Hematopoiesis

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Today's Discussion

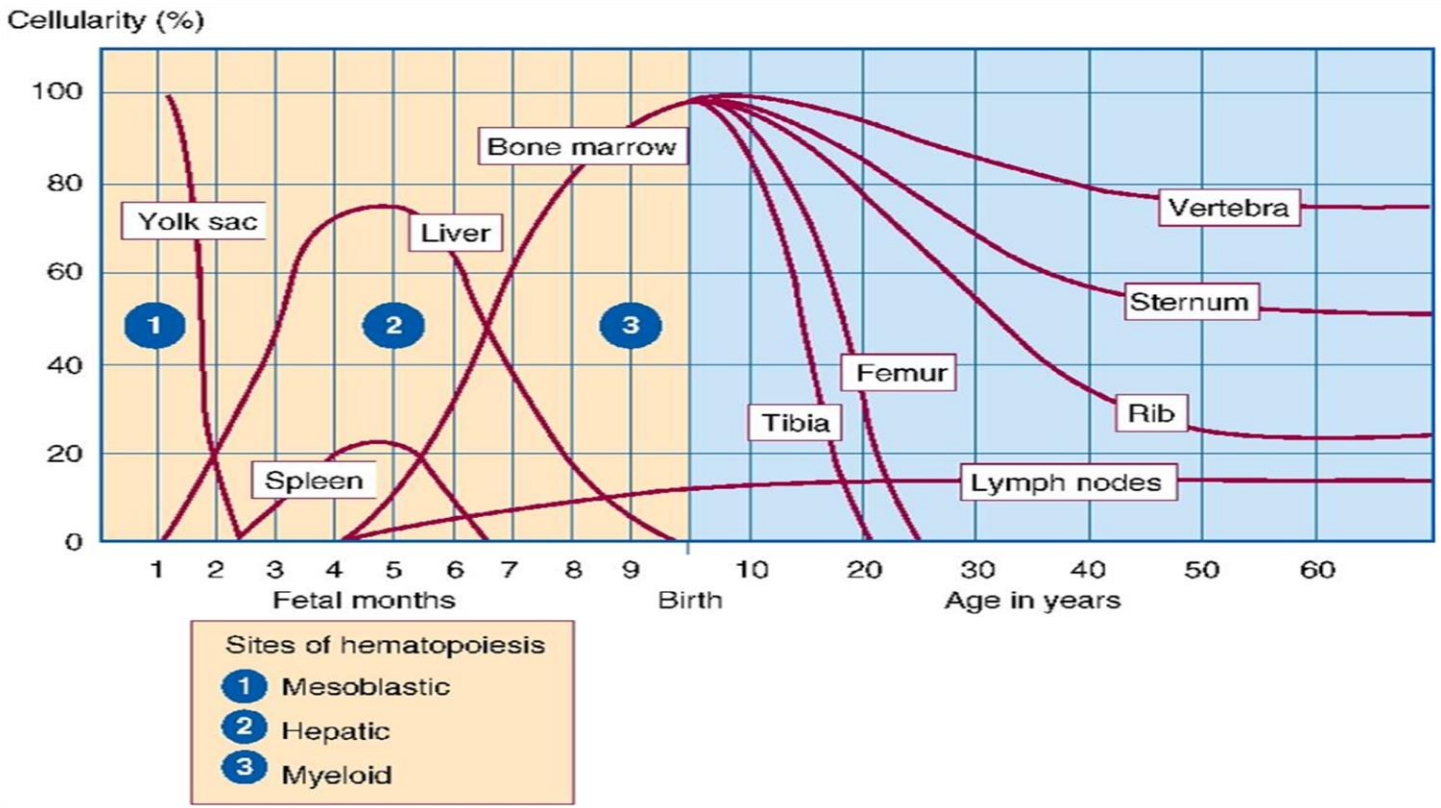
- Hematopoiesis Sites by Age
- Active Sites of Hematopoietic Tissue
- Hematopoietic Stem Cells and Cytokines
- Lineage Specific Hematopoiesis

Hematopoiesis Sites by Age

Hematopoiesis

- Continuous, regulated process involving the proliferation, differentiation and maturation of all functional blood cells released from bone marrow into circulation
- Hematopoietic stem cells (HSCs) are capable of self-renewal and directed differentiation into all required cell lineages

Hematopoiesis sites by Age

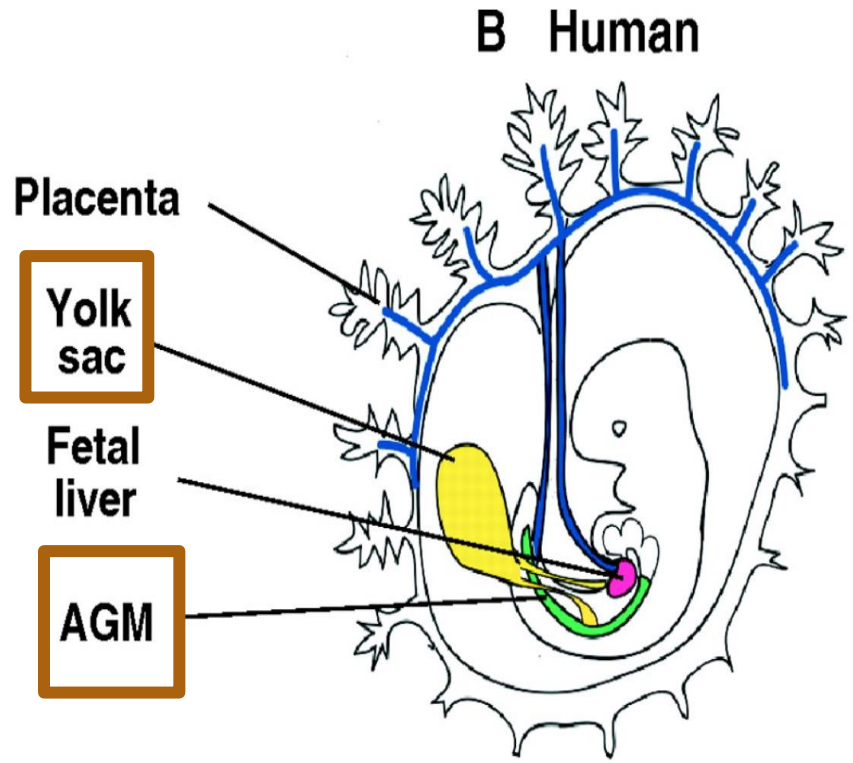


https://doctorlib.info/hematology/rodak-hematology-clinical-principles-applications/8.html

