Histology - HLS

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Hematopoiesis

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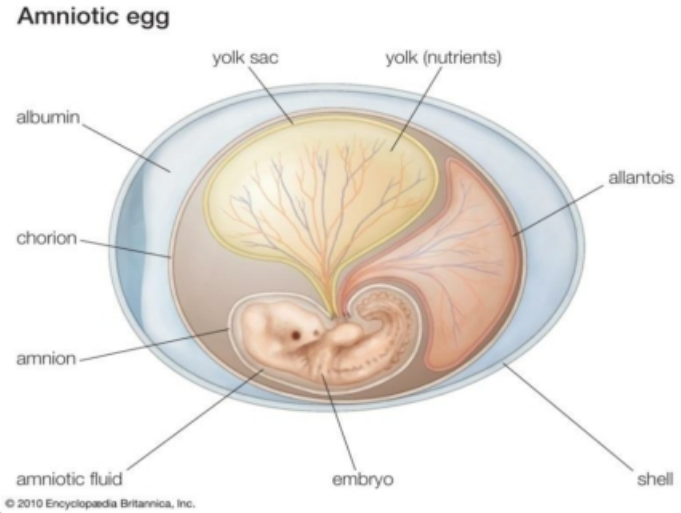
Blood Cell Formation (Hematopoiesis)

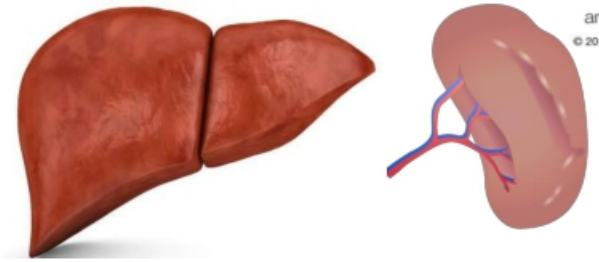
Mature blood cells have a relatively short life span and must be continuously replaced with new cells from precursors developing during hemopoiesis/ hematopoiesis (Gr. haima, blood + poiesis, a making).

At the third month stem cells will populate from the yolk sac to the liver causing enlargement of the liver

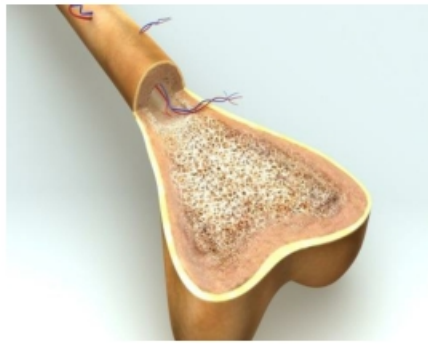


Early embryo
Yolk sac mesoderm

Second trimester
Developing liver and spleen



Third trimester
Bone marrow

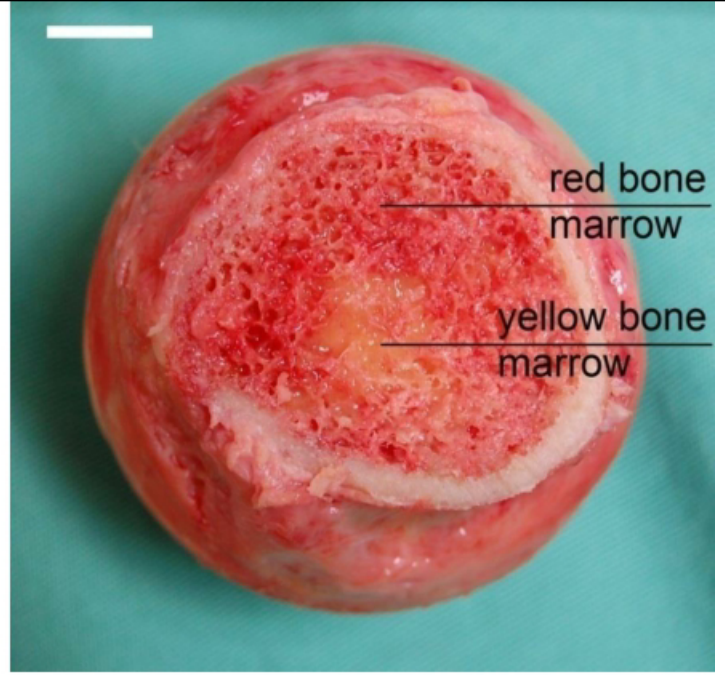


After birth, all blood cells originate in bone marrow

Bone marrow

Stroma : reticular tissue
Parenchyma: blood cells (stem cells, maturing cells)

