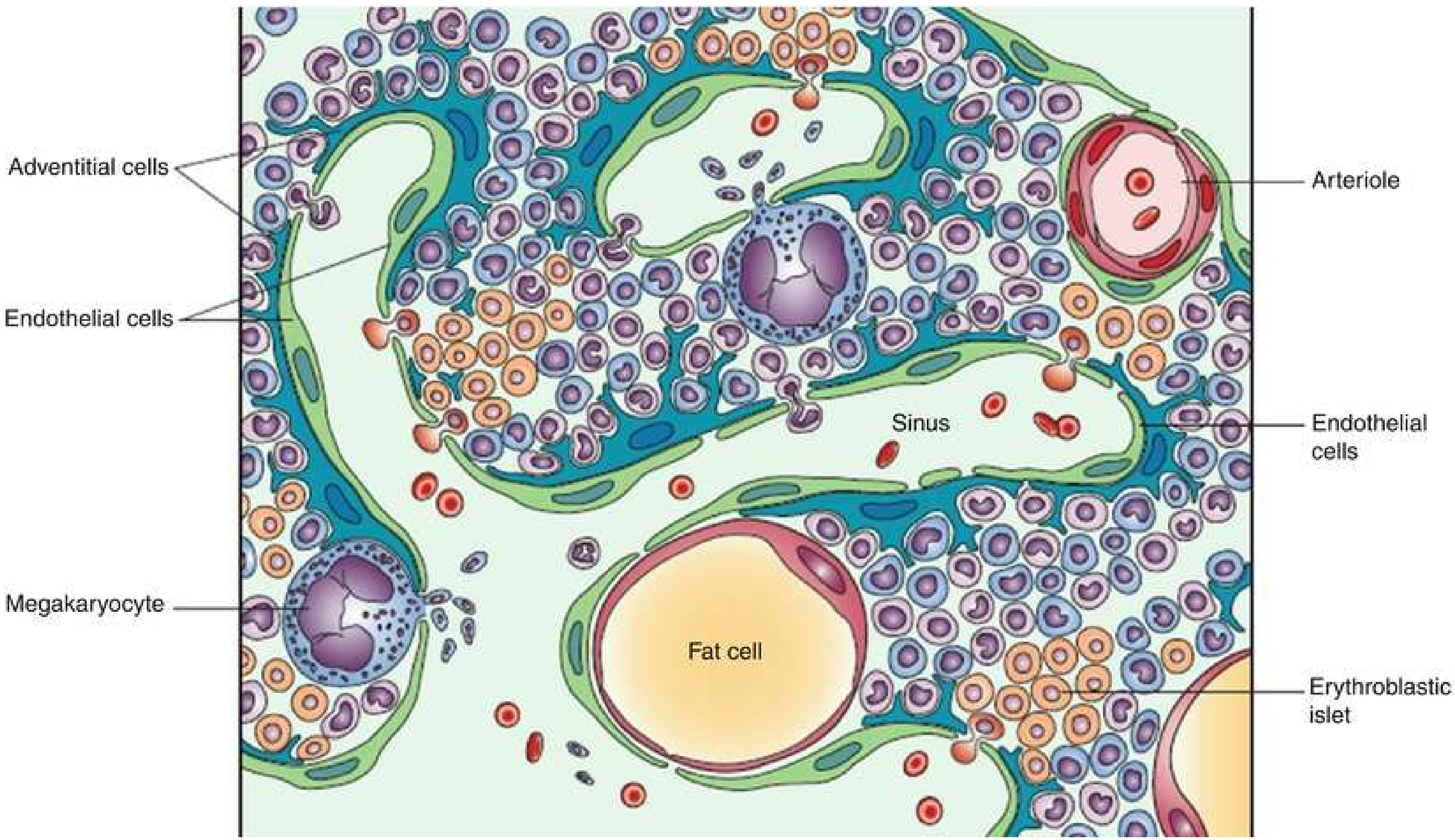
Adventitial (reticular) cells

- They send leaf-like appendages to hematopoietic cell cords and acts as a support during the development of blood cells.
- Responsible for the production of reticular fibers
- It allows the precursor cells to be differentiated into blood cells by the various cytokines that they secrete (colony-stimulating factors, IL-5, IL-7).
- Differentiated or matured cell is replaced with the adventitial cell and approaches the sinusoid and is released into the circulation by connecting with the endothelium.

Adventitial (reticular) cells

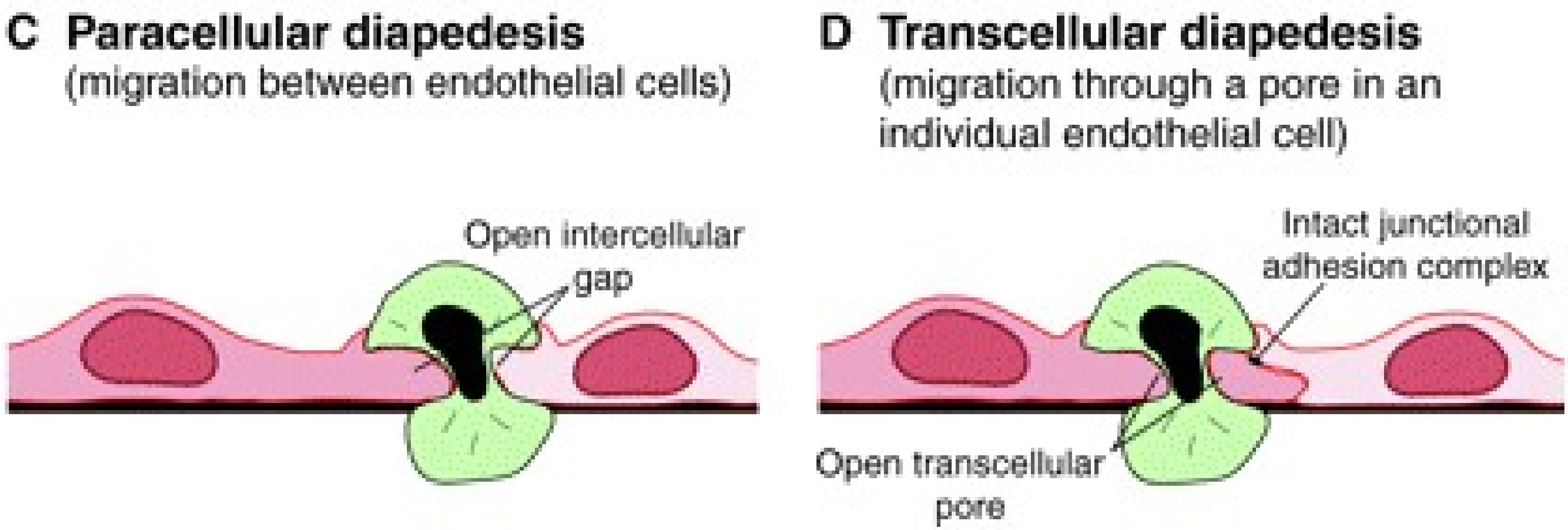
- It is similar to fibroblasts of connective tissue and is of mesenchyme origin.
- They are stained pale, difficult to spot between hematopoietic cells
- Unlike fibroblasts, they form cell networks
- Fat cells in the stroma are formed by storing fat in the cytoplasm of these cells.

The **sinusoid** wall consists of an **endothelial lining**, a **discontinuous basement membrane**, and an incomplete covering of **adventitial cells**.



Venous sinuses-Sinusoids

- Lined with squamous endothelial cells, connected by intercellular complexes
- It is a closed circulatory system in the bone marrow. Maturing cells must cross the endothelium and enter the sinusoids
- A maturing cell or a piece of megakaryocyte pushes the endothelial cell membrane, membrane is pressed against the luminal plasma membrane until they fuse, thus forming a transitory opening or aperture.
- This is a trans-cellular transition. (NOT inter-cellular or para-cellular)
- After the transition, the endothelium repairs itself and closes the aperture


C Paracellular diapedesis
(migration between endothelial cells)
Open intercellular gap
D Transcellular diapedesis
(migration through a pore in an individual endothelial cell)
Intact junctional adhesion complex
Open transcellular pore

Functions of the red bone marrow

1- Making of blood cells.

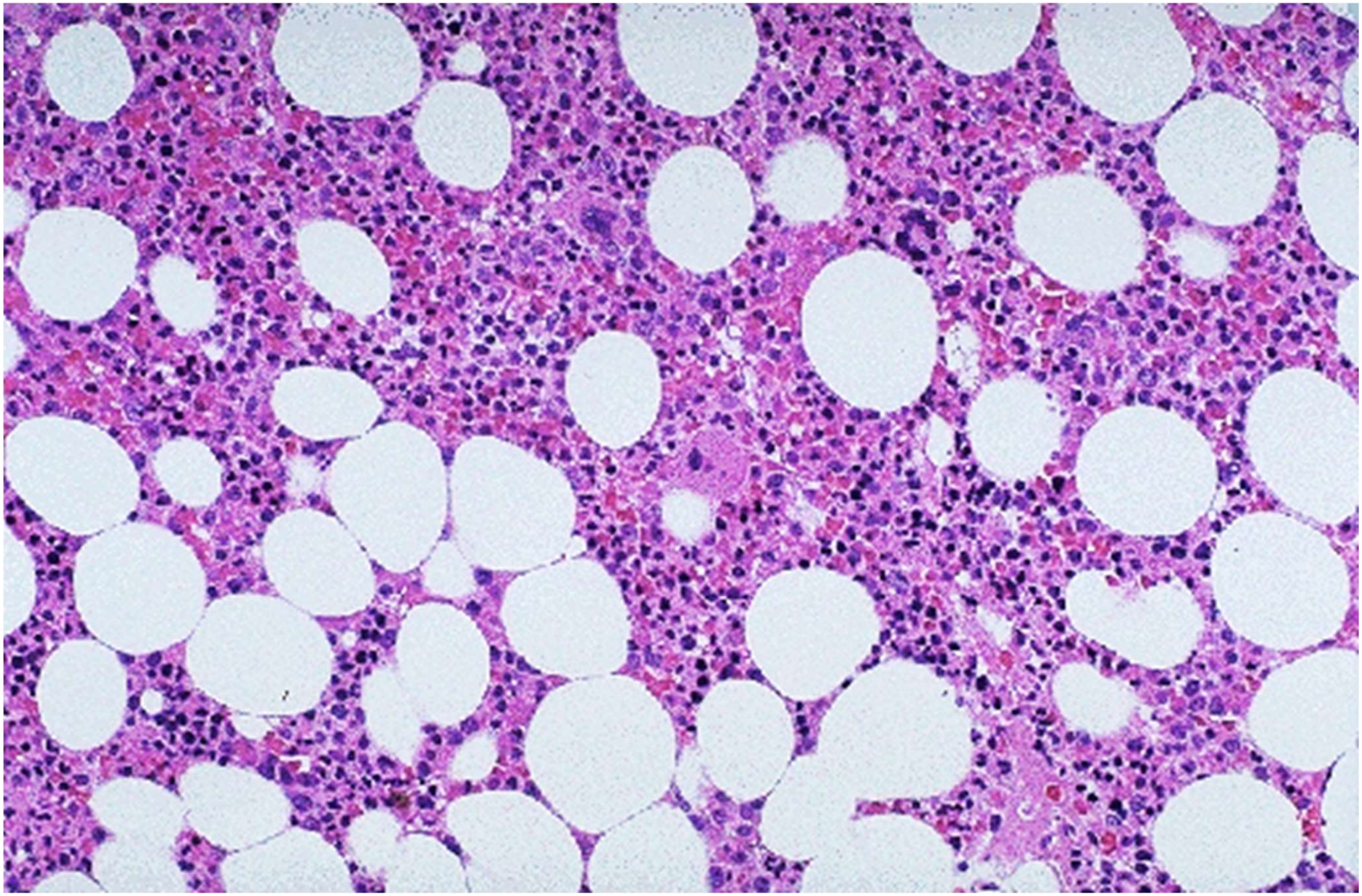
2- Degradation of erythrocytes and storage of iron released as a result of destruction.