- Fetal
  - Sites of hematopoiesis
    - Mesoblastic
      - Yolk sac
    - Hepatic
      - Liver
    - Myeloid
      - Bone marrow
- Adult
  - Primary location of hematopoiesis is bone marrow

Mesoblastic Phase

- 19th day of embryonic development
- Cells from mesoderm migrate to the yolk sac and form primitive erythroblasts and angioblasts
  - Primitive Erythroblasts
    - Central cavity of the yolk sac
    - Produce hemoglobin to deliver O_2
      - Gower-1, Gower-2, and Portland
  - Angioblasts
    - Form around the central cavity of the yolk sac
    - Form blood vessels
- Cells migrate from the yolk sac to the aorta-gonad-mesonephros (AGM)
  - At 4-week gestation
  - Will give rise to the HSCs for definitive adult hematopoiesis



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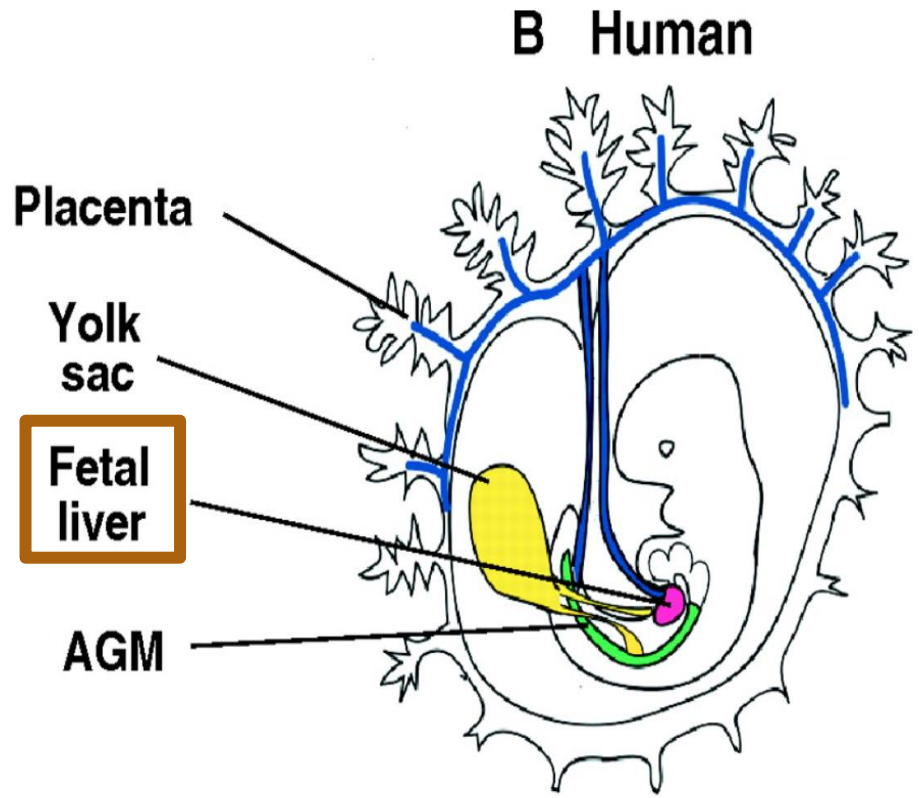
Hepatic Phase

- Begins at 5 to 7 gestational weeks
- Characterized by a recognizable cluster of developing progenitors
  - Erythroblasts, granulocytes, and monocytes
  - Colonize the fetal liver, thymus, spleen, placenta, and lastly the bone marrow
- Hematopoiesis is now extravascular
- Liver is the major site of hematopoiesis during the second trimester of fetal life
- Thymus (1st fully developed organ in the fetus)
  - T- cell production
- Kidney and Spleen
  - B-cell production



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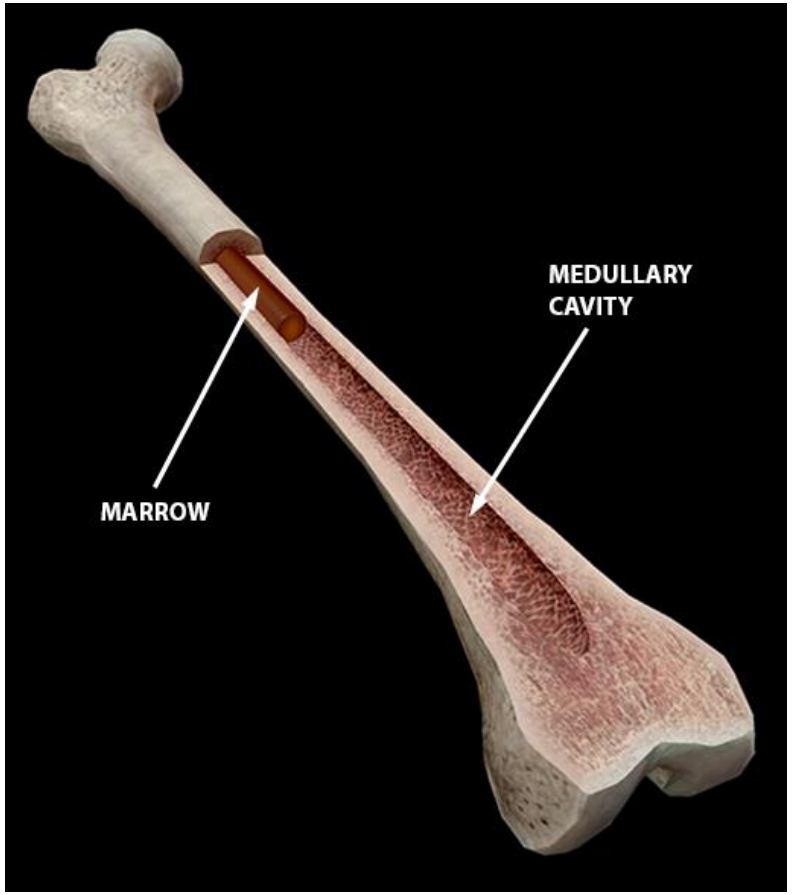
Medullary (Myeloid) Phase