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)

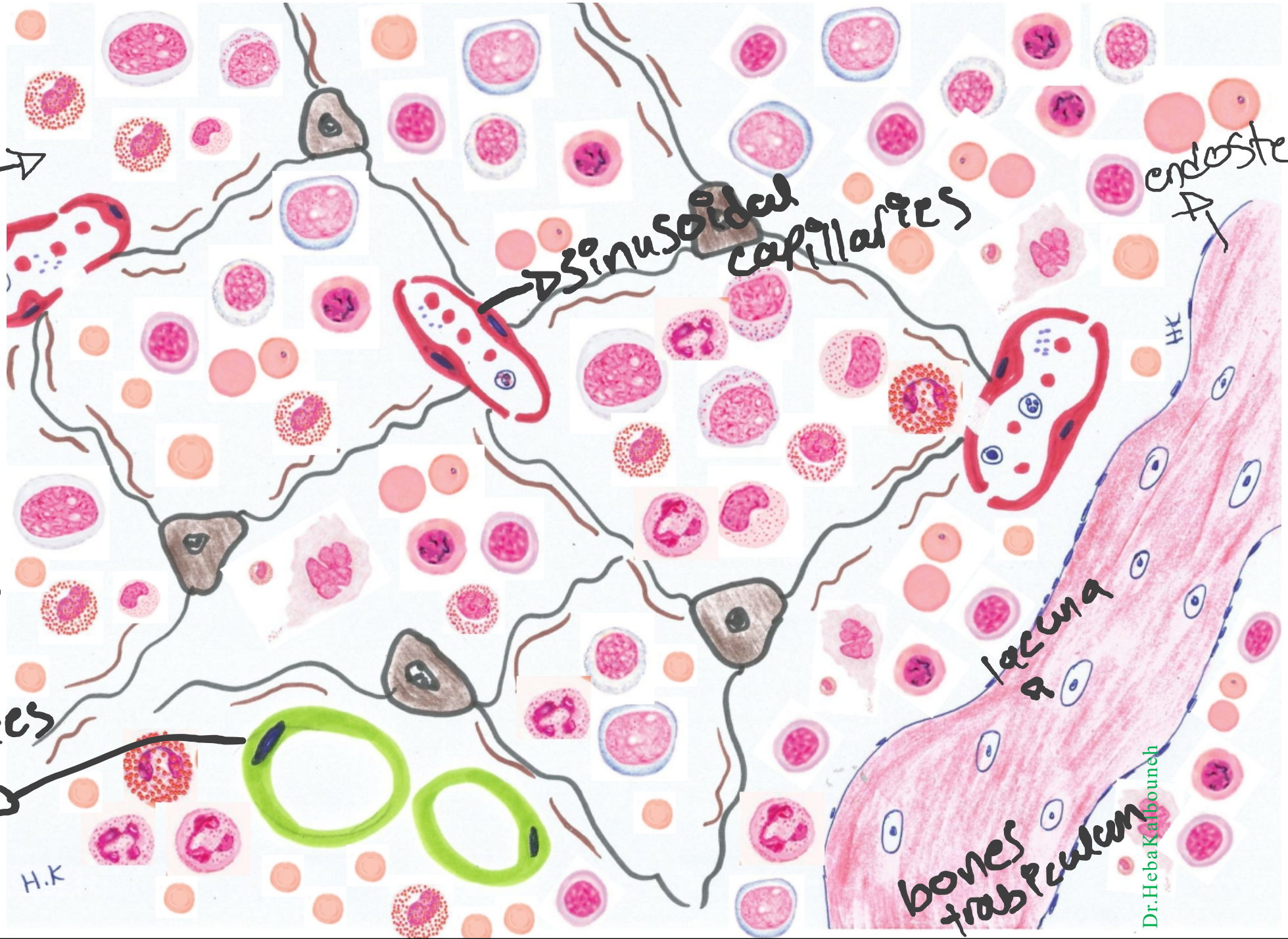
Under certain conditions (severe bleeding or hypoxia), yellow marrow revert to red