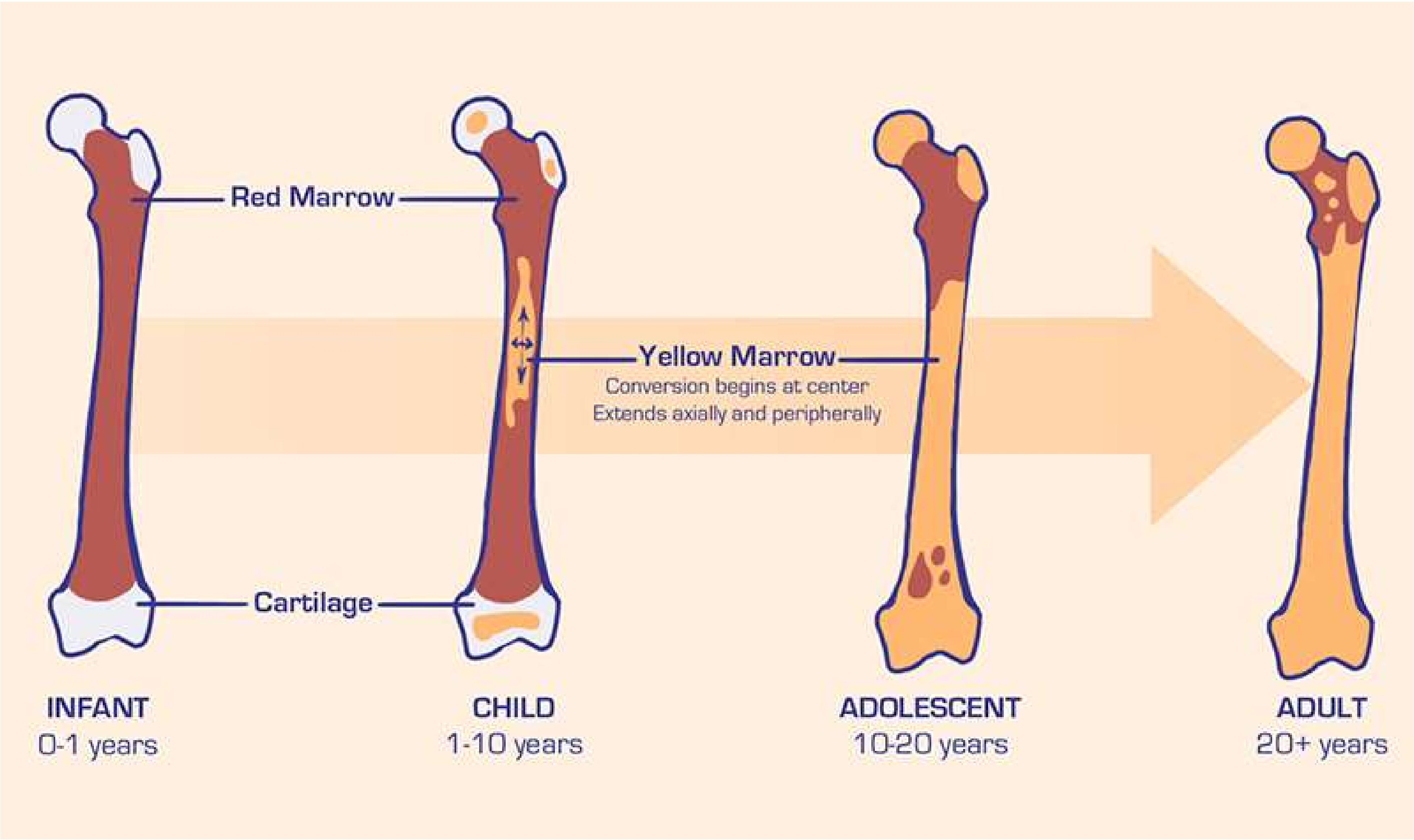
Iron is stored in the cytoplasm of reticular cells and macrophages in the form of ferritin and hemosiderin. Apart from bone marrow, iron is also stored in liver cells, striated muscle fibrils and spleen macrophages.

3- Indifferentiated T and B-lymphocyte production

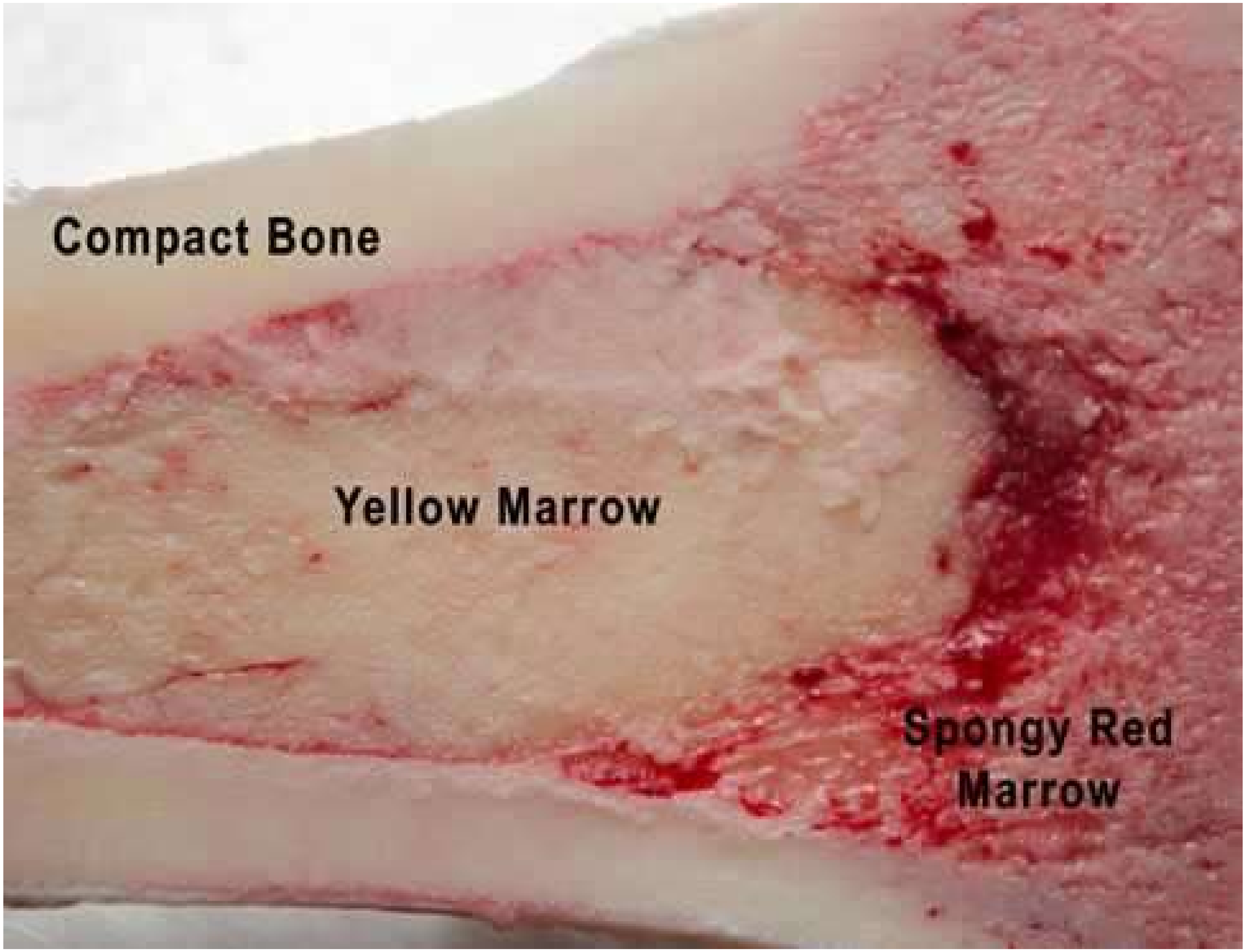
Bone marrow contains mainly 3 cell populations

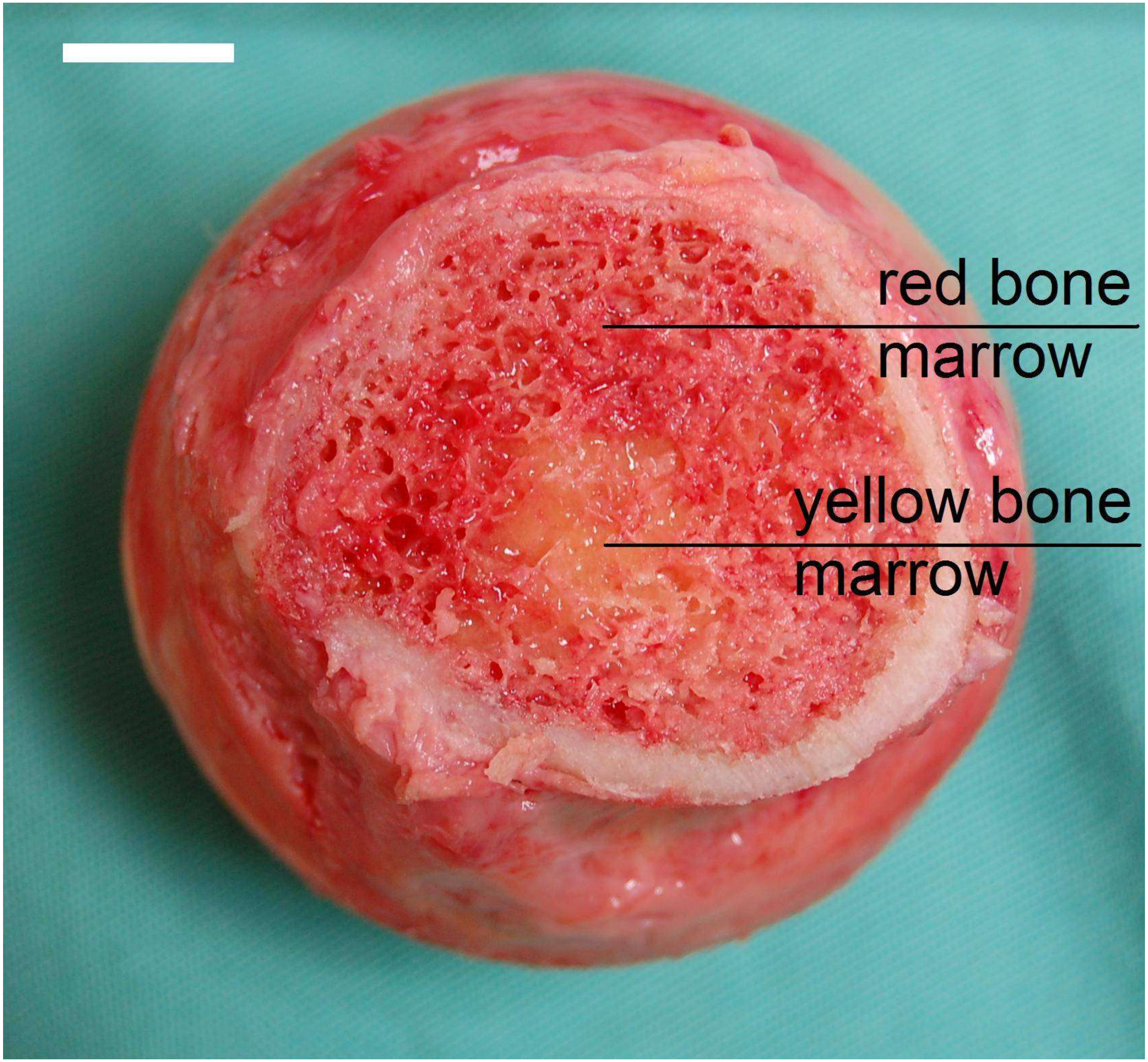
1. **Stem cells**: They are cells that can renew themselves.
    - Stem cells are morphologically indistinguishable from other cells, they can only be recognized by specific cell surface markers.
    - Construction of blood cells in the bone marrow depends on the presence of high potential hematopoietic stem cells (pluripotent stem cell)
2. **Progenitor cells:** It provides the formation of different cell lines.
3. **Mature cells**: It is a mature blood cell and is the cell that participates in the bloodstream.





Red Marrow
Yellow Marrow
Conversion begins at center
Extends axially and peripherally
Cartilage
INFANT
0-1 years
CHILD
1-10 years
ADOLESCENT
10-20 years
ADULT
20+ years


Compact Bone
Yellow Marrow
Spongy Red
Marrow


red bone marrow
yellow bone marrow

Homing within the bone

- Hematopoietic stem cells are located in areas close to bone surfaces. This is called endosteal bone marrow-hematopoietic stem cell niche.
- The area near the sinusoids is called vascular bone marrow-hematopoietic stem cell niche.
- Adipose cells can be used as an energy source, as well as undertake the synthesis of growth factors.

Yellow bone marrow

- The number of adipose cells increases in the inactive bone marrow and the blood production stops reversibly, this structure is seen in the feature of adipose tissue.
- In adulthood, hematopoiesis has stopped in the diaphyseal region of all long bones and appears covered with fat cells.
- Even in the flat bone marrow with active production, more than half of the tissue is filled with **adipocytes**.