- Begins 4th-5th month of fetal development
- Hematopoiesis in the bone marrow
  - Medulla/inner part of the bone cavity
- HSCs and mesenchymal cells migrate to the core
- Myeloid activity increases
  - Myeloid: erythroid ratio 3:1 to 4:1 (adult levels)
- End of 24 weeks primary site of hematopoiesis
- Increase in growth factors
  - EPO, G-CSF, GM-CSF
- HbF and HbA is detected
- Various stages of maturation can be seen in all bone lineages



https://www.visiblebody.com/blog/3d-skeletal-system-compact-bone-spongy-bone-and-osteons

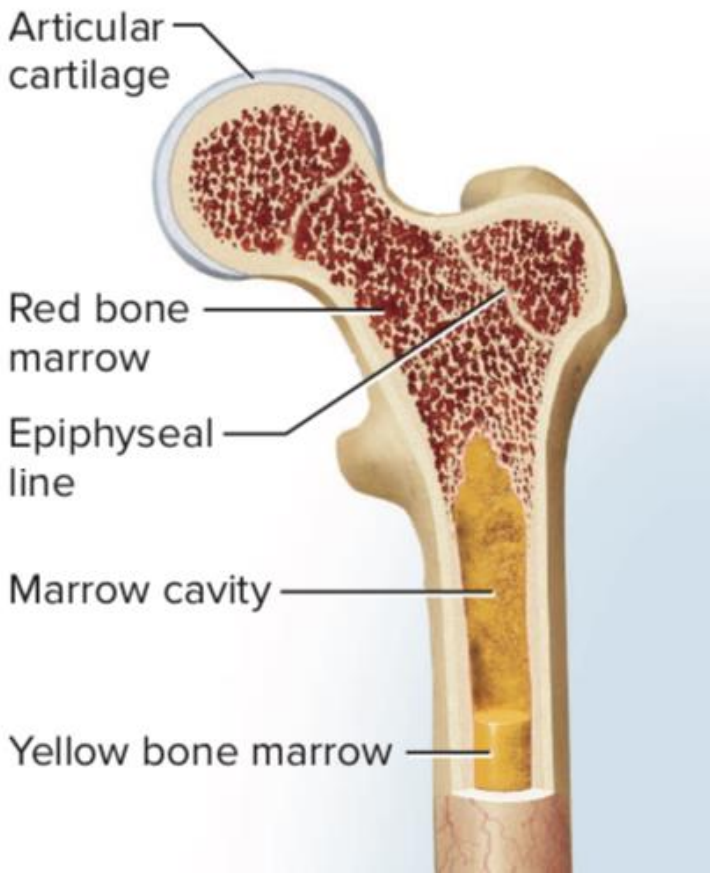
Active Sites of Hematopoietic Tissue

Active Sites of Hematopoietic Tissue

- Bone marrow
- Lymph nodes
- Spleen
- Liver
- Thymus

Bone Marrow

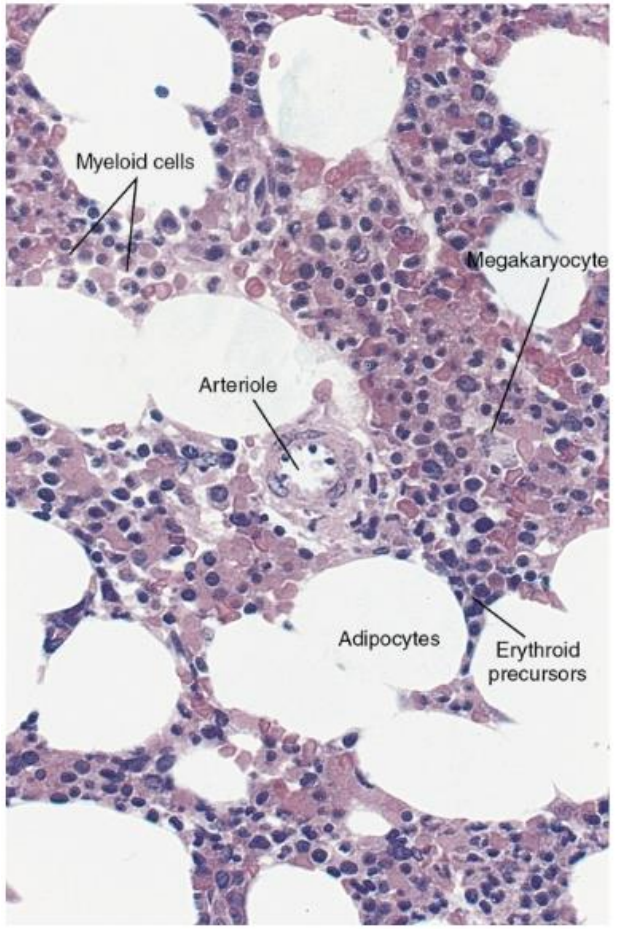
- Primary site of hematopoiesis
- Located in the cavities of cortical bone
  - Trabeculae- projections of calcified bone that radiate out into the central space and provide support for developing cells
- Composed of 2 major components
  - Red Marrow
  - Yellow Marrow
- Retrogression: process of replacing active marrow by adipocytes (yellow marrow)
  - Begins around 5 to 7 years of age
  - Adult marrow restricted to:
    - Sternum, vertebrae, scapulae, pelvis, ribs, skull, and proximal portion of long bones



https://www.quora.com/Is-bone-marrow-considered-an-organ

Bone Marrow

- Marrow Cellularity: ratio of red: yellow marrow
  - Will decrease with age
- Yellow marrow is capable of reverting back to active marrow in extreme cases
  - Excessive blood loss, hemolysis
- Bone marrow contains hematopoietic cells, stromal cells, and blood vessels
- Stromal cells
  - Originate from mesenchymal cells that migrate to the central cavity of the bone
  - Includes: endothelial cells, adipocytes, macrophages, lymphocytes, osteoblasts, osteoclasts, and fibroblasts (reticular endothelial cells)
  - Secrete extracellular matrix fluid that anchors developing cells in the cavity
  - Crucial in cell survival and differentiation