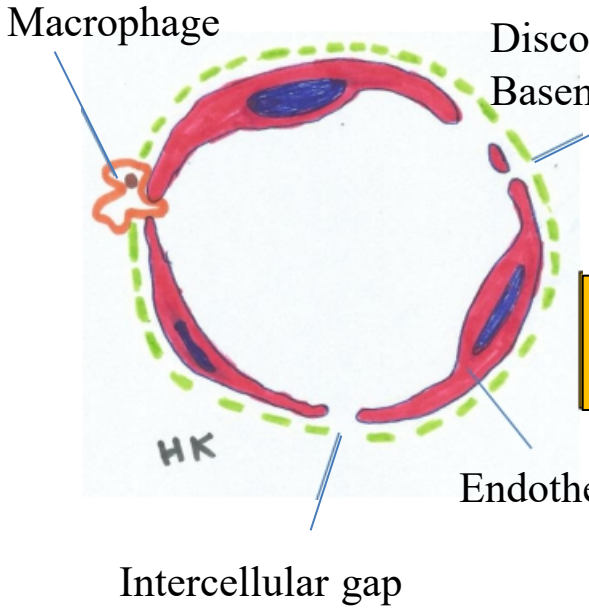
- Inside the red bone marrow we have small amount of adipocytes
- Inside the yellow bone marrow we can find small number of hematopoietic stem cells.

After birth all of our bones contain red bone marrow (active form) but due to aging the peripheral bones (limbs) start accumulating fat causing the red bone marrow to convert to yellow bone marrow.

In adults the red bone marrow is restricted to the axial skeleton .

Here we have hematopoietic stem cells at different stages of development and differentiation forming the parenchyma

