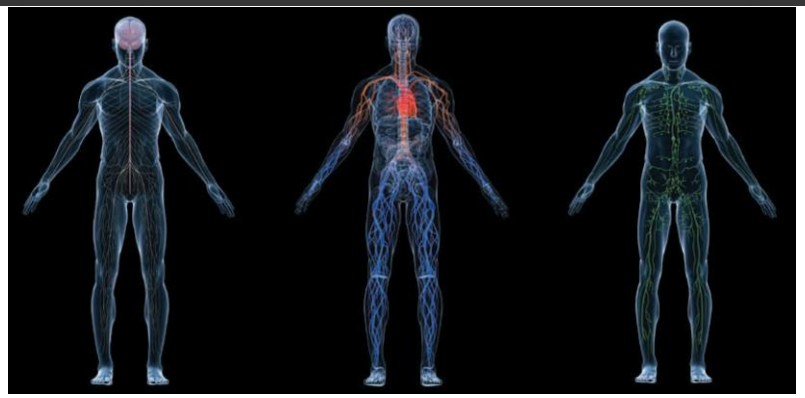
UNIT VI

Chapter 34:



Resistance of the Body to Infection: I. Leukocytes, Granulocytes, the Monocyte- Macrophage System, and Inflammation

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Defense Against Infection
Leukocytes

- **Microorganisms coexist with us and within us , which can be beneficial or harmful.**
- **Phagocytes can ingest and destroy invading organisms and participate in tissue reactions that “wall off” infection.**
- **Other white cells (lymphocytes, chapter 35) mediate responses that destroy or neutralize *specific* microorganisms.**

White Blood Cells

- **Circulate in blood and may enter the tissues**
- **<u>Are of six types</u>:**
  - **Polymorphonuclear neutrophils**
  - **“ eosinophils**
  - **“ basophils**
  - **Monocytes**
  - **Lymphocytes (plasma cells)**
  - **Platelets (from megakaryocytes)**