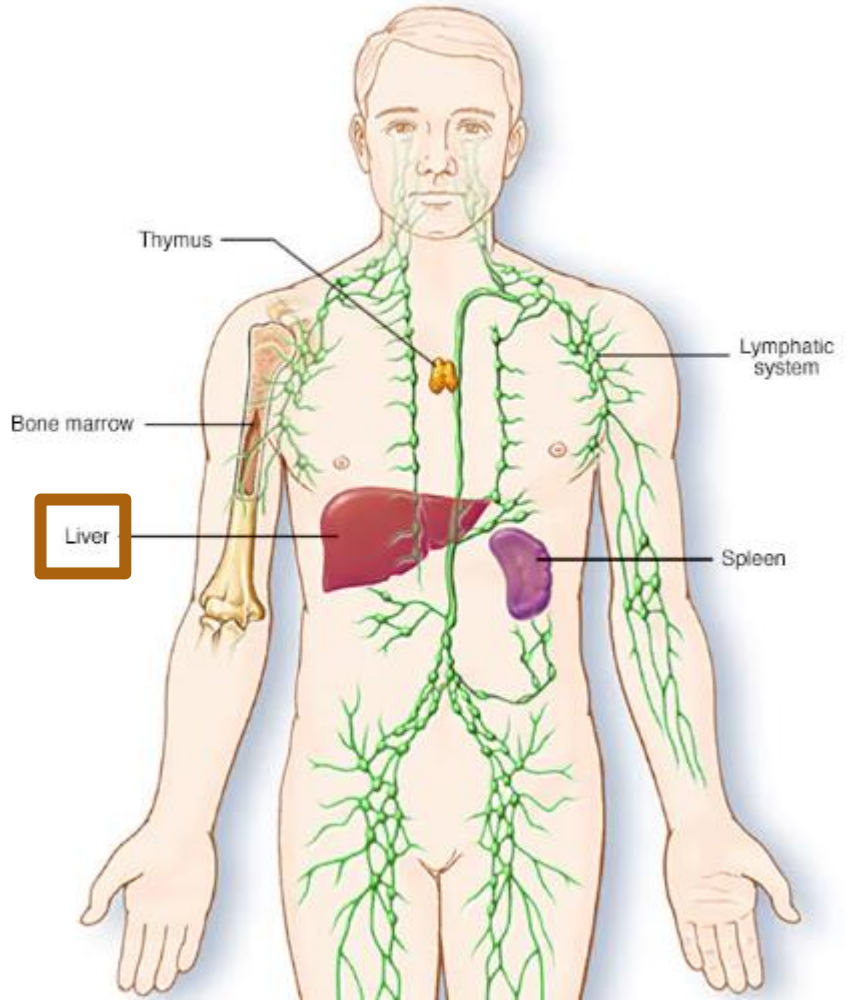
Rodaks' Hematology 6th Edition

Bone Marrow Cell Storage

- Hematopoietic capabilities of bone marrow include:
  - Stem cell pool- unipotential and multipotential stem cells available
  - Bone marrow pool- maturing and proliferating cells, some being stored for later use (storage pool)
- Hematopoietic capabilities of peripheral blood include:
  - Functional and storage cells
    - RBCs- 100% functional
    - Granulocytes- 50% functional and 50% lining vessels
    - Platelets- 70% functional and 30% stored in the spleen

Liver

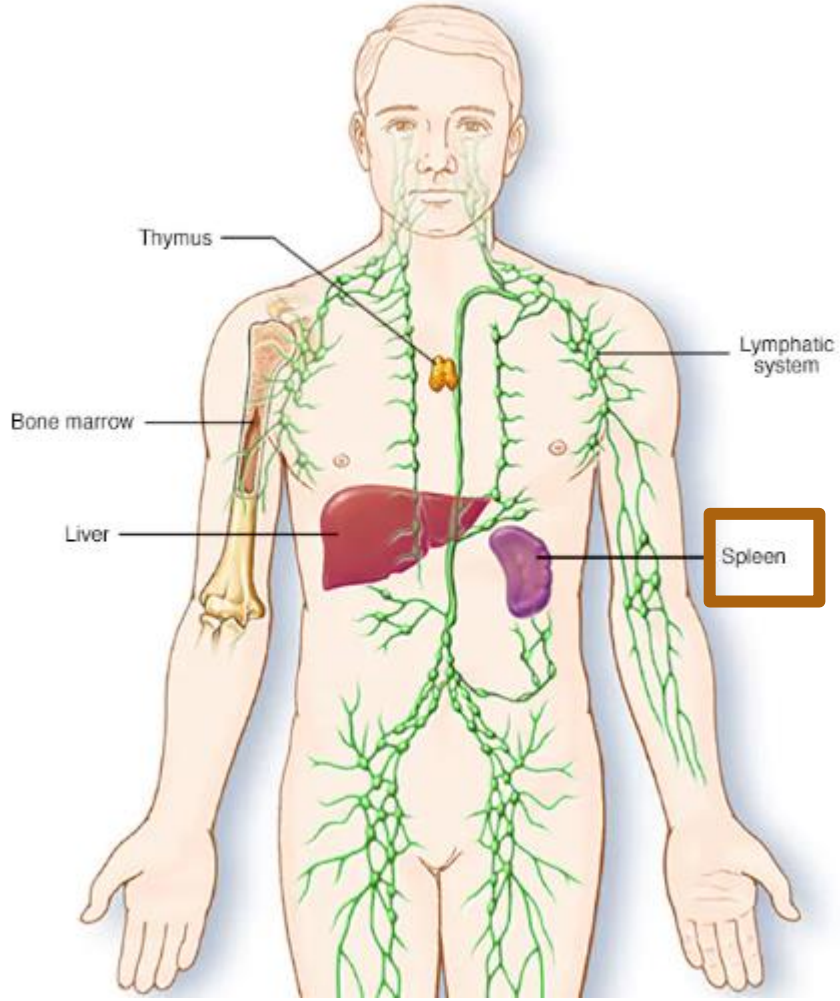
- Major site of blood cell production during the 2nd trimester
- Contain **Kupffer cells** in the lumen
  - Macrophages that remove senescent cells and foreign debris from the liver
  - Secrete mediators that regulate protein synthesis in hepatocytes
- Ability to maintain hematopoietic and progenitor cells to produce various cell types as a response to infectious agents or in pathologic myelofibrosis of the bone marrow
- Site of extramedullary hematopoiesis



https://www.mayoclinic.org/diseases-conditions/swollen-lymph-nodes/multimedia/lymphatic-system/img-20007995