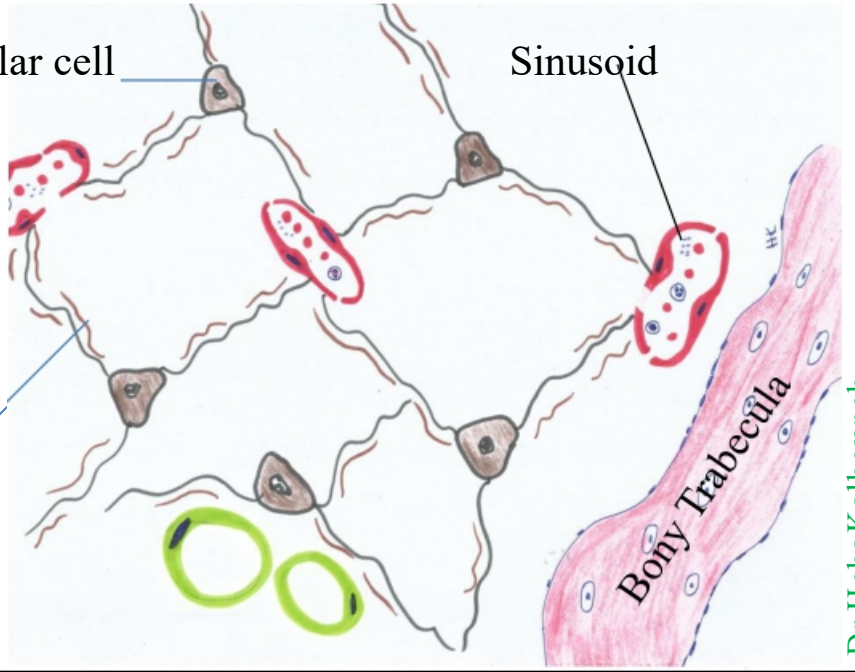




Sinusoidal capillary

Continuous capillary

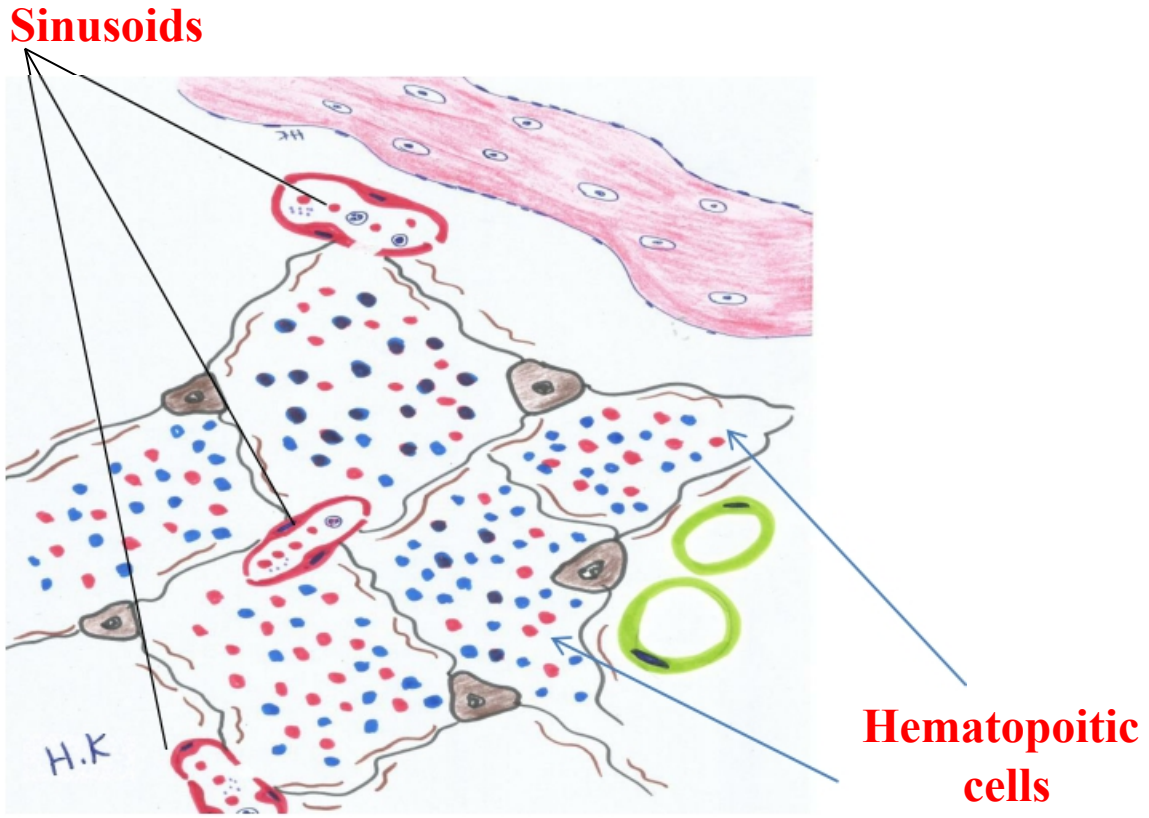
Reticular tissue forming the stroma of the bone marrow