White Blood Cell Counts

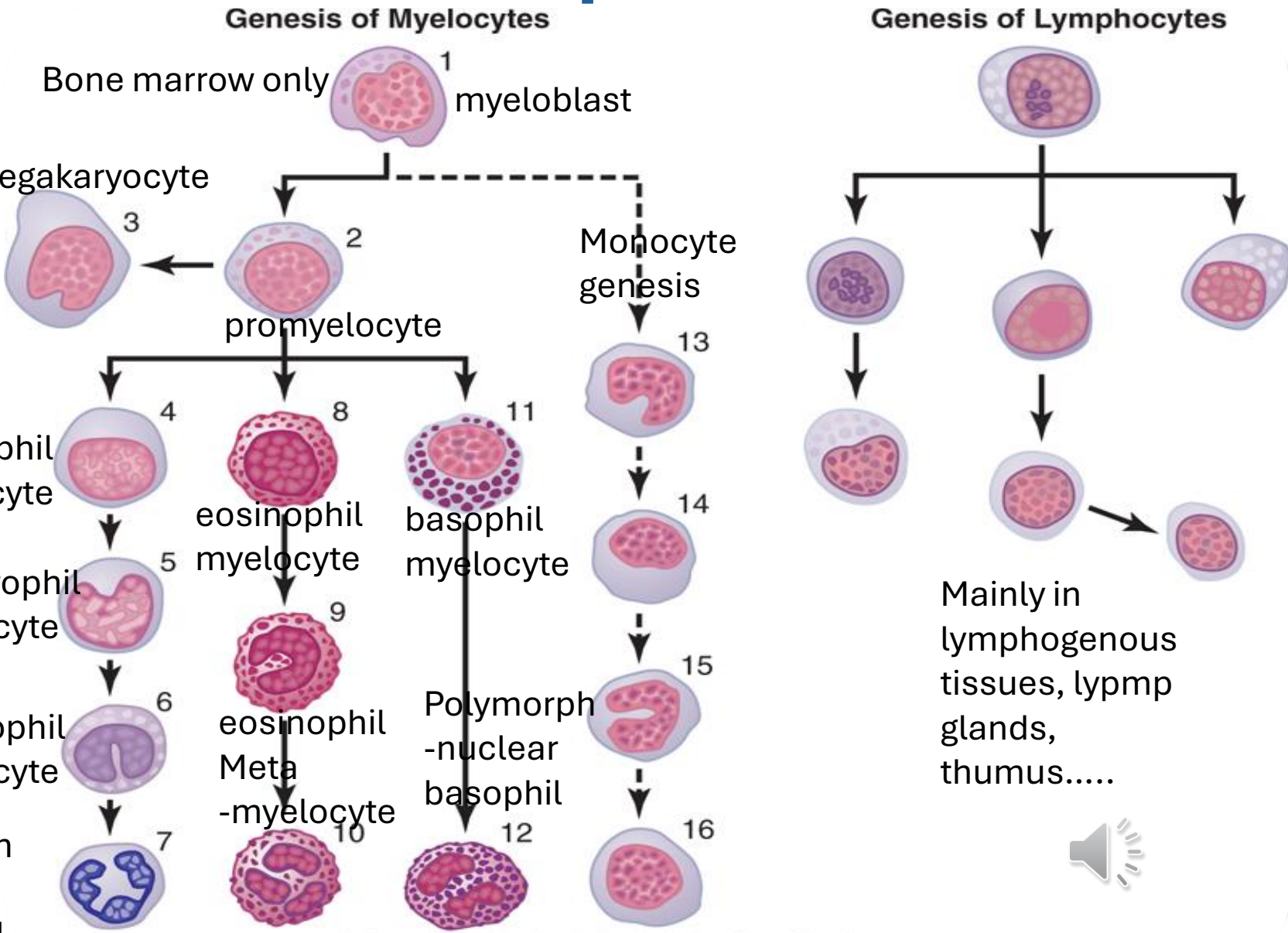
- **Total WBC ~ 7,000 / mm^3**

  (almost 1,000-fold fewer than RBCs)

- **Proportions:**
  - **Neutrophils** **62%**
  - **Eosinophils** **2.3%**
  - **Basophils** **0.4%**
  - **Monocytes** **5.3%**
  - **Lymphocytes** **30%**

- **Platelets ~ 300,000 / mm^3**

Leukopoiesis



Genesis of White Blood Cells

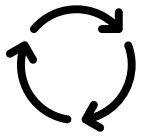
- **Granulocytes and monocytes develop in the bone marrow, and most remain there until needed peripherally (number in marrow ~3x blood; 6-day supply)**
- **Lymphocytes develop mostly in the peripheral lymphoid organs (thymus, spleen, tonsils, lymph nodes, Peyer's patches), less found in blood**
- **Megakaryocytes develop and reside in the marrow, fragment to release platelets**

Life Span of White Blood Cells

- **Granulocytes:**
  - **Circulating, 4 – 8 hours**
  - **In the tissues, 4 – 5 days**
    (shorter timelines with infection, inflammation)

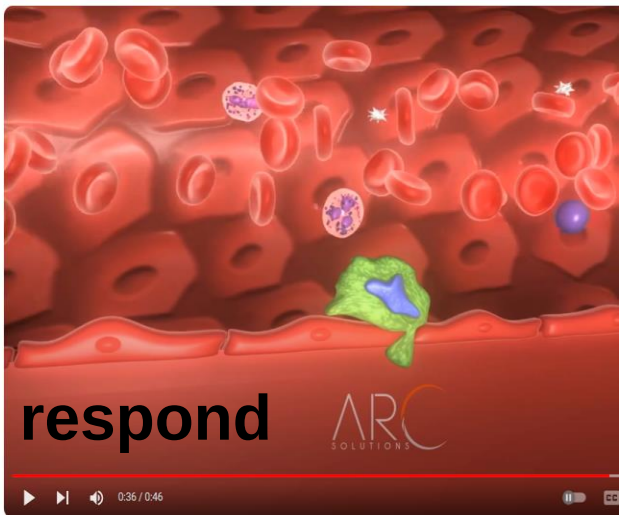
- **Monocytes / Macrophages:**
  - **Circulating, 10 – 20 hours**
  - **As tissue macrophages, months or longer**

- **Lymphocytes:**
  - **Continuously re-circulate:**
    lymph…nodes…blood.. tissues (diapedesis)
  - **Long-lived… weeks, months, longer**