Spleen

- Largest secondary lymphoid organ
- Filters circulating blood
- 30% of platelets sequestered in the spleen
- Made up of white pulp, red pulp, and marginal zone
  - White pulp: germinal cells with lymphs, macros, and dendritic cells
  - Red pulp: vascular sinuses separated by cords of reticular cell meshwork (cords of billroth) containing loosely connected macros, spongelike
    - Removal of senescent or abnormal RBCs from circulation through culling and pitting
      - Culling: cells are phagocytized with degradation of cell organelles
      - Pitting: splenic macrophages remove inclusions or damaged surface membrane from circulating RBCs
  - Marginal zone: surround white pulp and contain macros, memory B cells, and CD4 T cells
- Site of extramedullary hematopoiesis



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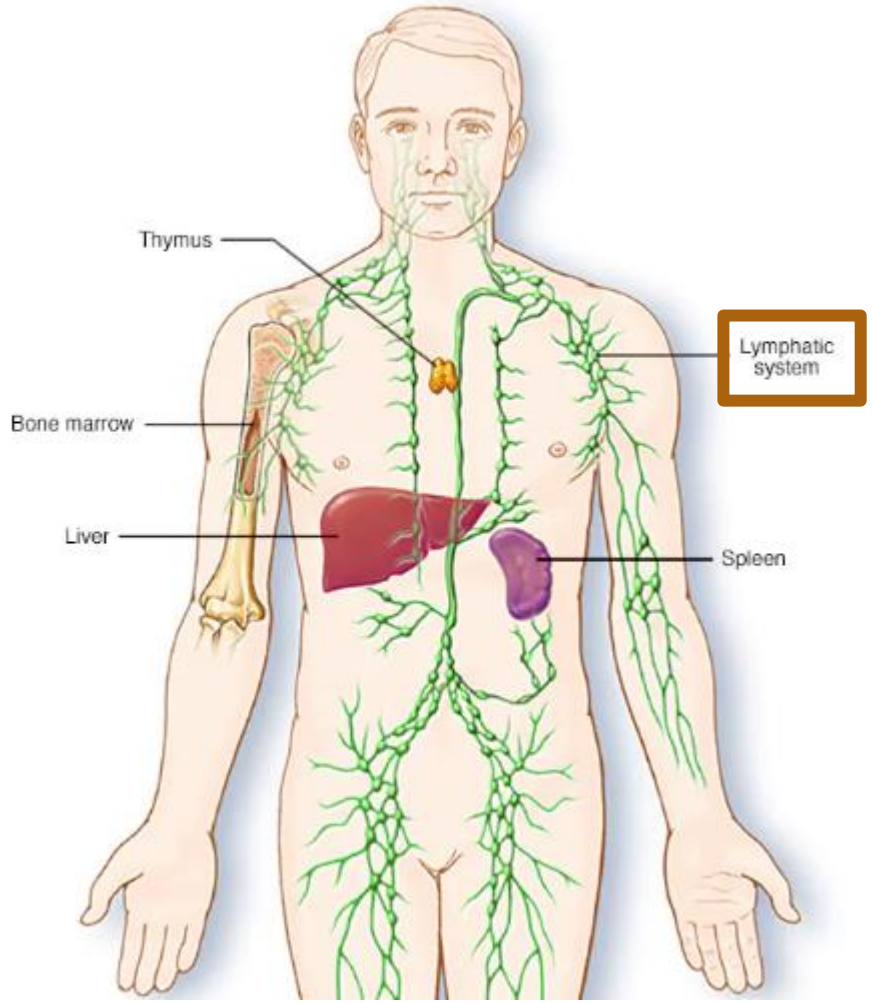
Lymph Nodes

- Bean structure separated into the cortex, medulla, and paracortex
  - Outer capsule forms trabeculae that goes into the cortex
    - Divides the lymph nodes into follicles
    - Secondary follicle
      - Develop foci of activated B cell proliferation called germinal centers
      - Occurs after antigenic stimulation
    - Primary follicle
      - No germinal center
  - Medullary cords interior- plasma cells and B cells
  - Paracortex predominately T cells and macros
    - Located between the cortex and the medulla
- 3 main functions
  - Site of lymphocyte production
  - Involved in initiation of specific immune response to foreign antigens
  - Filter particulate matter, debris, and bacteria that is in the lymph



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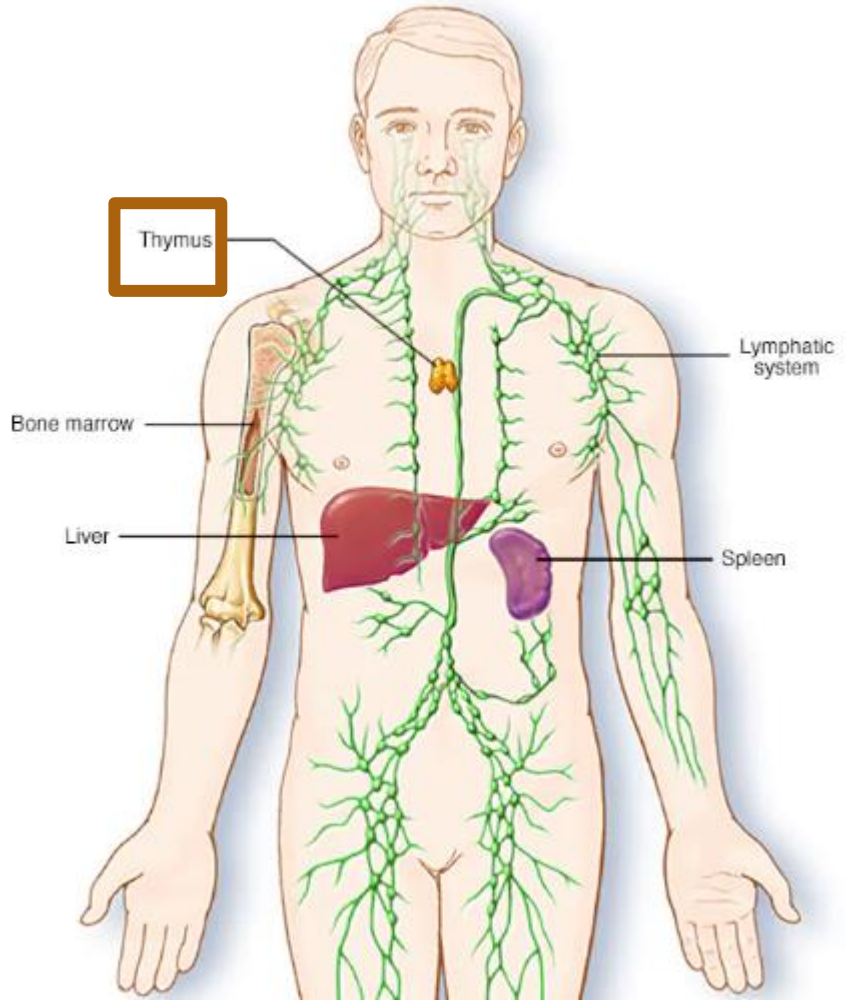
Thymus