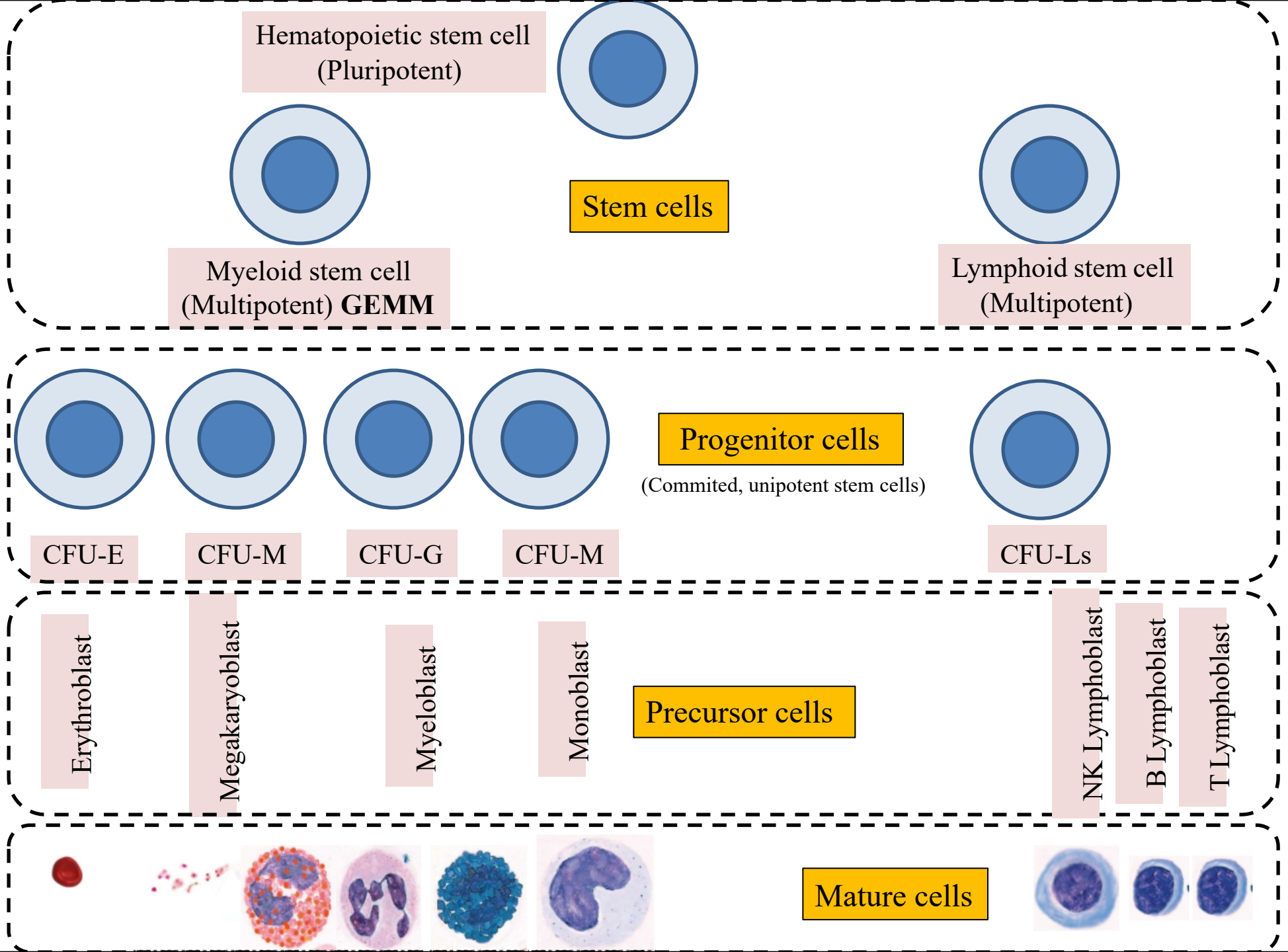
- Both types of capillaries are surrounded by a loose type of C.T .
- But sinusoidal capillaries are surrounded by a special type of C.T called perisinusoidal connective tissue rich in macrophages

These macrophages extend their processes into the lumen of the capillary to identify abnormal and old RBCS for phagocytosis

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.

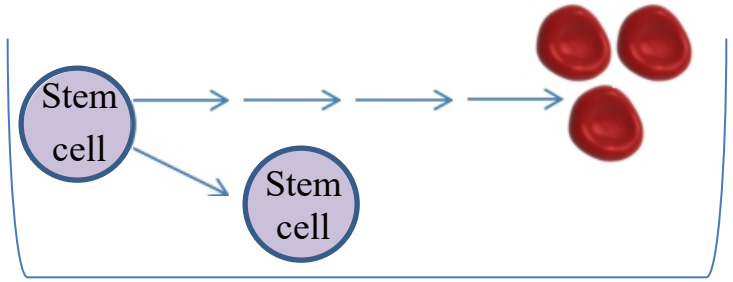

Hematopoietic stem cell
(Pluripotent)
Stem cells
Myeloid stem cell
(Multipotent) GEMM
Lymphoid stem cell
(Multipotent)
Progenitor cells
(Commited, unipotent stem cells)
CFU-E
CFU-M
CFU-G
CFU-M
CFU-Ls
Erythroblast
Megakaryoblast
Myeloblast
Monoblast
Precursor cells
NK Lymphoblast
B Lymphoblast
T Lymphoblast
Mature cells