- **Platelets: ~ Replaced every ten days~ 30K each day**

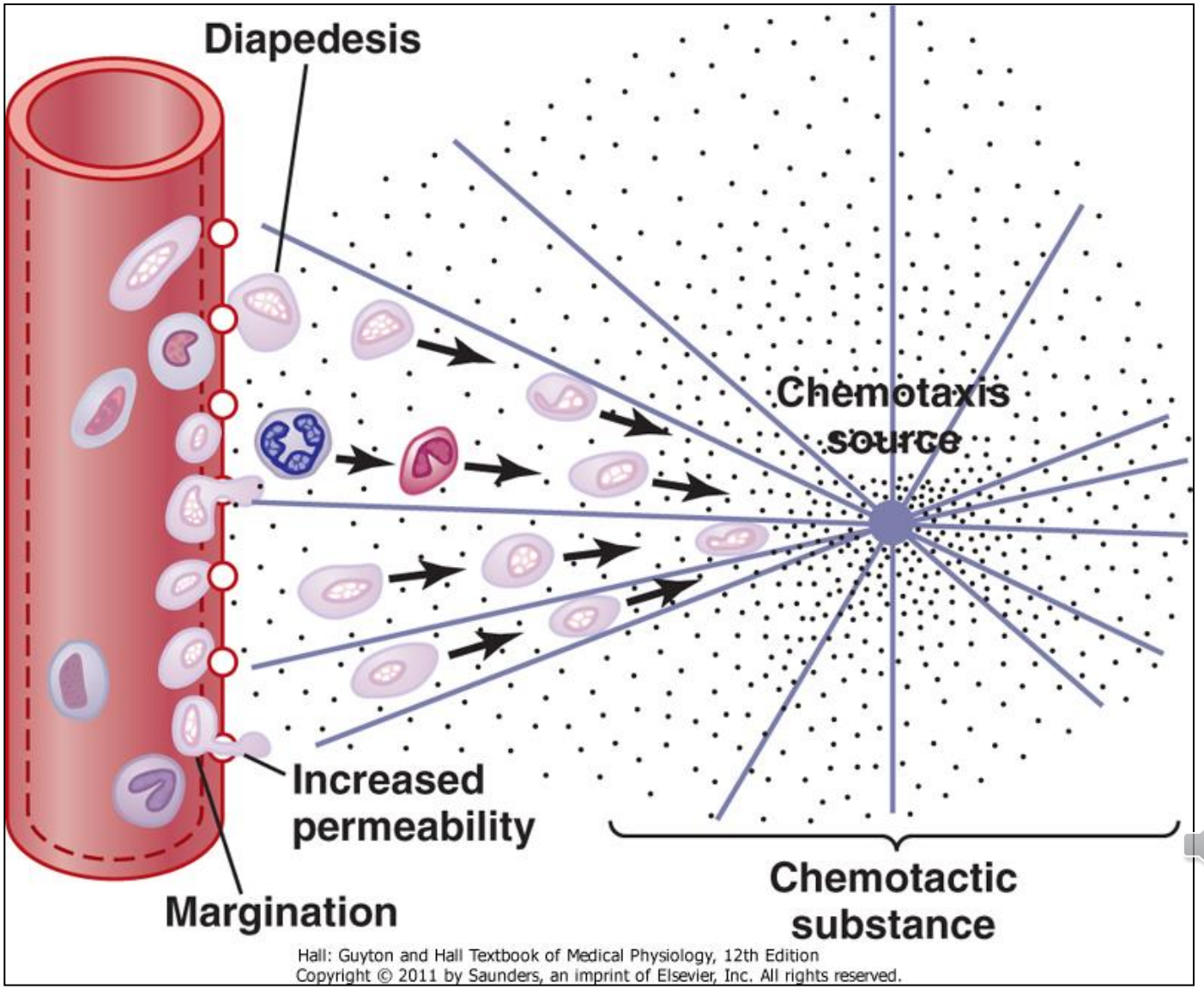
Neutrophils and Macrophages



- **Neutrophils are mature cells that can respond immediately to infection**
- **Monocytes mature in the tissues to become macrophages (monocytes in blood little ability)**
- **Both exhibit motility:**
  - **Diapedesis**

  Diapedesis - Medical Animation by Arc Solutions - YouTube
  - **Ameboid motion**
  - **Chemotaxis (Chemoattractants: bacterial or tissue degradation products, complement fragments, other chemical mediators)**

Neutrophil Margination & Migration



Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

Phagocytosis

- **"Phagocytosis" is the ingestion of particles**
- **Phagocytes must distinguish foreign particles from host tissues**
- **Appropriate phagocytic targets:**
  - **May have rough surfaces**
  - **Lack protective protein coats**
  - **May be immunologically marked for phagocytosis by *antibodies* or *complement components* that are recognized by receptors on the phagocytes**