- 1st developed organ in the fetus
- Made up the cortex and medulla
- T cell progenitors migrate from bone marrow to the thymus for further maturation
  - Enter as “double negative” then move to the cortex and express CD4 and CD8 “double positive”
  - When mature, will switch to either CD4 or CD8
- Mature T cells migrate to the spleen, lymph nodes, and other lymphoid tissue
- Underdeveloped thymus results in lack of T lymphocytes- failure to thrive, uncontrollable infections or death



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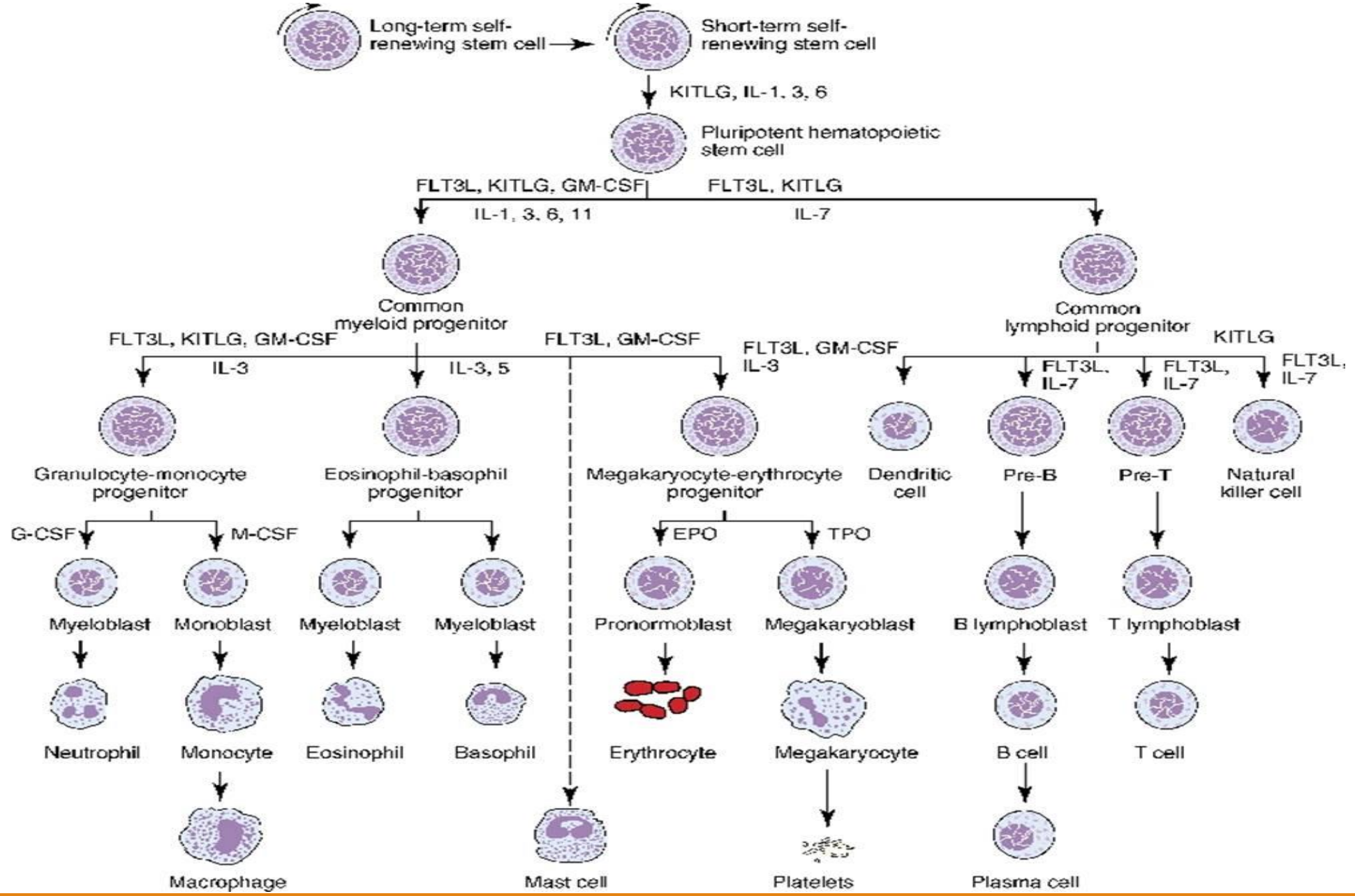
Hematopoietic Stem Cells and Cytokines

Hematopoietic Stem Cell Theory

- 1961 Till and McCulloch conducted experiments on irradiated spleens and bone marrow of mice
  - Mice were aplastic and were then injected with marrow cells
  - Colonies of HSCs were seen in 7-8 days
  - They called these colonies colony forming units-spleen (CFU-S)
- CFU-S represent what we know as:
  - Committed myeloid progenitors
    - As known as Colony Forming Unit- Granulocyte, Erythrocyte, Monocyte, and Megakaryocyte (CFU-GEMM)
- Hematopoietic progenitor cells divide into 2 groups:
  - Noncommitted/undifferentiated HSC
  - Committed progenitor cells
- HSCs are capable of self renewal, pluripotent, and can differentiate
  - Common lymphoid progenitor
  - Common myeloid progenitor