- This process starts with the hematopoietic stem cell (mother cell) which produces all types of blood cells hence the name pluripotent(pluri: all ,potent : potential)
- Stem cells : are undifferentiated cells and you need to know that when a stem cell divides it produces two cells one cell will continue the pathway (different stages of differentiation and development) to give us mature products, the other cell will be added to the original population to maintain the number of these cells in the bone marrow and this is called self renewal
- Multipotent : meaning that it gives many cell types but not all (multi : many , potent : potential).
- Progenitor cells: these cells are comitted to produce a certain type of mature cells.

- We call progenitor cells colony forming units(CFU) because when we culture the progenitor cells inside a culture dish these progenitor cells are going to form a colony of the product they are committed to form, even if you have a histological section from a bone marrow we will see that these progenitor cells tend to form colonies inside the red bone marrow .
- for example myeloid stem cell divides and differentiate to produce four types of progenitor cells (CFU-M , CFU-E,CFU-M, CFU-G) and each progenitor cell is a stem cell and by that CFU-G only produces granulocytes and so on.
- We have small pool of stem cells compared to the larger pool of progenitor and precursor cells
- Pluripotent, multipotent and even unipotent are stem cells that maintain their number by self renewal property but precursor cells don't have it.

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** **(to keep lower number of stem cells)**

Rapid in **progenitor and precursor cells**

Progenitor cells/ CFUs

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

Precursor cells/ Blasts

Selectedprecursorsofdifferentbloodcells

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

Lymphoid stem cells

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

Progenitor and precursor cells

- T lymphocyte
- B lymphocyte
- Natural killer cells

Pluripotent hematopoietic stem cells

Myeloid stem cells

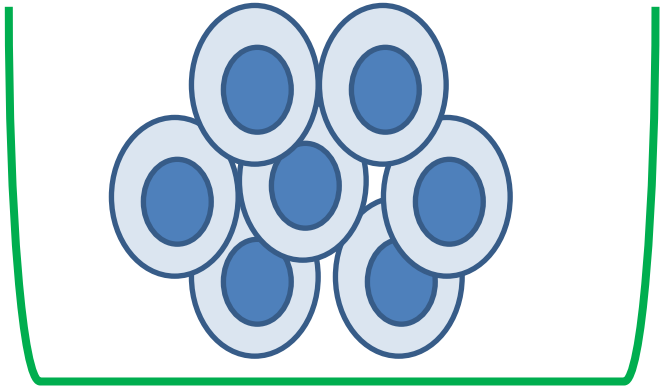
Progenitor cells/CFUs

- 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.



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

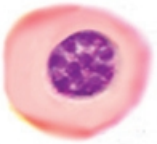
Remember
Lymphopoiesis occurs in the marrow and in the lymphoid organs to which precursor cells migrate from marrow.

This pathway starts with the precursors

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)**

- Nuclear maturation: the nucleus gets smaller in size and condenses until it’s completely extruded (disappears)
- Cytoplasmic maturation: basophilic cytoplasm is converted to acidophilic cytoplasm by synthesizing the hemoglobin (Hb is a basic protein meaning that it’s an acidophilic molecule)

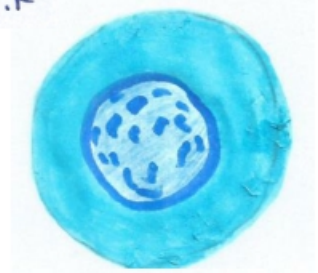
There is a decrease in the size of precursor cells by 2 micrometer

Proerythroblast

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

Ribosome synthesis

H.K



Basophilic erythroblast

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

Start synthesizing hemoglobin

Red+ blue (multiple colors)

Polychromatophilic erythroblast

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

Maybe it's called normoblast because it has the future normal color of an RBC

Normoblast (Acidophilic erythroblast!!!)