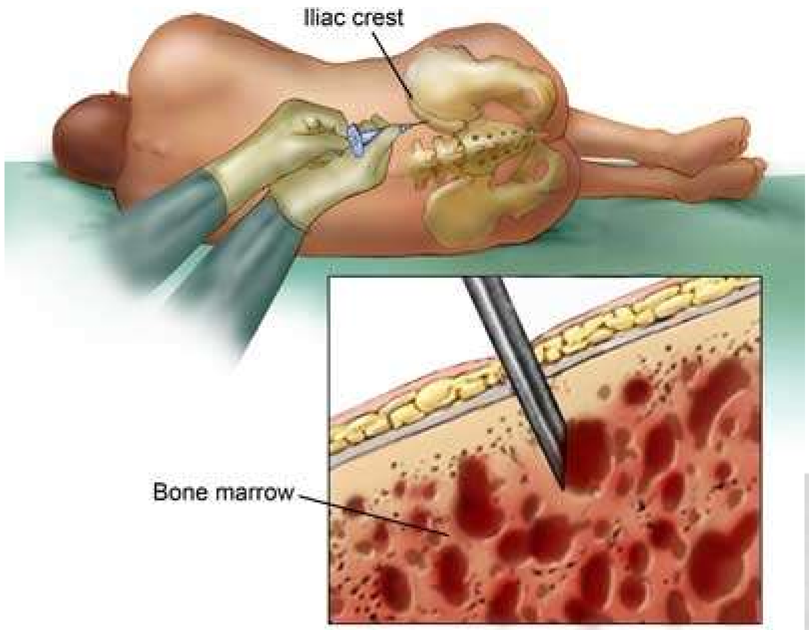
Macroscopically Bone Marrow…

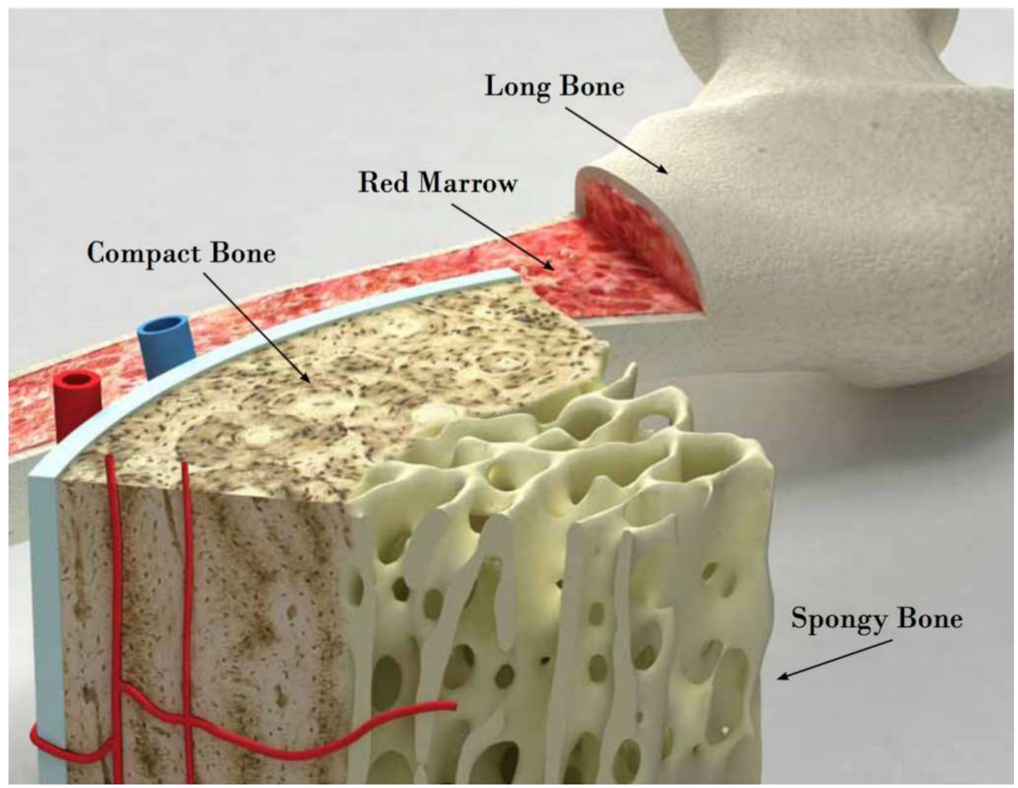
Red BM

- Its red color comes from the large number of erythrocytes and developing erythrocyte series.
- Fetal and newborn bones contain only red BM.
- Formation of blood cells
- Degradation of erythrocytes and storage of iron resulting from destruction
- Indifferentiated T and B lymphocyte production

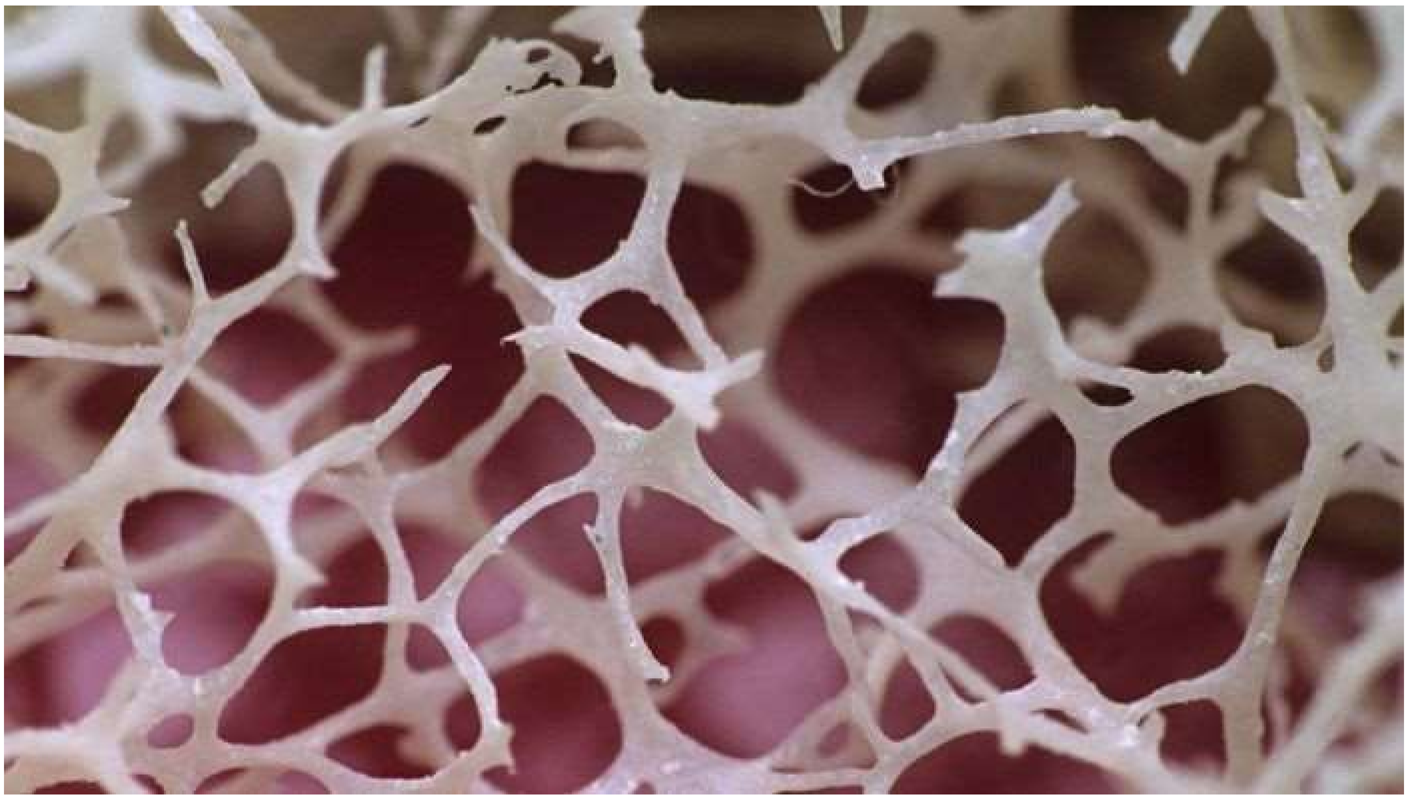
Yellow BM

- Its yellow color is because of its rich fat content.
- Transformation begins at the age of 5-6
- The adult's diaphyses of the long bones contain yellow BM
- Blood cells are not made in the yellow marrow.
- In heavy bleeding or hypoxia, the yellow marrow turns into a red marrow.
- Spare hematopoetic tissue


Iliac crest
Bone marrow

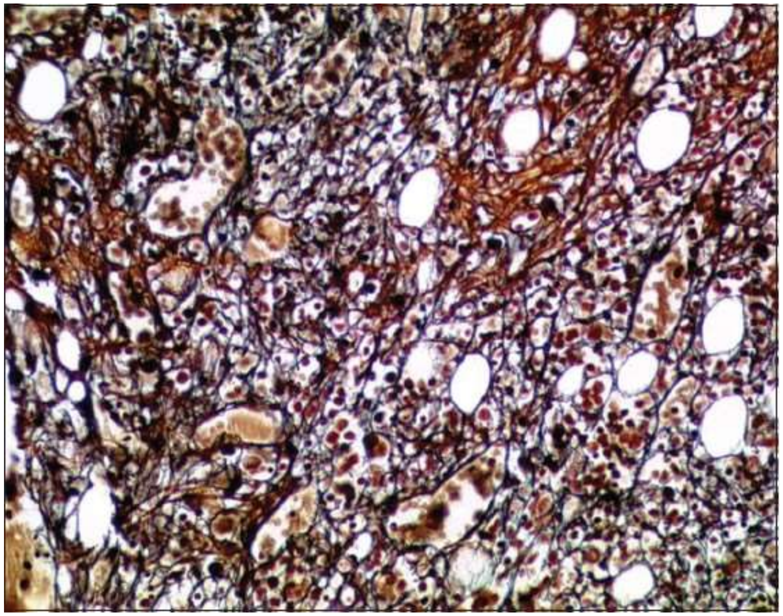

Long Bone
Red Marrow
Compact Bone
Spongy Bone

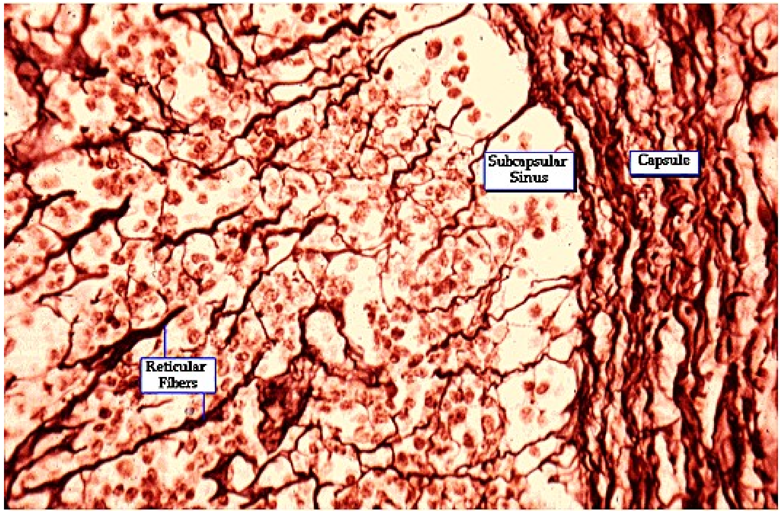
Reticular Connective Tissue

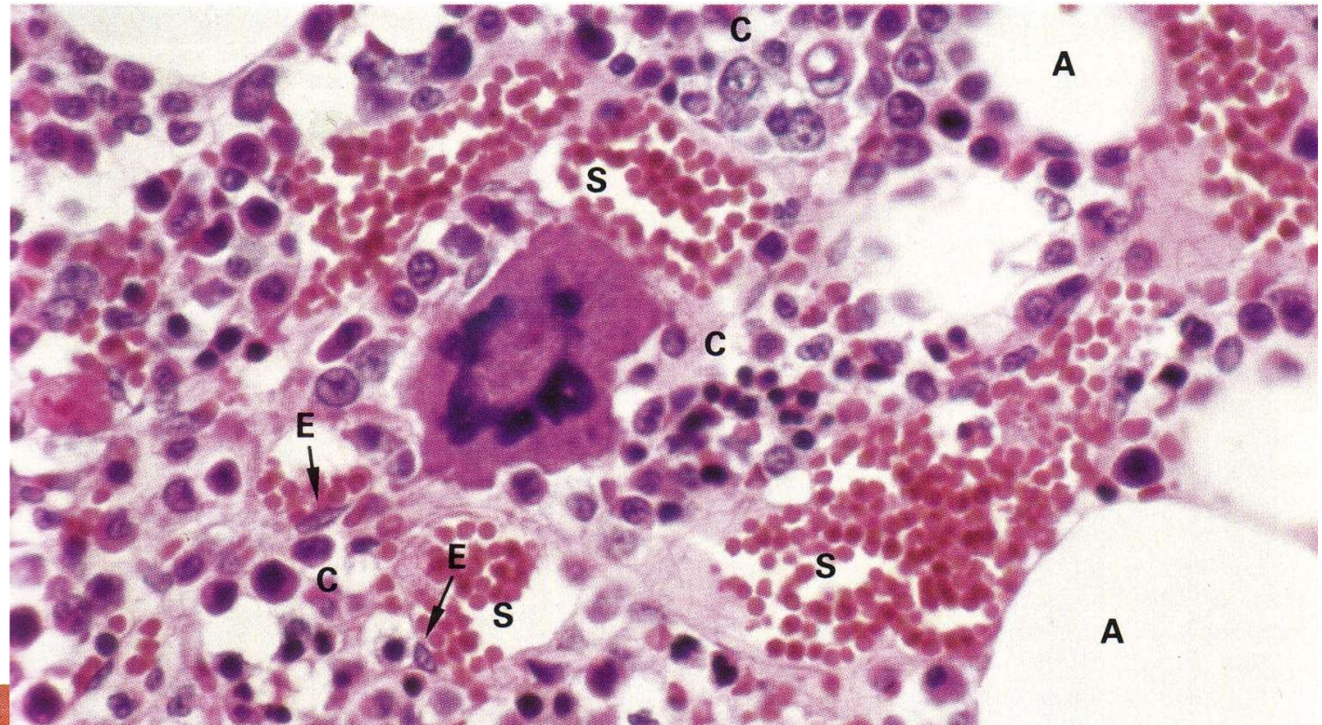


Reticular Connective Tissue

- It is a kind of loose connective tissue in which reticular fibrils are concentrated and forms the skeleton of lymphoid organs (lymphoreticular) and bone marrow (myeloreticular).
- It forms the supporting core of tissues containing various cells.
- Reticular fibrils are of type-III collagen structure and cannot be observed by routine staining methods.
- They have very thin diameters of up to 20 nm, they branch out but do not join together to form thicker fibrils.
- Since they contain large amount of sugar groups (glycosaminoglycans) on them, it is possible to display them specifically with some techniques:
    - silver impregnation method → argyrophilic
    - periodic acid – Schiff (PAS) reaction