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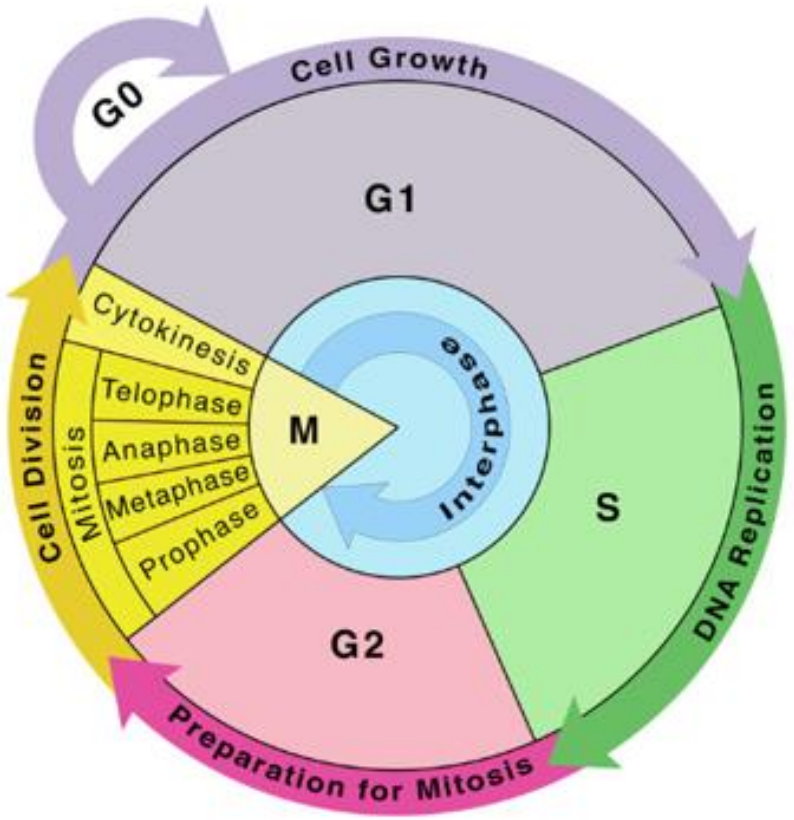
Stem Cell Cycle Kinetics

- HSCs are capable of many mitotic divisions when stimulated by the appropriate cytokines
- Mitosis- creation of 2 identical daughter cells
- After mitosis,
  - Some cells reenter cycle
  - Some cells go into resting (G_0)
    - Can reenter cycle and divide again
    - Can be directed to terminal differentiation
- Mitotic index
  - Percentage of cells in mitosis to total number of cells
  - Normally 1% to 2%
  - Increased mitotic index= proliferation



https://www.sciencefacts.net/cell-cycle.html

Cytokines (Growth Factors)

- Group of specific glycoproteins that regulate proliferation, differentiation, and maturation of hematopoietic progenitor cells
  - Ex. Interleukins (ILs), monokines, interferons, chemokines, and colony stimulating factors (CSFs)
- Stimulation or inhibition
  - Positive influence
    - Impact on HSC and progenitors with multilineage potential
    - KIT ligand, FLT3, GM-CSF, IL-1, IL-3, IL-6, and IL-11
  - Negative influence
    - Growth factor B, tumor necrosis factor δ, and interferons
- Hematopoietic progenitor cells require cytokines constantly for survival and growth
  - Prevent apoptosis
  - Signal cells to divide

Cytokines (Growth Factors)

- Colony Stimulating Factors (CSF)
  - High specificity for their target cells and active at low concentrations
  - Produced by many different cell lineages
- Interleukins
  - Proteins that regulate autoimmune and inflammatory reactions and steps in hematopoiesis
  - Effective at low concentrations
- Multilineage growth factors
  - KIT Ligand (“Stem Cell Factor”)- KIT is a receptor-type tyrosine-protein kinases expressed on HSCs
    - Stimulates cells to differentiate and proliferate
    - Down-regulated with differentiation
  - FLT3 ligand- tyrosine-protein kinase synergistic with KIT ligand and IL-3

Lineage Specific Hematopoiesis

Lineage-specific hematopoiesis

- Erythropoiesis
- Leukopoiesis
  - Myelopoieis
  - Lymphopoiesis
- Megakaryopoiesis

Erythropoiesis

- Occurs in the bone marrow, regulating process for maintaining adequate numbers erythrocytes in peripheral blood

- CFU-GEMM → BFU-E → CFU-E

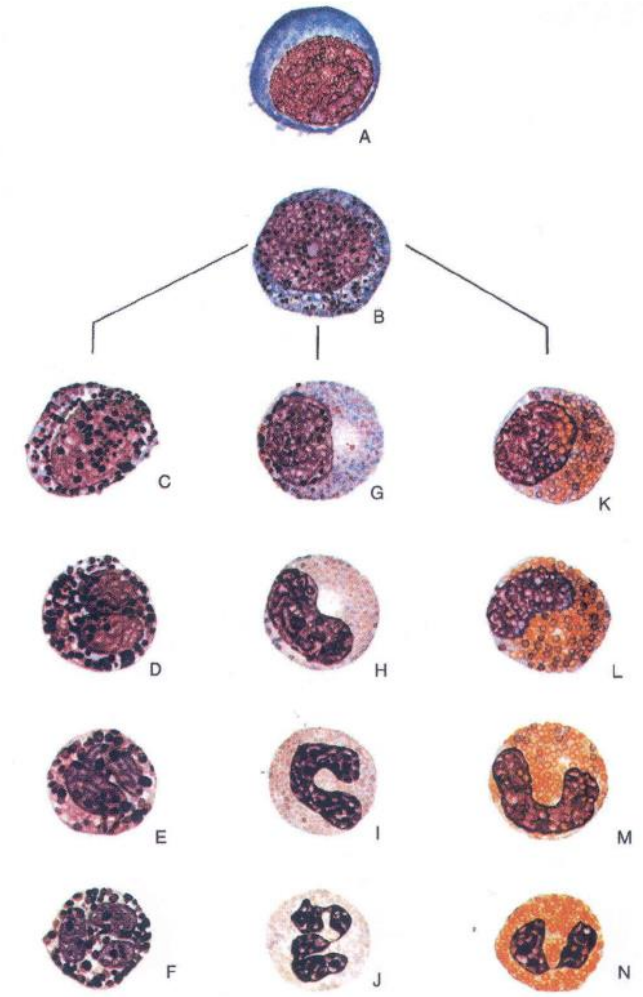
  - Colony-forming unit-erythroid (CFU-E)
    - Created when BFU-E is under the influence of IL-3, GM-CSF, TPO- and KIT ligand
    - High affinity for erythropoietin (EPO)
      - Differentiation factor that causes CFU-E → pronormoblast
      - Pronormoblast: earliest erythrocyte precursor in the bone marrow