    … this immunologic marking is called "opsonization"

Phagocytosis

- **Neutrophils: can ingest 3-20 bacteria**
- **Macrophages: After being activated in the tissues, are extremely effective phagocytes (up to ~100 bacteria)**
- **Macrophages can ingest larger particles…**
  - **Damaged RBCs**
  - **Malarial parasites**
- **Macrophages can extrude digestion products and survive and function for many months**

Digestion of Ingested Particles

- **In both neutrophils and macrophages, *phagosomes* fuse with *lysosomes* and other granules to form *phagolysosomes* (*digestive vesicles*)**

- **These contain *proteolytic enzymes*, and in macrophages, *lipases* (important in killing tuberculosis bacillus and some other bacteria)**

Bactericidal Agents

- **Bacteria may be killed even if they are not digested**
- **Enzymes in the phagosome or in *peroxisomes* generate strongly bactericidal *reactive oxygen species…***
  - ***Superoxide*** **(O_2^-)**
  - ***Hydrogen peroxide*** **(H_2O_2)**
  - ***Hydroxyl ions*** **(OH^-)**
  - ***Myeloperoxidase*** **catalyzes**

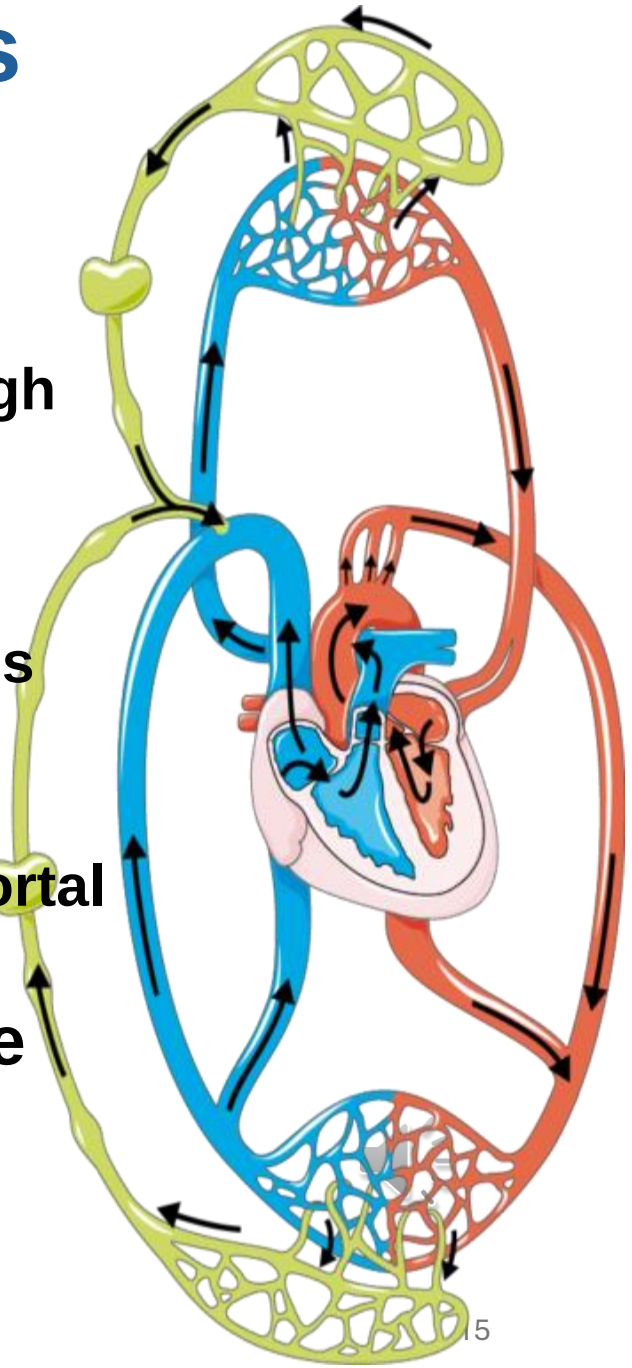
$$H_2O_2 + 2\ Cl^- \longrightarrow 2\ H^+ + 2\ ClO^-$$