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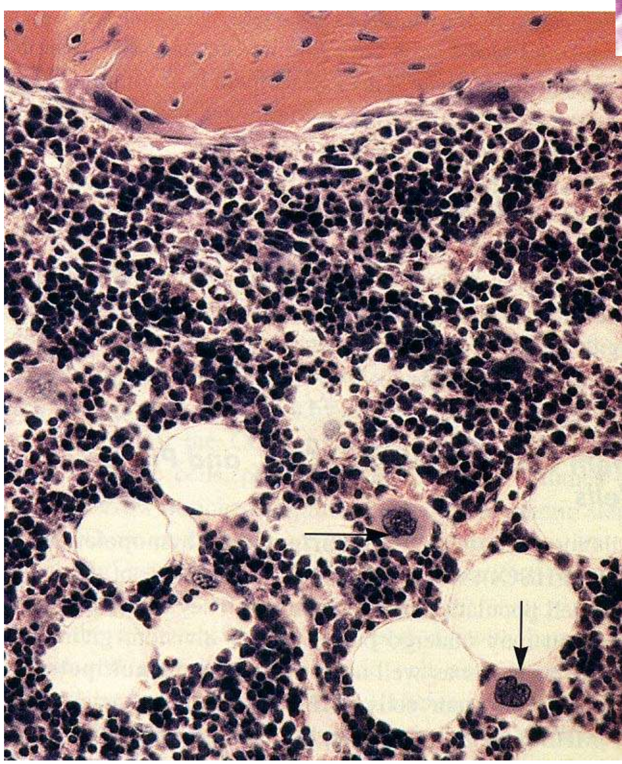
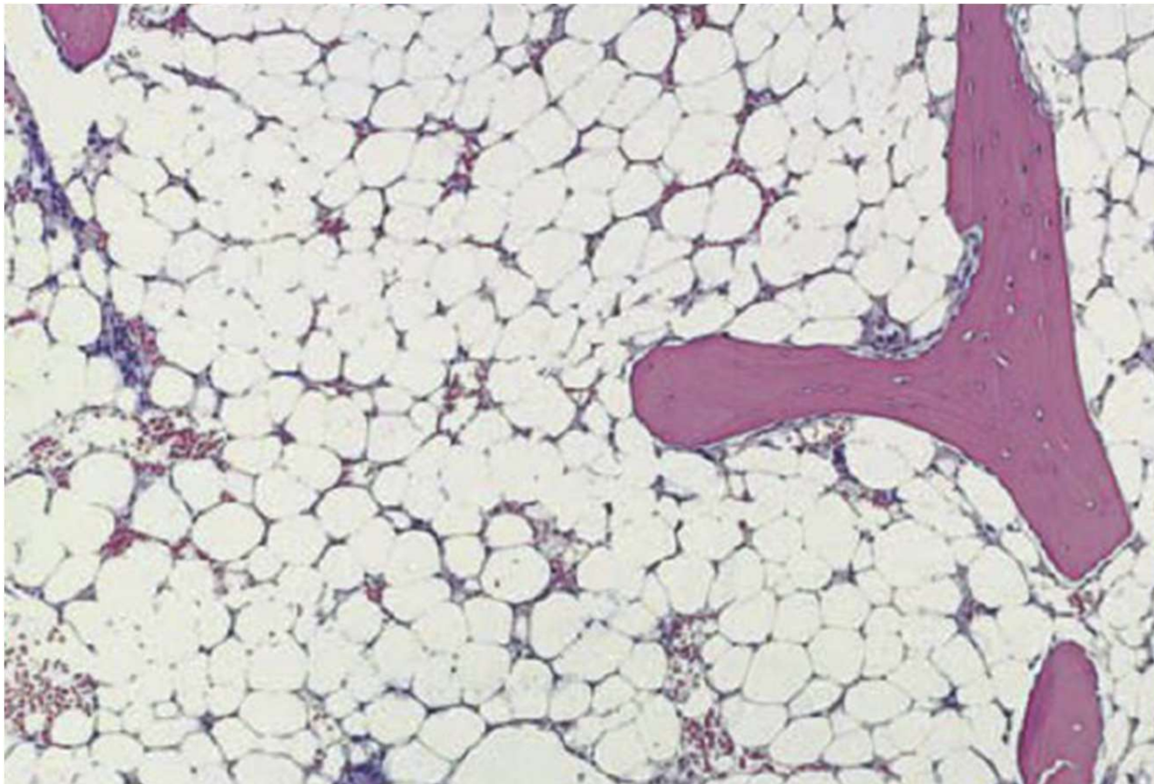
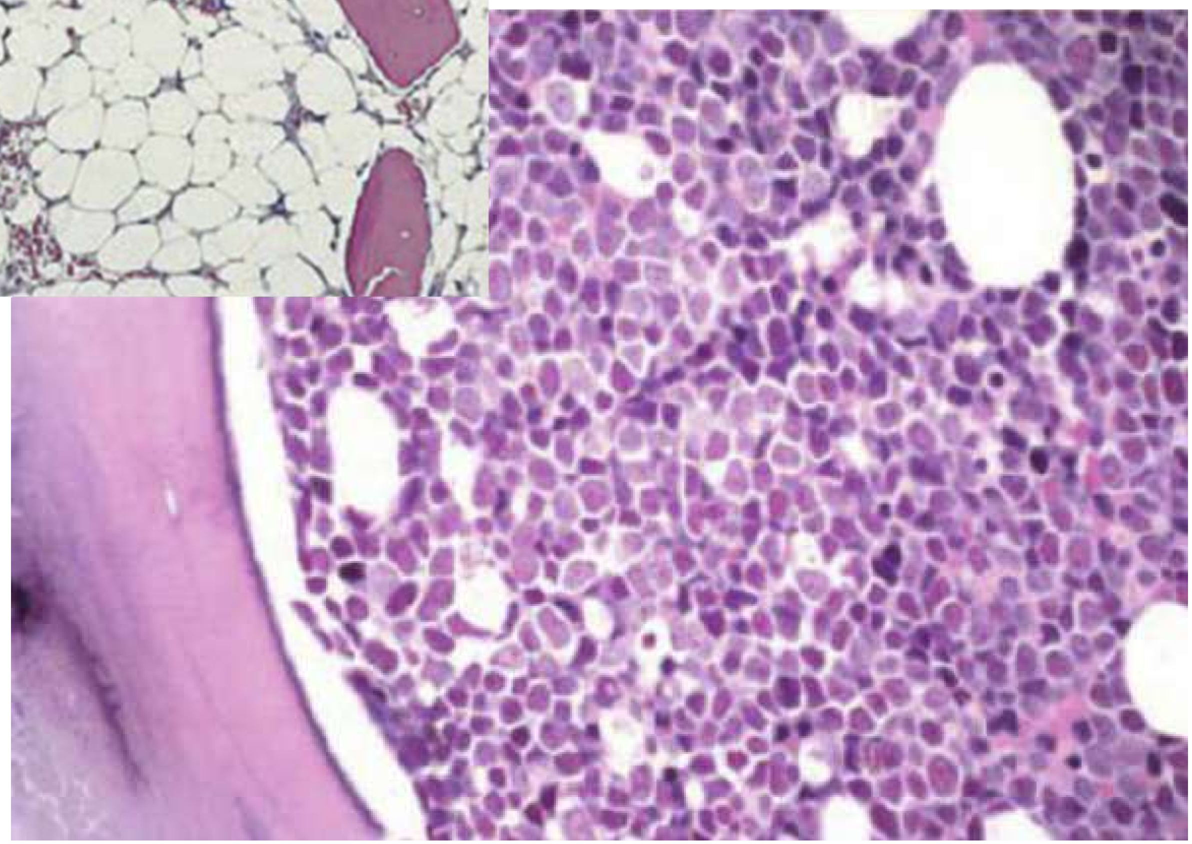
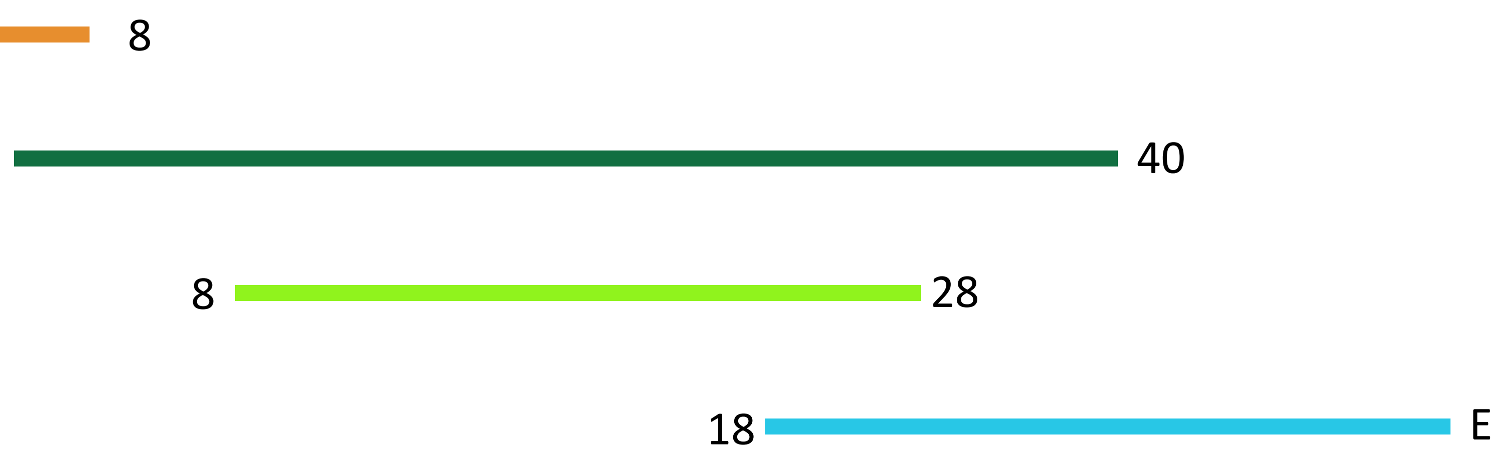