Leukopoiesis

- Divided into 2 major categories
  - Myelopoiesis
  - Lymphopoiesis
- Myelopoiesis
  - CFU-GEMM → neutrophils, monocytes, eosinophils, and basophils
    - Differentiation promoted by GM-CSF, G-CSF, M-CSF, IL-3, IL-5, IL-11, and KIT ligand
- Lymphopoiesis
  - Common lymphoid progenitor → B cells, T cells, dendritic cells, and NK cells
    - Differentiation promoted through interactions with numerous interleukins (IL-2, IL-7, IL-12, IL-15, etc)

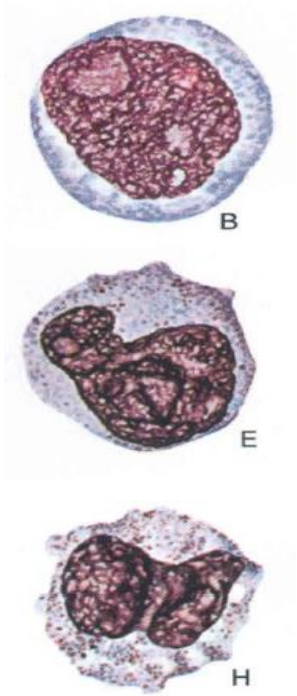
Myelopoiesis

Granulocytic Differentiation



Basophil Neutrophil Eosinophil

Monocytic Differentiation



Courtesy of Dr. Eric Hsi's PowerPoint on Hematopoiesis

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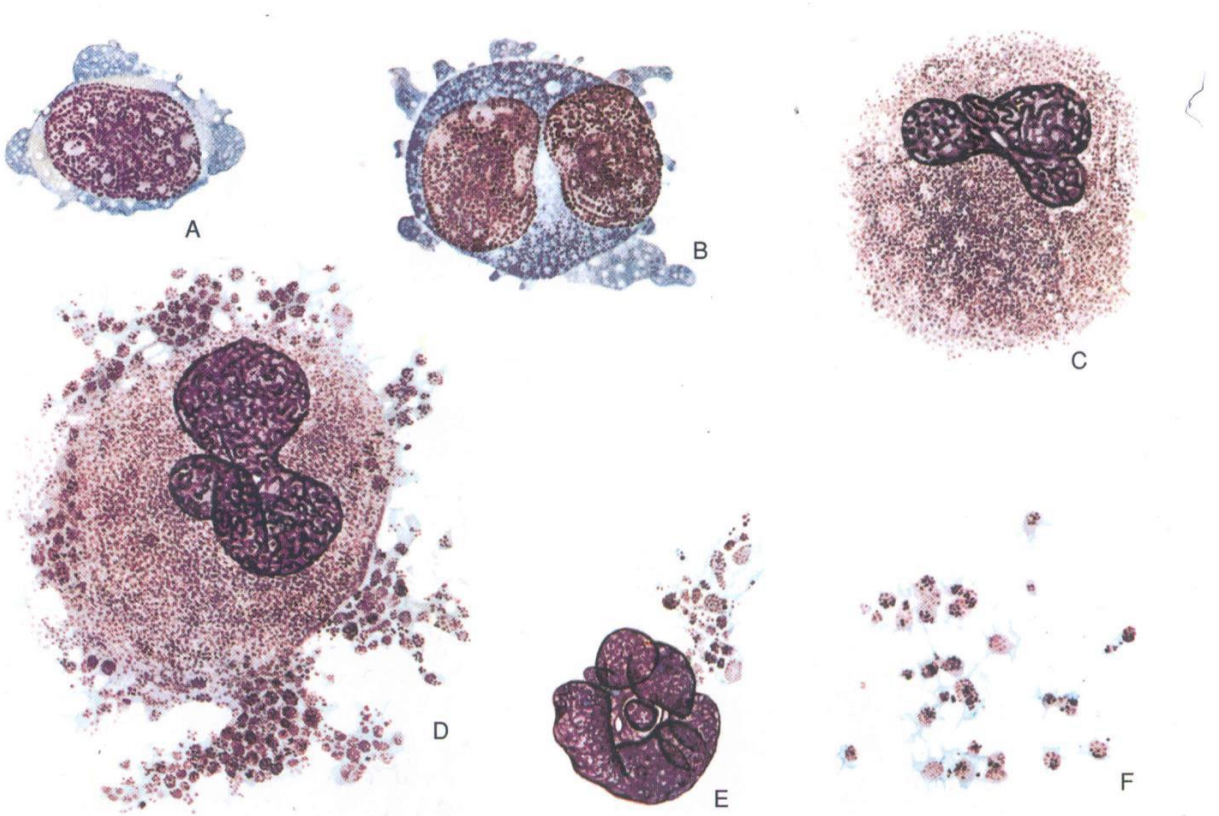
Lymphopoiesis

- B-cells develop in bone marrow (hematogones) and then migrate to peripheral (secondary) lymphoid organs such as lymph node, Waldeyer's ring, and the spleen as naïve B-cells
  - Exposure to antigen results in further maturation from naïve B-cells to memory B cells and plasma cells (terminal differentiation)

- T-cells develop in the thymus and migrate to secondary lymphoid organs as functional immune cells

Megakaryopoiesis

- CFU-GEMM → megakaryocyte
  - Influenced by GM- CSF, IL-3, IL-6, IL-11, KIT Ligand, and TPO (produced in the liver)
    - TPO and IL-11 control the release of platelets
- Differentiate/mature via endomitosis
  - Duplication/reduplication of nuclear material without nuclear division
- Platelets develop by cytoplasmic fragmentation in the bone marrow sinus
- One megakaryocyte can make thousands of platelets



7. Megakaryocytic system.
A. Megakaryoblast, *B*. Promegakaryocyte, *C*. Megakaryocyte, *D*. Metamegakaryocyte, *E*. Metamegakaryocyte Nucleous, *F*. Thrombocytes (platelets).

Courtesy of Dr. Eric Hsi's PowerPoint on Hematopoiesis

References

- Rodak's Hematology, Clinical Principles and Applications 6th Edition
- Additional material courtesy of Dr. Eric His and Dr. James Cook