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

Increase in Hb, decrease in ribosomes

Also called orthochromatophioic

Thenucleusisextrudedatthisstage

Reticulocyte

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

Erythrocyte

Reticulocytes

Very important

➢Are immature red blood cells (last stage)

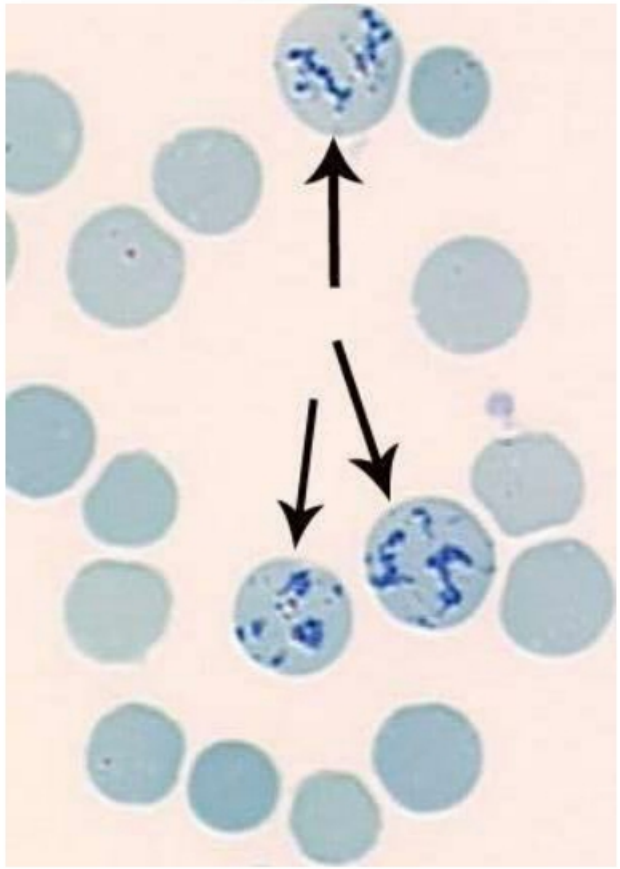
➢The cell has extruded its nucleus, but is still capable of producing hemoglobin(small amount of ribosomes)

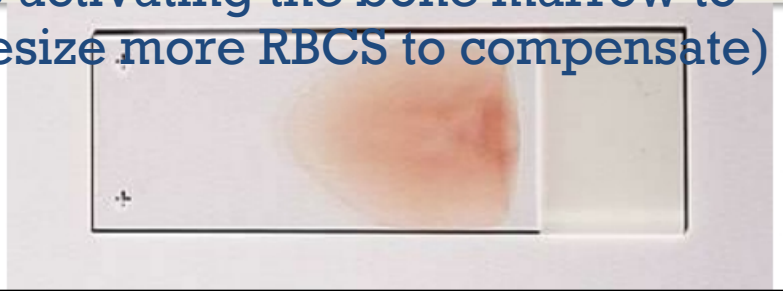
➢Supravital dye: precipitation of reticulum in the cytoplasm (brilliant cresyl blue)

➢Normally, only about 1% of all red blood cells in the bloodstream are reticulocytes