Pre_ and postnatal hematopoiesis

You Love a Smart Bunny

Yolk sac	Liver	Spleen	Bone marrow
3-8 weeks	6 w → birth	8 w → 28 w	18 w → adult



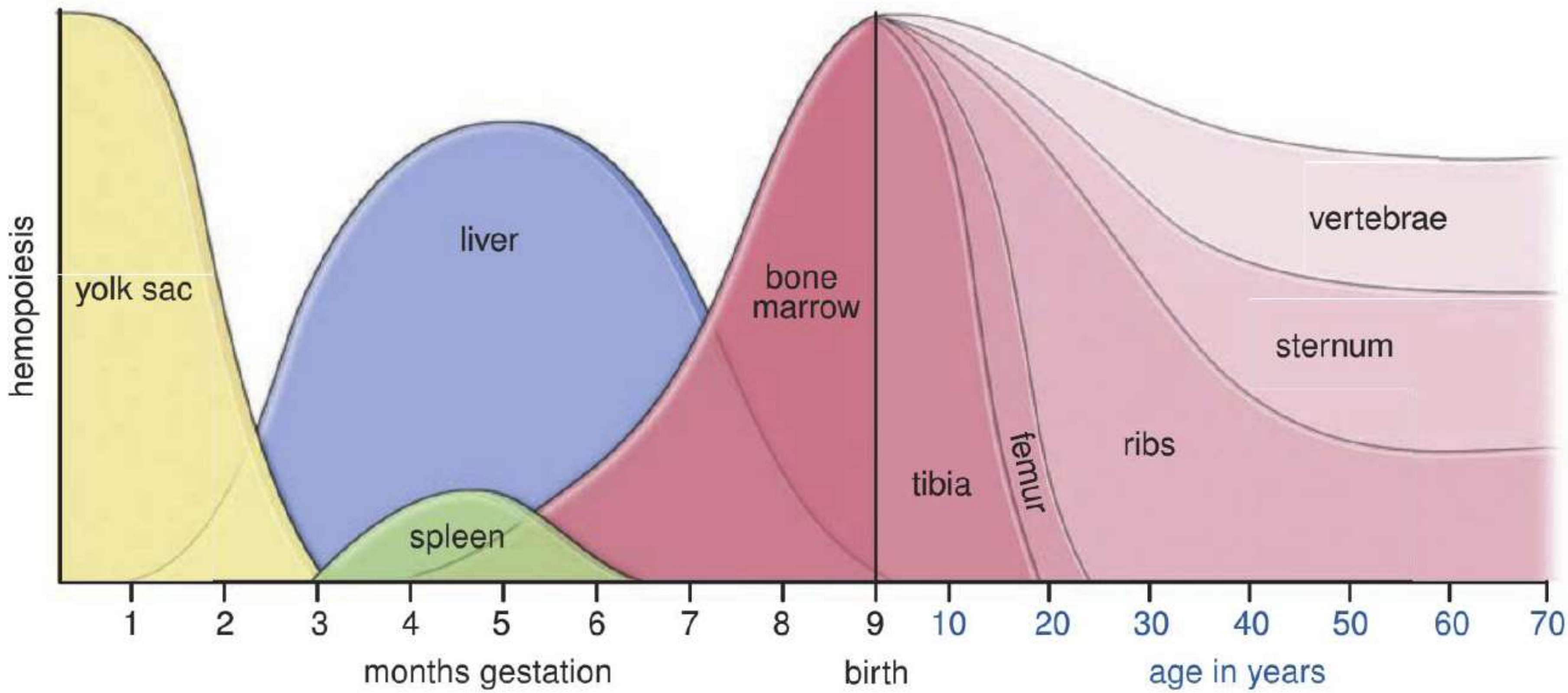
Hemopoiesis (Hematopoiesis)

- It is carried out in hematopoietic organs.

- Erythropoiesis
- Leukopoiesis
- Thrombopoiesis

- Erythrocytes, platelets and granulocytes (neutrophils, eosinophils, basophil leukocytes) of blood cells are produced in myeloreticular tissue (red bone marrow).

- Agranulocytes (lymphocytes and monocytes); they are made both in the red bone marrow and in the lymphoreticular tissues (lymphoid organs).


hemopoiesis
yolk sac
liver
spleen
bone
marrow
tibia
femur
ribs
sternum
vertebrae
1
2
3
4
5
6
7
8
9
10
20
30
40
50
60
70
months gestation
birth
age in years

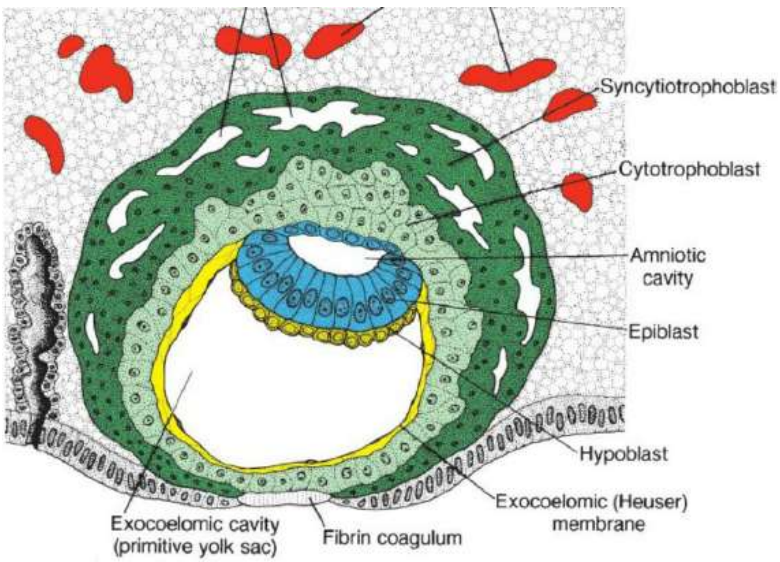
Ensuring continuity

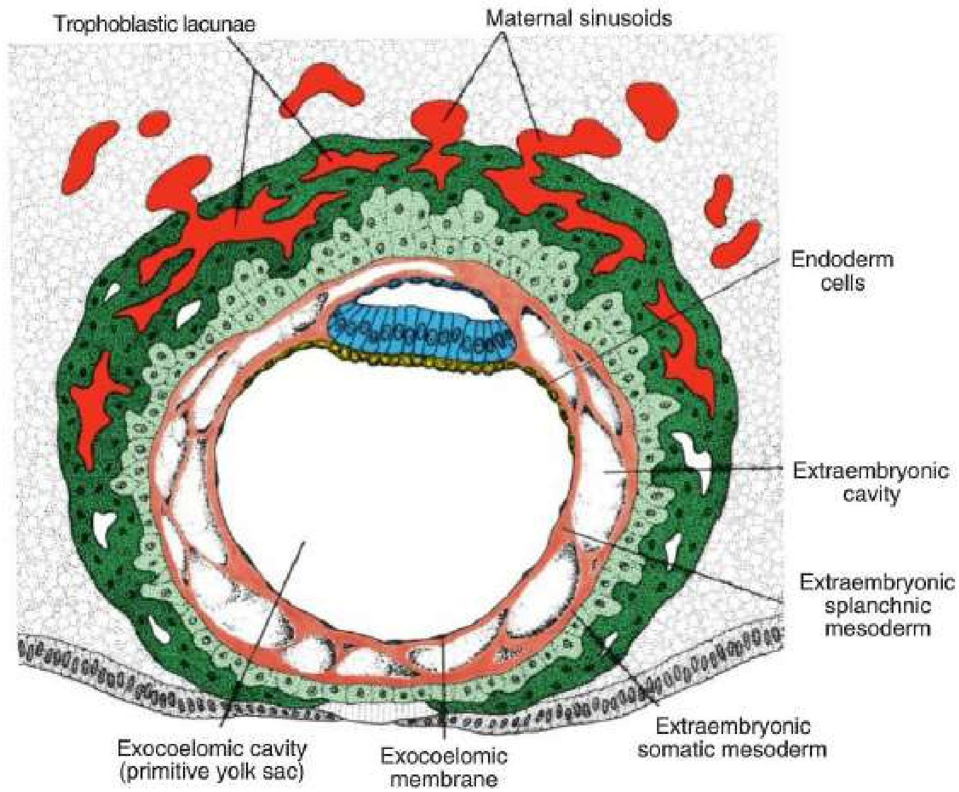
- The circulating blood cells have certain lifetimes. The cells are constantly destroyed and renewed. Therefore, a continuous production dynamics is needed.

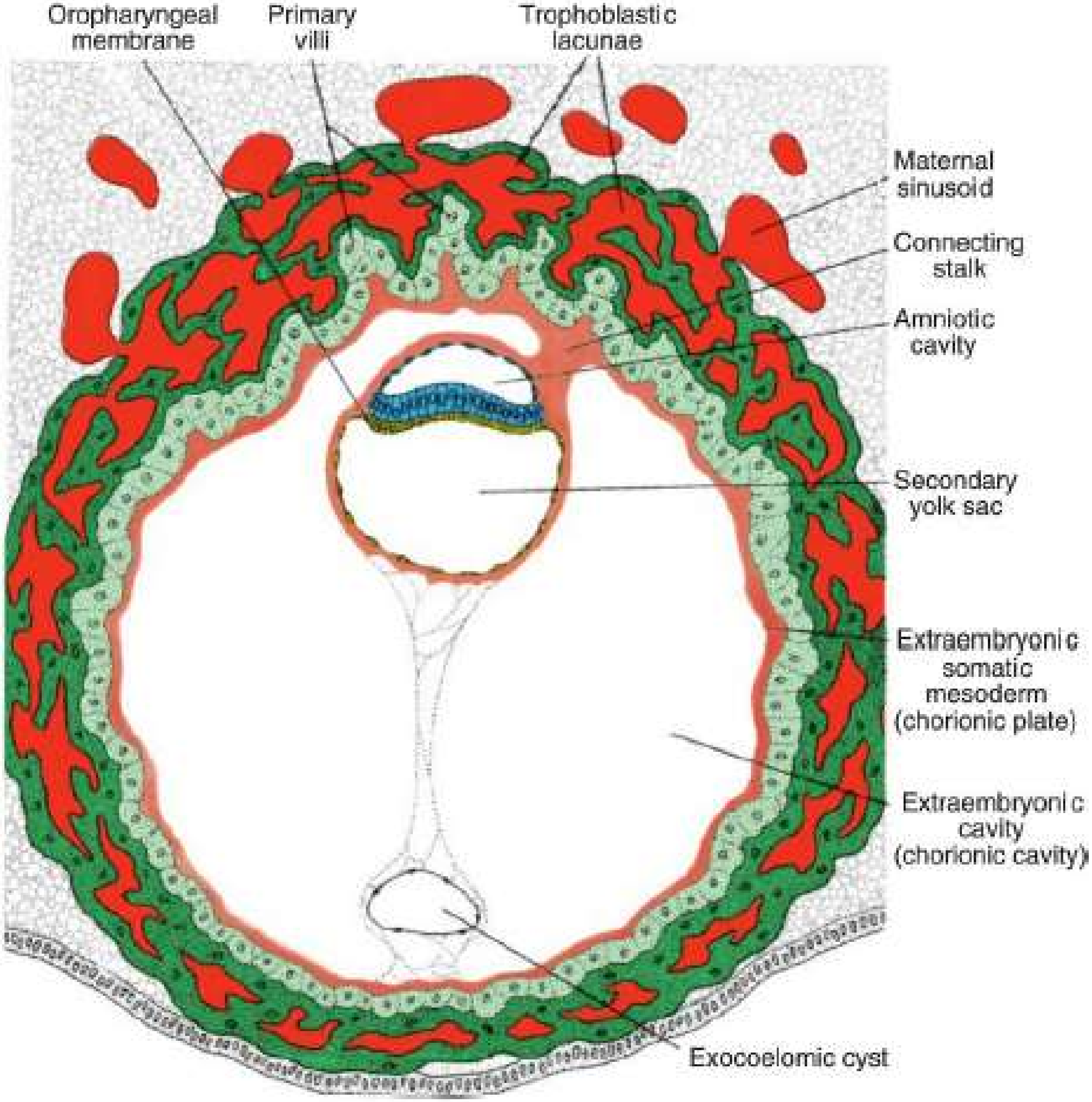
Blood product	Life span
Red blood cells	120 days
Fetal red blood cells	90 days
Platelets	7-12 days
Transfused platelets	36 hours
Neutrophils	8-12 hours in circulation 4-5 days in tissue