The Reticuloendothelial System

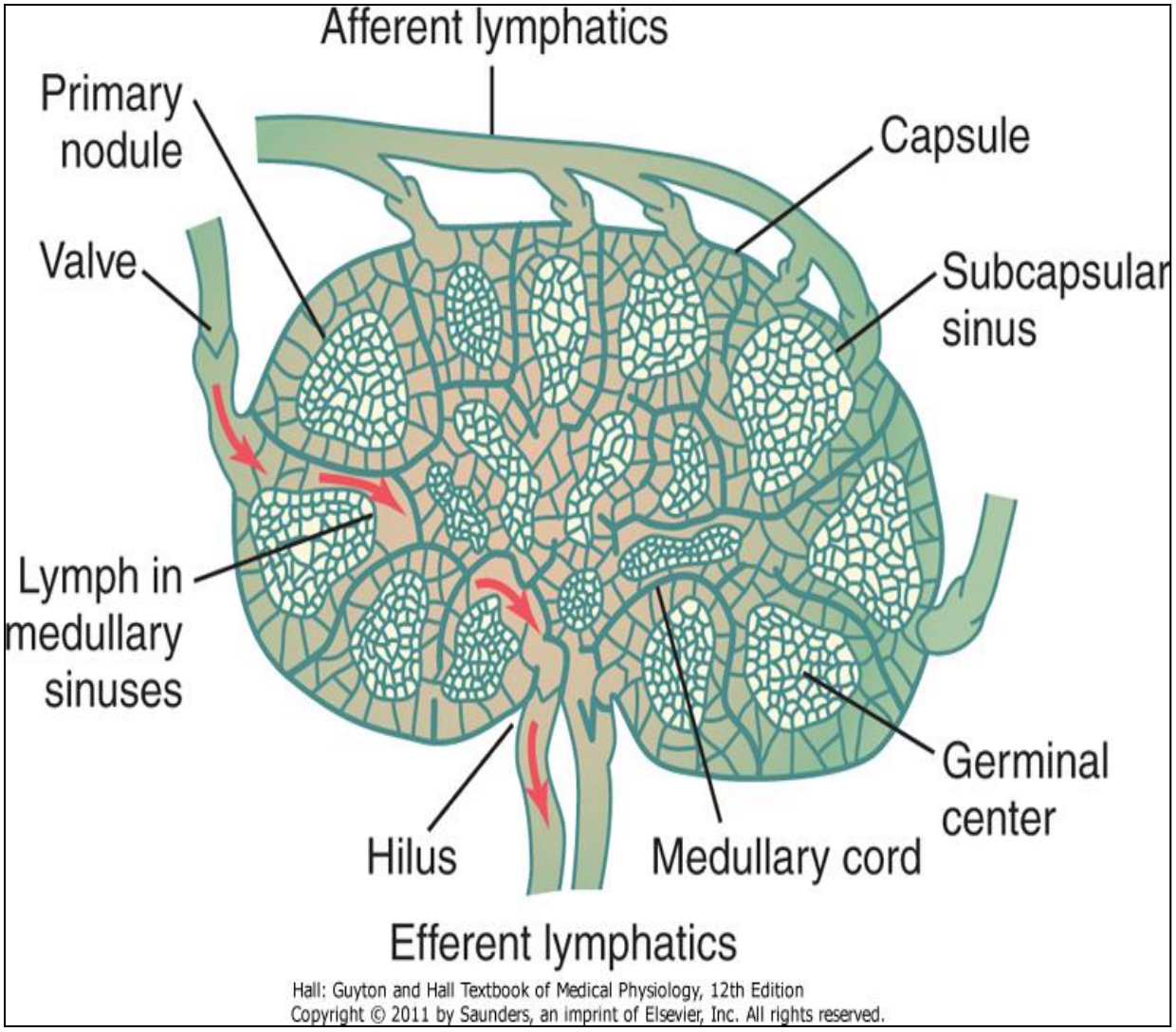
- **After entering the tissues, macrophages become fixed and may be resident for years**
- **When appropriately stimulated they can break away and move to sites of inflammation**
- **Circulating monocytes, mobile macrophages, fixed tissue macrophages, and some specialized endothelial cells form the *reticuloendothelial system*, almost all derived from monocytes, comprising a phagocytic system located in all tissues**