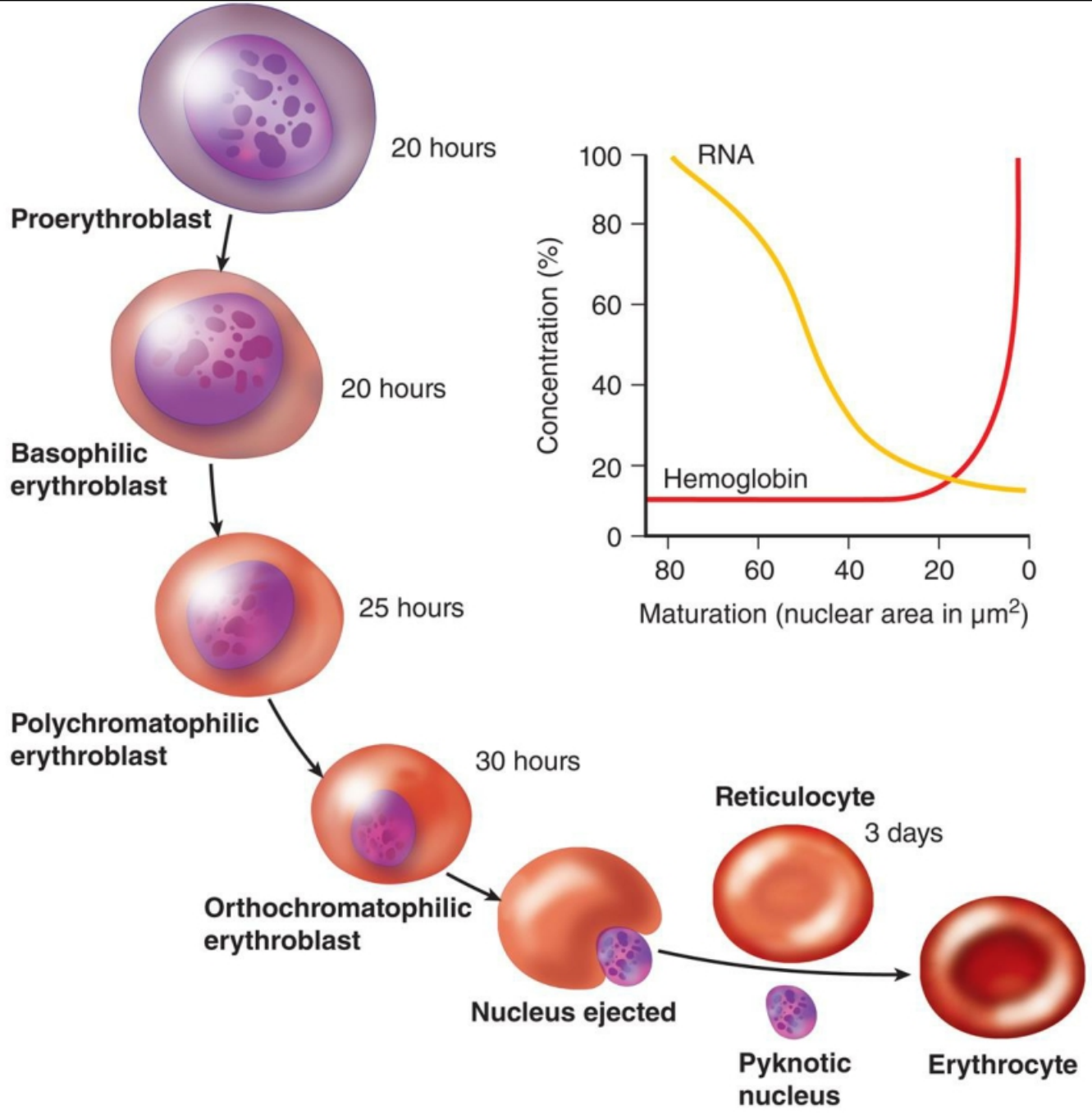
➢They circulate for about 1-2 days before developing into mature red blood cells (still maturing)

➢An increase in reticulocytes ---- blood loss (hemorrhage) (it will increase more than 2% due to activating the bone marrow to synthesize more RBCS to compensate)





- Vital stain means to stain living cells inside the living animal -injection of this Stain into the blood of an animal for example you inject Indian ink -and as this dye is circulating inside the blood it's going to be encountered by the resident macrophages in different locations and this macrophages will consider this stain as a foreign exogenous material so they are going to phagocytose this stain and when you take section from this animal you will find that the macrophages at different locations they are pigmented with the same dye you have used (if it was green in color it'll be pigmented with a green color and so on)
- we have another type of stain called supravital stain which means to stain in living cells but outside the body (you bring a test tube and you take let's say about 2 millimeter of fresh blood so you have living cells but outside the body then you apply your stain which called Berlin blue we have the mature red blood cell).
- As reticulocytes mature more they lose the remanence of the ribosomes within the cytoplasm to end up with a smaller cell with an average diameter of seven micrometer in diameter and this is the mature red blood cell)


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)