Prenatal hematopoiesis

- Yolk sac Stage

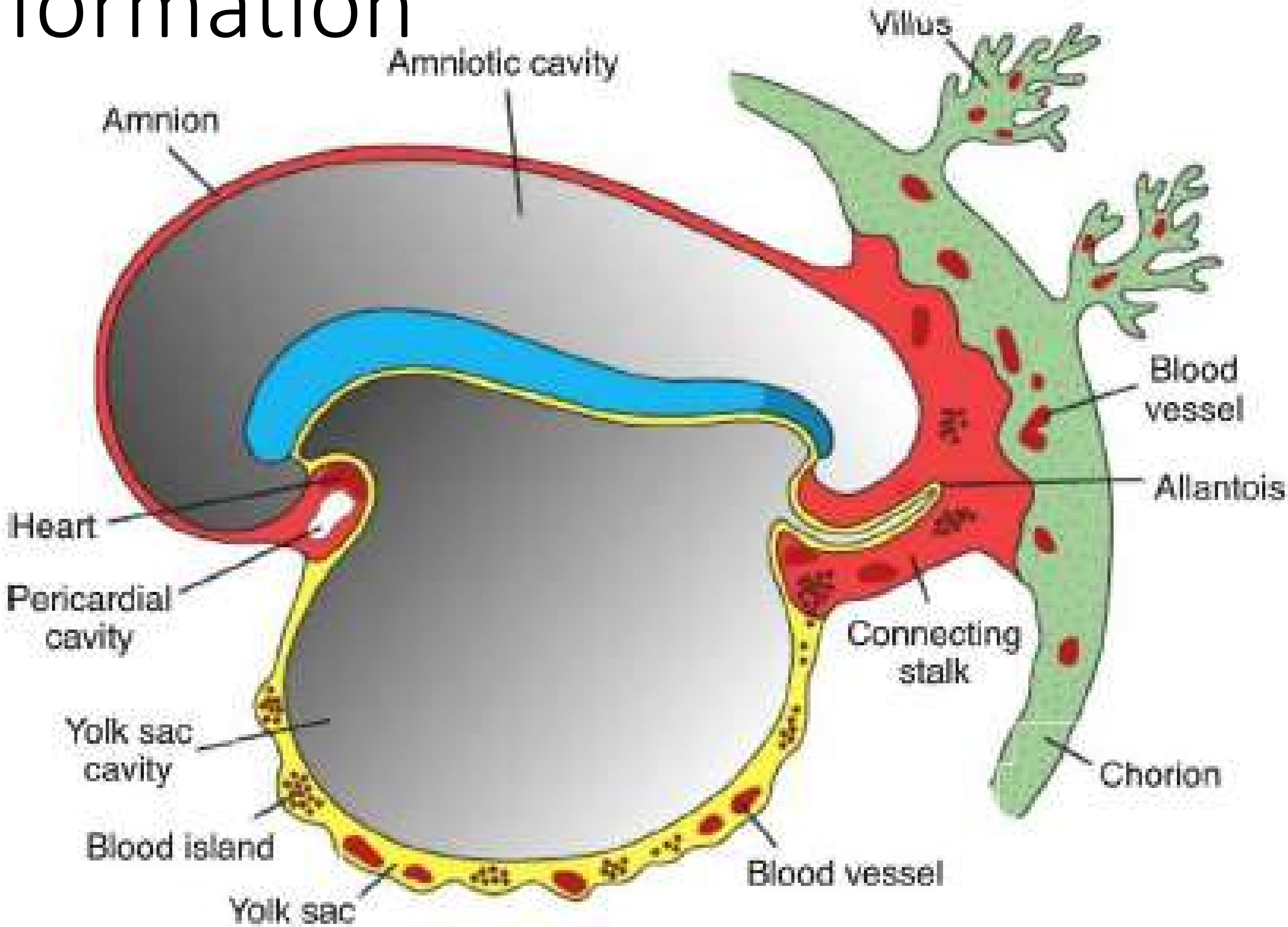






Oropharyngeal membrane
Primary villi
Trophoblastic lacunae
Maternal sinusoid
Connecting stalk
Amniotic cavity
Secondary yolk sac
Extraembryonic somatic mesoderm (chorionic plate)
Extraembryonic cavity (chorionic cavity)
Exocoelomic cyst

3rd Week → Hemangioblast formation



Prenatal Hemopoez

- Mesoblastic phase

(2nd week-mesoderm of the yolk sac)

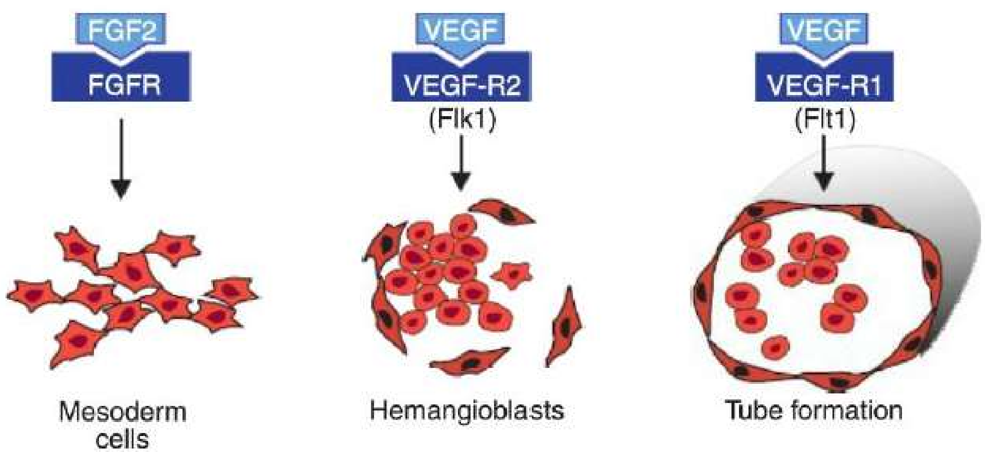
- Hepatosplenothymic phase
  - ✓ Liver (6th week)
  - ✓ Spleen (8th week)
  - ✓ Thymus (8th week)
- Medullalymphatic phase (3-5th month)

Temporary blood islets of the yolk sac

- In the 2nd-3rd week of embryological development, mesodermal cells in the yolk sac wall are differentiated into hemangioblast cells.
- These cells are the precursors of both blood cells and endothelial cells that will form the vascular system.
- Blood precursors formed in this region are temporary.
- The main hematopoietic stem cells develop from the mesoderm surrounding the aorta, called the **aorta-gonad-mesonephros region (AGM)**, next to the developing mesonephric kidney.
- These cells colonize the liver and form the main fetal hematopoietic organ (2-7th month of pregnancy)
- Cells in the liver then settle into the bone marrow, and from the 7th month of pregnancy, the bone marrow becomes the final production center

1. Mesoblastic phase

- In the 2nd-3rd week of pregnancy, when the first blood cells begin to develop from the mesoderm of the yolk sac and blood islets are formed.
- Peripheral cells in the islets make up the vascular wall, others with nucleated erythrocytes (hemocytoblast).

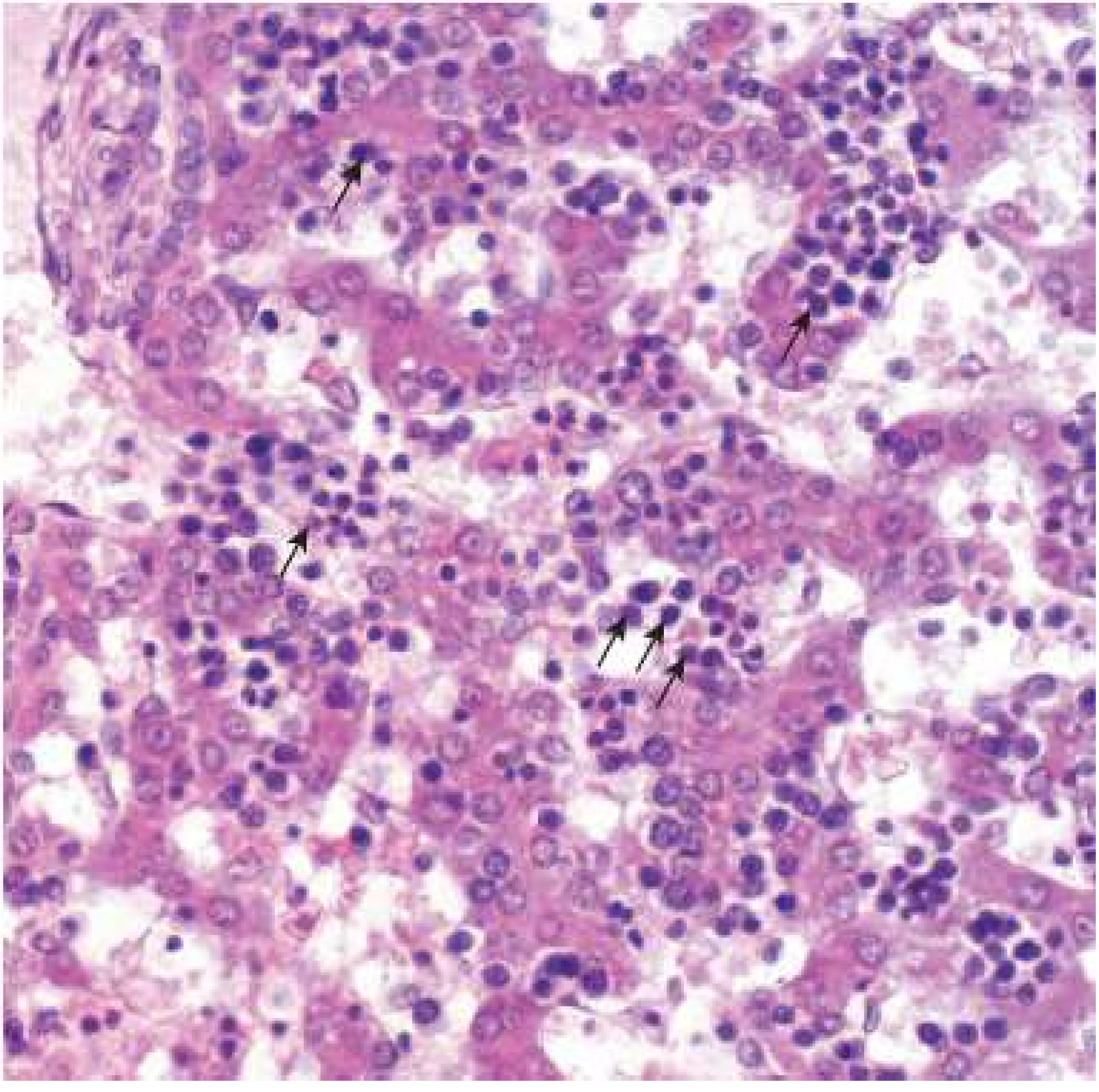


- The vascular system develops when the vessels from the blood islets connect with each other.
- From hemocytoblast; erythrocyte serial cells develop.
- Erythrocytes remain nucleated.
- The hemoglobin of erythrocytes from the yolk sac is different from that of other blood-forming organs (spleen, liver, bone marrow).
- These erythrocytes are larger than the erythrocytes made later. Therefore, named as megaloblastic erythropoiesis.
- **At this stage, only erythrocytes are made, there are no granulocytes and platelets.**

Further reading: *The hemangioblast: from concept to authentication.*
Cao N1, Yao ZX.Anat Rec (Hoboken). 2011 Apr;294(4):580-8. PMID: 21370498

2. Hepatic phase

- It replaces the mesoblastic phase at the 6th week of pregnancy. During the 2nd trimester, liver is the major blood-making organ.
- Erythrocytes are still with nucleus.
- Leukocytes appear at 8th week.



❖Hepatosplenothymic phase

- The liver is the second hematopoetic organ during development, begins blood production in about 6th week. The most active place of hemopoiesis until the middle of fetal life is the liver.
- Then its activity decreases gradually, normally the activity close to birth disappears completely.
- Although there are small erythroblast foci in the newborn, these foci are deleted in a short time.
- The adult liver is not a hematopoetic organ

3. Splenic phase

- Starts during second trimester
- Splenic ve Hepatic phase continue until the end of the pregnancy

4. Myeloid phase

- The phase when the hemopoiesis starts in bone marrow at the end of second trimester (5th month)

- Medullo-lymphatic stage

- The first hemopoetic activity in the bone marrow appears in the clavicula during 2nd and 3rd months.
- Bone marrow activity gained importance in the 4th month.
- It is the bone marrow that produces the major blood elements in the last 3 months of the fetal phase and throughout the post-natal phase.
- The lymph nodes are activated around birth

Postnatal Hemopoiesis

- Bone marrow
- If necessary…

Extramedullary Hemopoiesis

(Liver + Spleen + Lymph nodes)

(In some pathological events, in adults, the shift in formation of blood cells to the spleen, liver and lymph nodes is called extra-medullary hemopoiesis.)