Specialized Macrophages

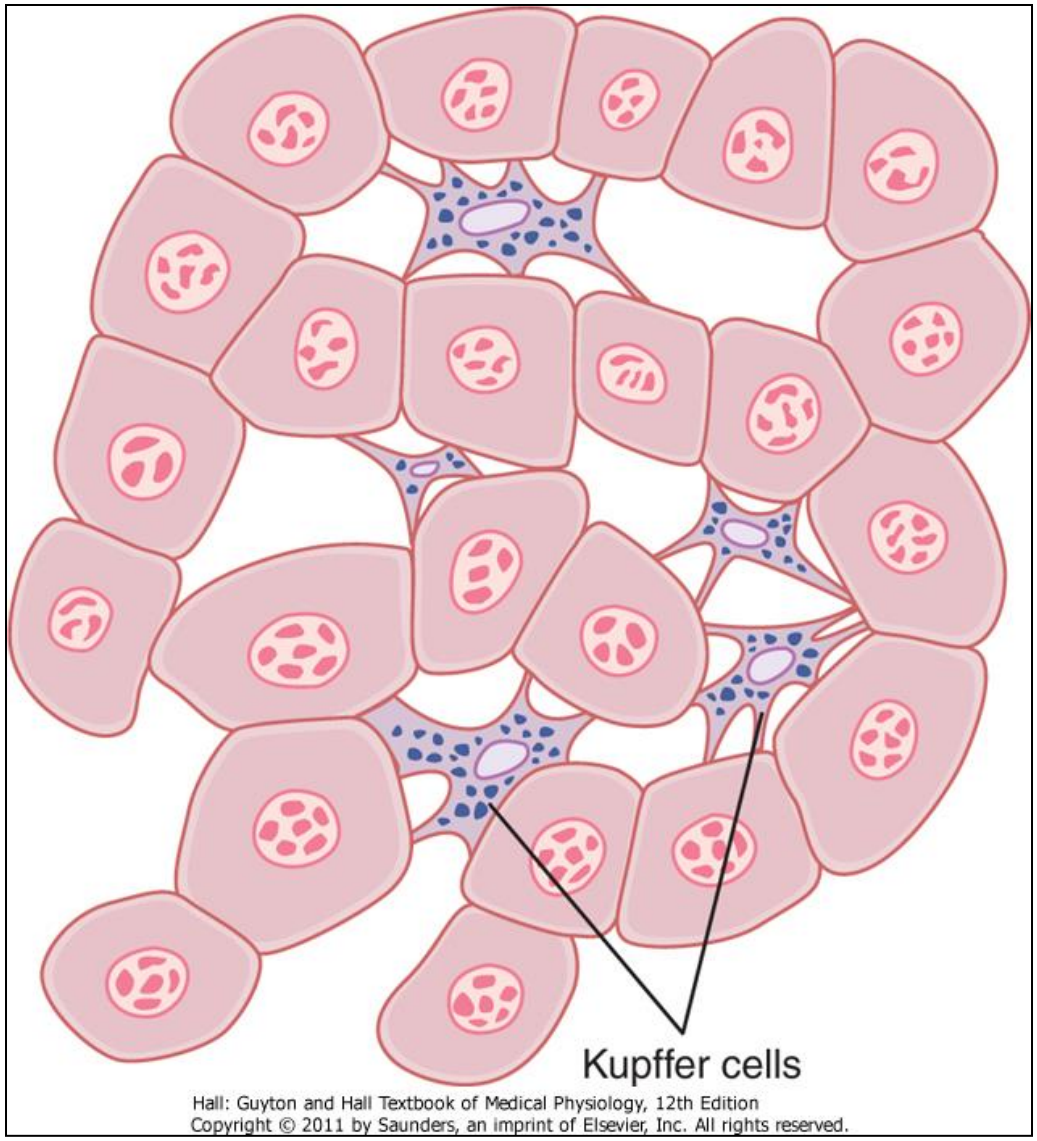
- Skin, subcutaneous (histiocytes)
- Lymph nodes
  - Ingest / sample particles arriving through the lymph
- Alveolar macrophages
  - Digest or entrap inhaled particles and microorganisms like silica, tuberculosis bacilli.
- Kupffer cells
  - Lining sinusoids, Surveillance of the portal circulation.
- Macrophages in the spleen and bone marrow
  - Surveillance of the general circulation