Postnatal Hemopoiesis

- Stem cell

  ↓
- Progenitor cells

  ↓
- Precursor cells (_blasts)

  ↓
- Mature cells

From stem cells…

- Erythropoiesis → Erythrocytes
- Granulopoiesis → Granular leukocytes
- Monocytopoiesis → Monocytes
- Megakaryocytopoiesis → Platelets
- Lymphopoiesis → Lymphocytes

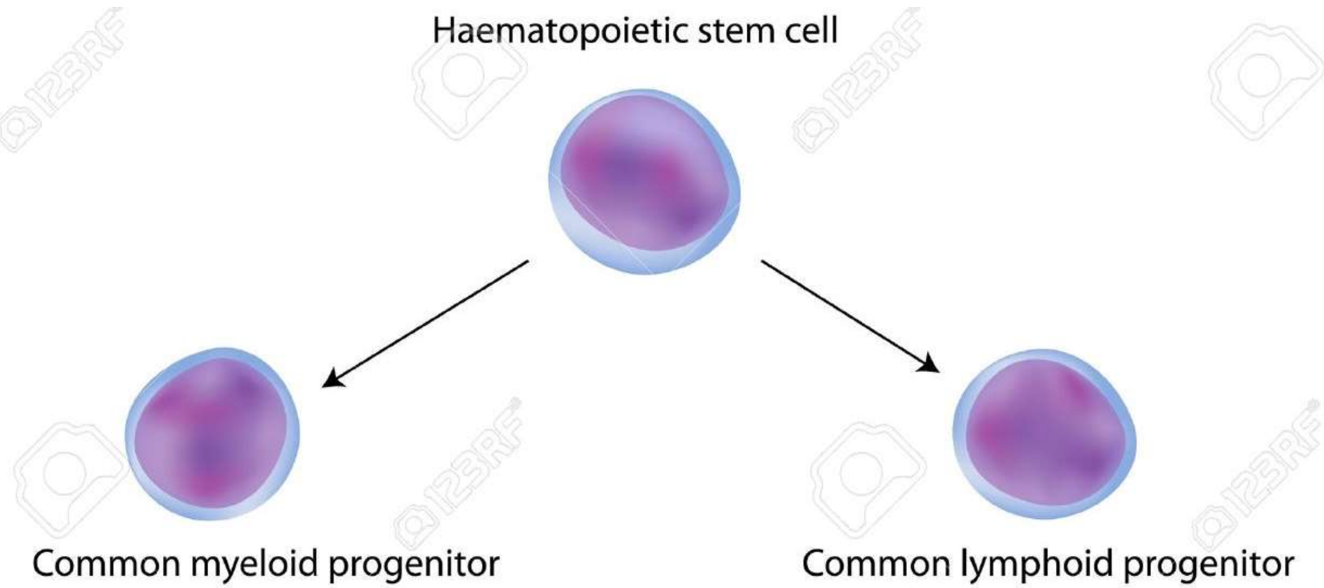
Monophyletic Theory of Hemopoiesis

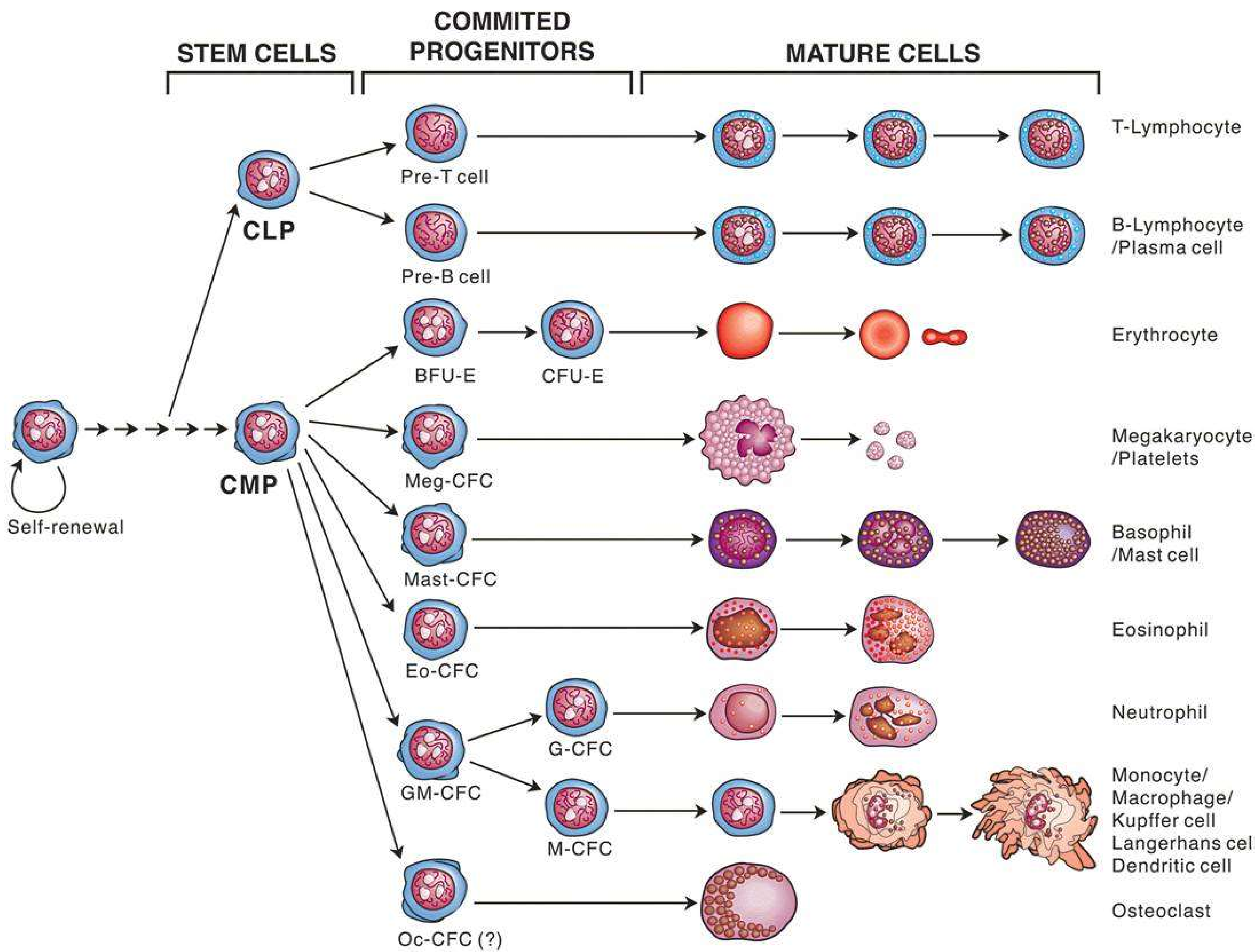
- It is the theory that all blood cells are derived from a common hemopoietic stem cell.
- The hemopoietic stem cell, also known as *pluripotential stem cell* (PPSC), is capable not only of differentiating into all the blood cell lineages but also of self-renewal.
- Recent studies indicate that HSCs also have the potential to differentiate into multiple non-blood cell lineages and contribute to the cellular regeneration of various tissues and multiple organs.
- Molecular surface markers are used to identify hematopoietic stem cells immunocytochemically

CD34+ AND CD90+ AND Lin- (lineage) AND CD38-

Progenitor stem cell

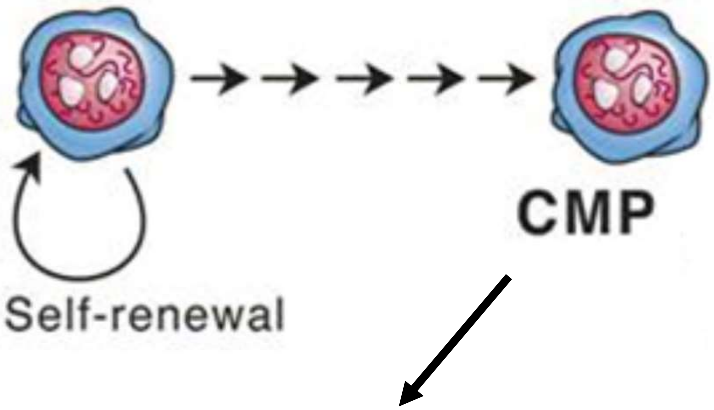
- Hemopoietic stem cell creates many progenitor stem cell colonies
- In the bone marrow, HSC is differentiated into two major progenitor cell colony serials
  - **Common myeloid progenitor cell**
  - **Common lymphoid progenitor cell**

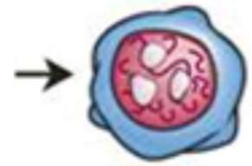




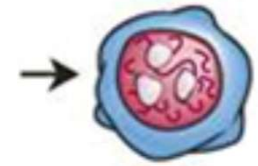
STEM CELLS
COMMITED PROGENITORS
MATURE CELLS
Self-renewal
CLP
CMP
Pre-T cell
Pre-B cell
BFU-E
CFU-E
Meg-CFC
Mast-CFC
Eo-CFC
GM-CFC
G-CFC
M-CFC
Oc-CFC (?)
T-Lymphocyte
B-Lymphocyte /Plasma cell
Erythrocyte
Megakaryocyte /Platelets
Basophil /Mast cell
Eosinophil
Neutrophil
Monocyte/ Macrophage/ Kupffer cell Langerhans cell Dendritic cell
Osteoclast

Common Myeloid Progenitor Cell





Megakaryocyte/erythrocyte progenitor (MEP)
Bi-potential



megakaryocyte - committed progenitor cells (MKP or CFU-Meg)
Mono potential

Formerly named:
colony-forming units–granulocyte, erythrocyte, monocyte, megakaryocyte
(CFU-GEMM)

erythrocyte - committed progenitor cells (ErP *or* CFU-E)
Mono potential

Erythropoiesis

MEP

ErP

1 wk

Proerythroblast
- 12–15 μm in diameter
- Mildly basophilic
- Large, round nucleus with 1–2 nucleoli

Basophilic erythroblast
- Smaller
- Very basophilic cytoplasm
- Smaller, more heterochromatic nucleus

Polychromatophilic erythroblast
- Last cell capable of mitosis
- Hemoglobin production begins
- Cytoplasm acquires gray or dull lilac color
- Smaller than basophilic erythroblast

Orthochromatophilic erythroblast (normoblast)
- Small, deeply stained nucleus
- Begins to acquire acidophilia
- Retains slight basophilia

Polychromatophilic erythrocyte (reticulocyte)
- Nucleus extruded
- Acidophilic cytoplasm with trace of earlier gray

Erythrocyte
- Acidophilic
- Biconcave disc
- 7–8 μm in diameter

Life span:
in blood, 1–120 days

MKP

5 days

Megakaryoblast
- Last cell capable of mitosis
- Slightly basophilic cytoblasm with multiple nucleoli
- 15–25 μm in diameter
- Round, invaginated nucleus; may be binucleate

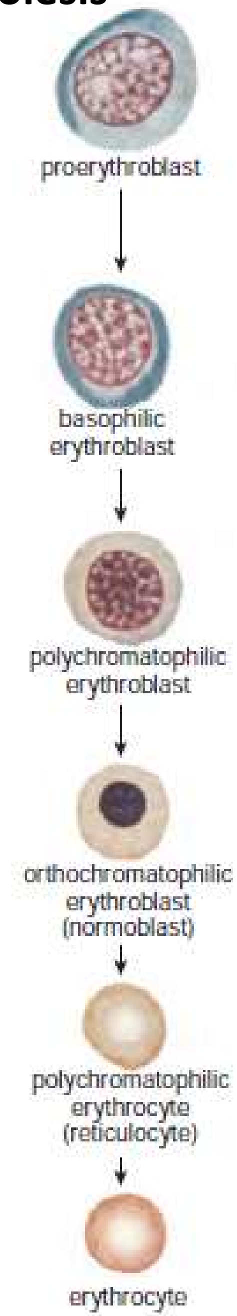
Promegakaryocyte
- 45 μm in diameter
- More abundant cytoplasm
- Nucleus enlarged

Megakaryocyte
- 50–70 μm in diameter
- Enlarges by endomitosis
- Polyploid (8–64n)

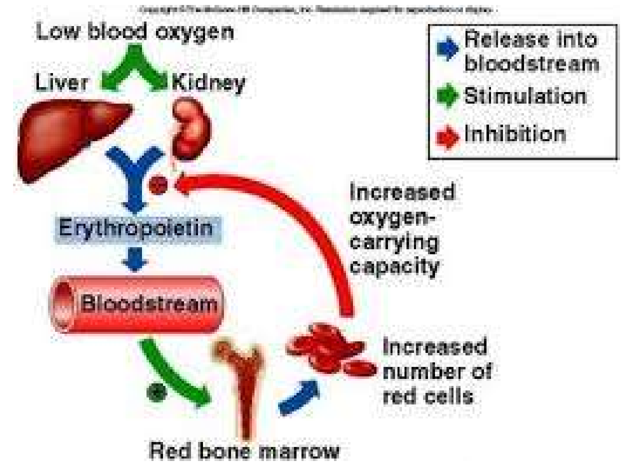
Life span:
in marrow, unknowm

Platelets (constantly produced in marrow)

Life span:
in blood, 7–10 days



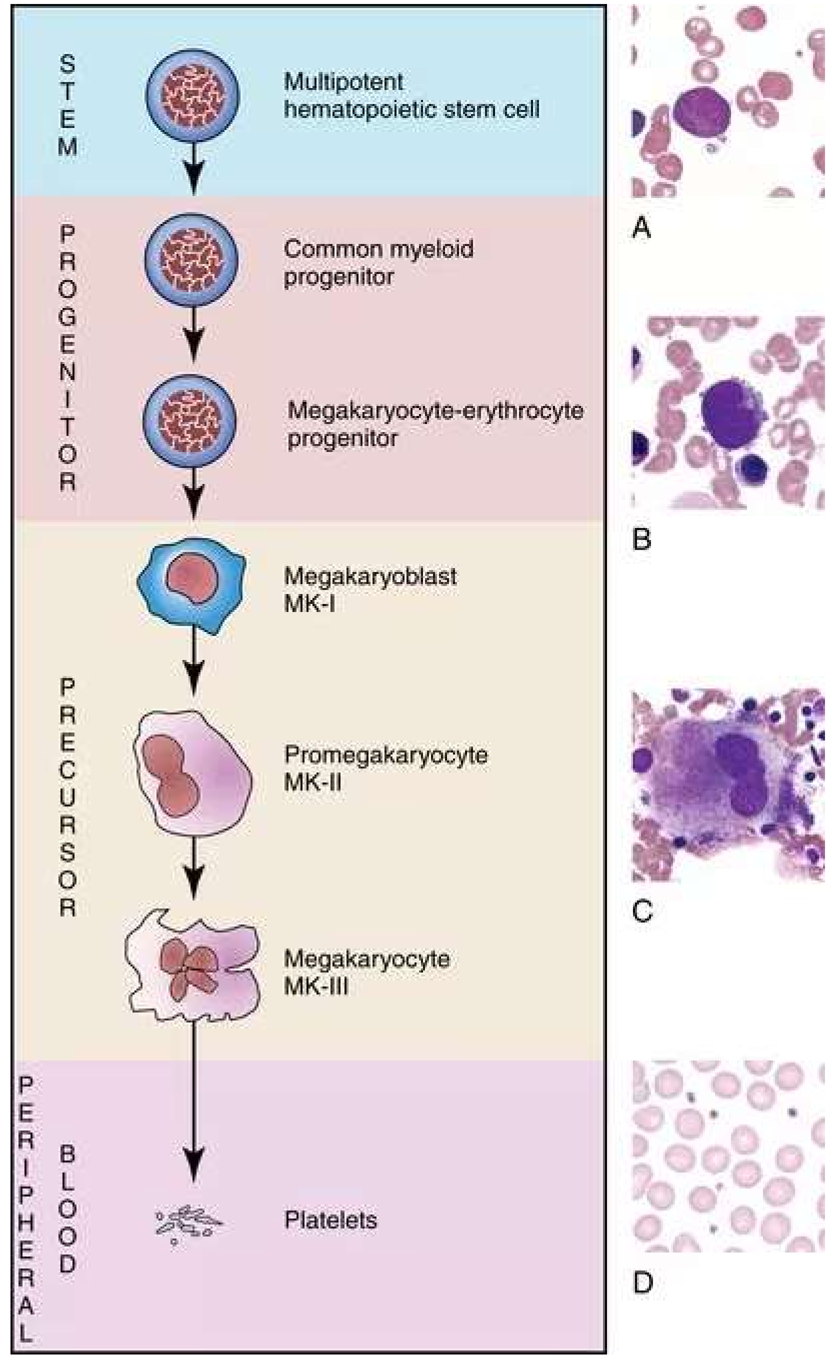
Erythropoietin



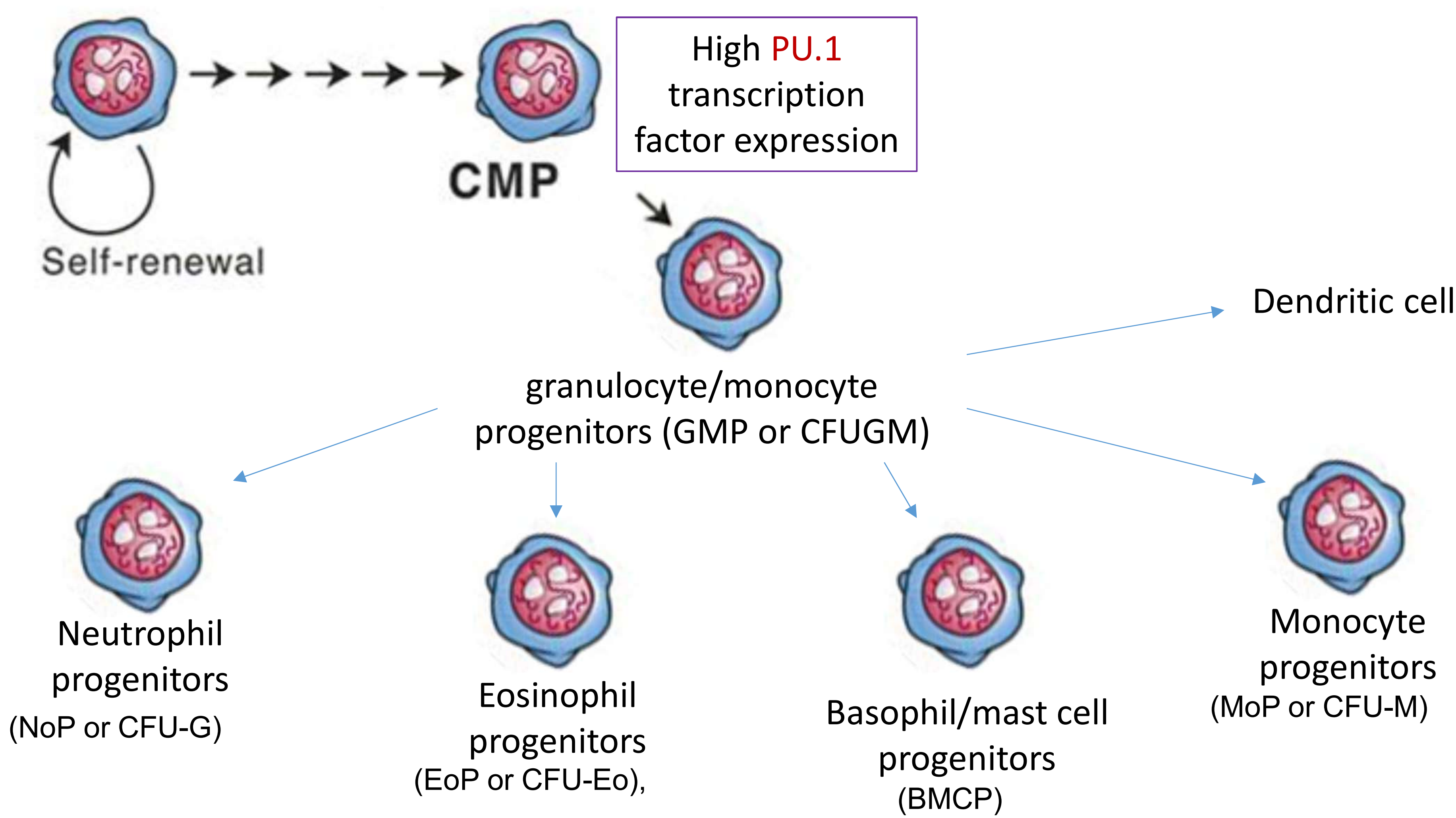
- Erythrocyte production and circulation is under the control of ERYTHROPOIETIN.
- It is a glycoprotein hormone released from **KIDNEY** followed by reduced blood oxygen concentration.
- The produced red blood cells are released into the blood stream immediately, not stored in the bone marrow.

Thrombopoiesis

- Each day, bone marrow of a healthy adult produces about 1 X 10^{11} platelets,
- **MEP cell → megakaryocyte-committed progenitor (MKP) cell → megakaryoblast.**
- After the formation of **megakaryoblast**, under the effect of thrombopoetin (produced in liver and kidney), the number of nuclei increases and **megakaryocyte** is formed.



Common Myeloid Progenitor Cell



GMP

NoP

Myeloblast
- 14–20 µm in diameter
- Large, euchromatic spherical nucleus; 3–5 nucleoli
- No granules
- Basophilic cytoplasm

Promyelocyte
- Azurophilic granules produced in this stage only
- Nucleus indented
- Nucleoli
- Increased size, 18–24 µm
- Chromatin becomes condensed

Neutrophilic myelocyte
- Last cell capable of mitosis
- Elliptical nucleus
- Specific granules appear and in number
  M-1 wk

1 wk

Neutrophilic metamyelocyte
- Nucleus becomes progressively indented and heterochromatic

Band cell
- Nucleus is elongate and acquires U shape

Neutrophil
- Nucleus, 3–5 segments or lobes
- Mature cells stored in marrow before release

Life span:
in blood, 8–12 hr
in CT, 1–2 days

MoP

55 hr

Monoblast
- Difficult to Identify

Promonocyte
- Last cell capable of mitosis
- 10–15 µm in diameter
- Nucleus large, slightly indented
- 1 or 2 nucleoli
- Basophilic cytoplasm
- No mature granules

Monocyte
- Large, kidney-shaped nucleus
- 2–3 nucleoli
- Azurophilic granules corresponding to lysosomes
- Pale basophilic cytoplasm

Life span:
in blood, 16 hr

Macrophage
- Can divide in CT
- Granules sometimes evident; represent lysosomes

Life span:
in CT, unknown

EoP

Myeloblast
- 14–20 µm in diameter
- Large, euchromatc spherical nucleus; 3–5 nucleoli
- No granules
- Basophilic cytoplasm

Promyelocyte
- Azurophilic granules produced in this stage only
- Nucleus indented
- Nucleoli
- Increased size, 18–24 µm
- Chromatin becomes condensed

Eosinophilic myelocyte
- Last cell capable of mitosis
- Nucleus indented
- Refractile-specific granules appear and in number
  M-1 wk

1 wk

Eosinophilic metamyelocyte

Eosinophil
- Nucleus bilobed
- Mature cells stored in marrow before release

Life span:
in blood, 8–12 hr
in CT, unknown

BMCP

BaP

Myeleblast
- 14–20 µm in diameter
- Large, euchromatic spherical nucleus; 3–5 nucleoli
- No granules
- Basophilic cytoplasm

Promyelocyte
- Azurophilic granules produced in this stage only
- Nucleus indented
- Nucleoli
- Increased size, 18–24 µm
- Chromatin becomes condensed

Basophilic myelocyte
- Last cell capable of mitosis
- Nucleus elliptical
- Specific granules appear and in number
  M-1 wk

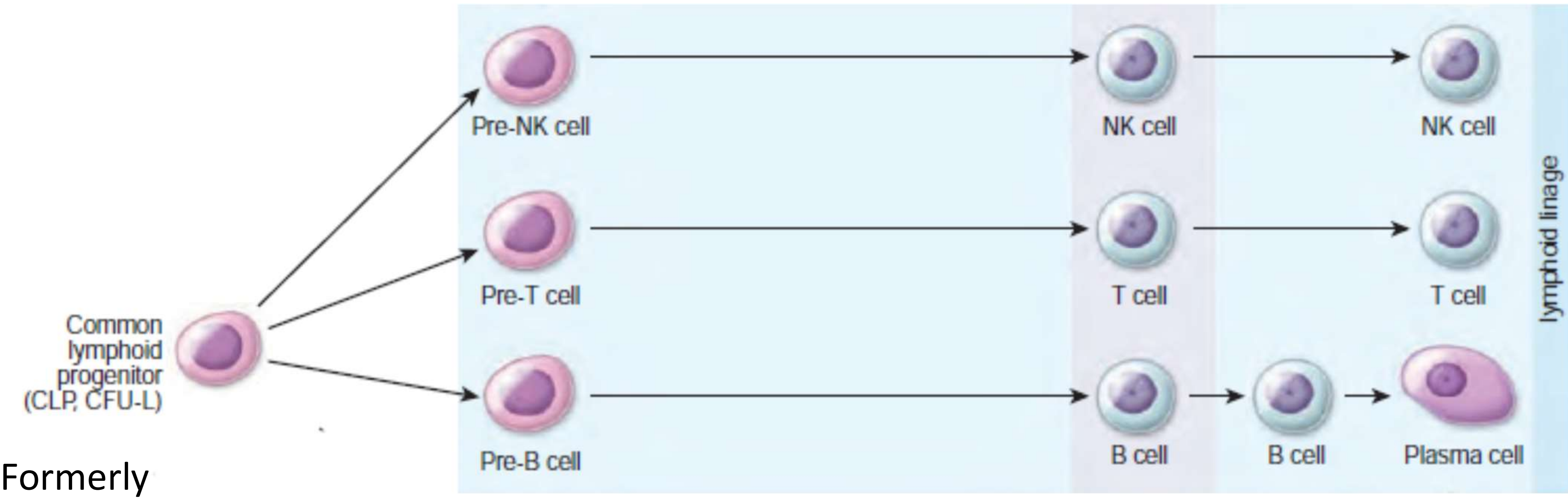
1 wk

Basophilic metamyelocyte

Basophil
- Nuclear shape obscured by granules
- Mature cells stored in marrow before release

Life span:
in blood, 8 hr
in CT, unknown

Common Lymphoid Progenitor Cell



Formerly named: *colony-forming units–lymphoid* **(CFU-L)**