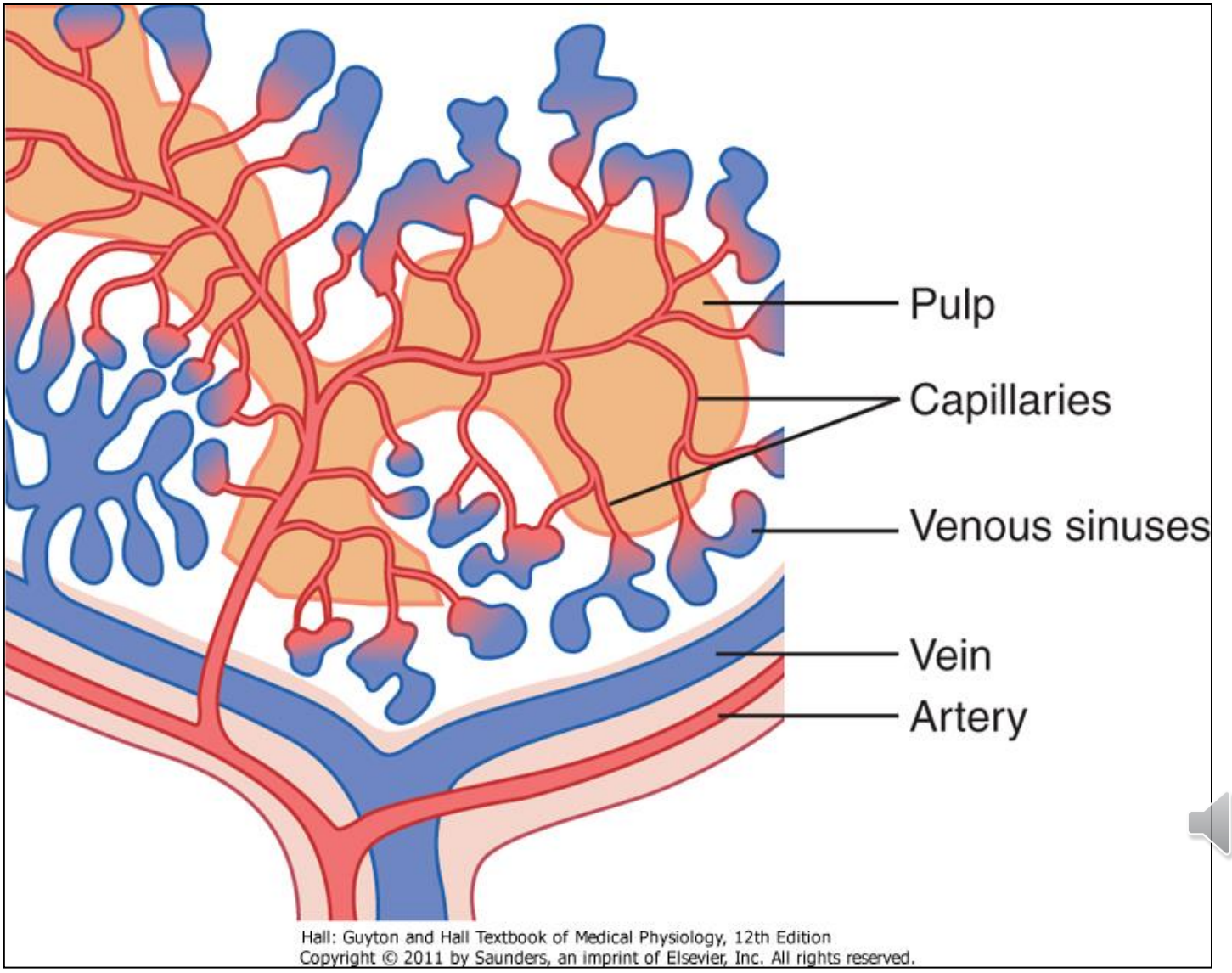
Structure of a Lymph Node



Kupffer Cells in the Liver Sinusoids



Structure of the Spleen



Neutrophils, Macrophages & Inflammation

- **Inflammation is driven by chemical mediators and characterized by heat, redness, swelling, and pain**

- **Physiologically, it involves…**
  - **Vasodilatation and increased blood flow**
  - **Increased capillary permeability**
  - **Coagulation of interstitial fluids**
  - **Accumulation of granulocytes and monocytes**
  - **Swelling of tissue cells**

- **Mediators:** ***histamine, bradykinin, serotonin, prostaglandins, complement products, clotting components, lymphokines***

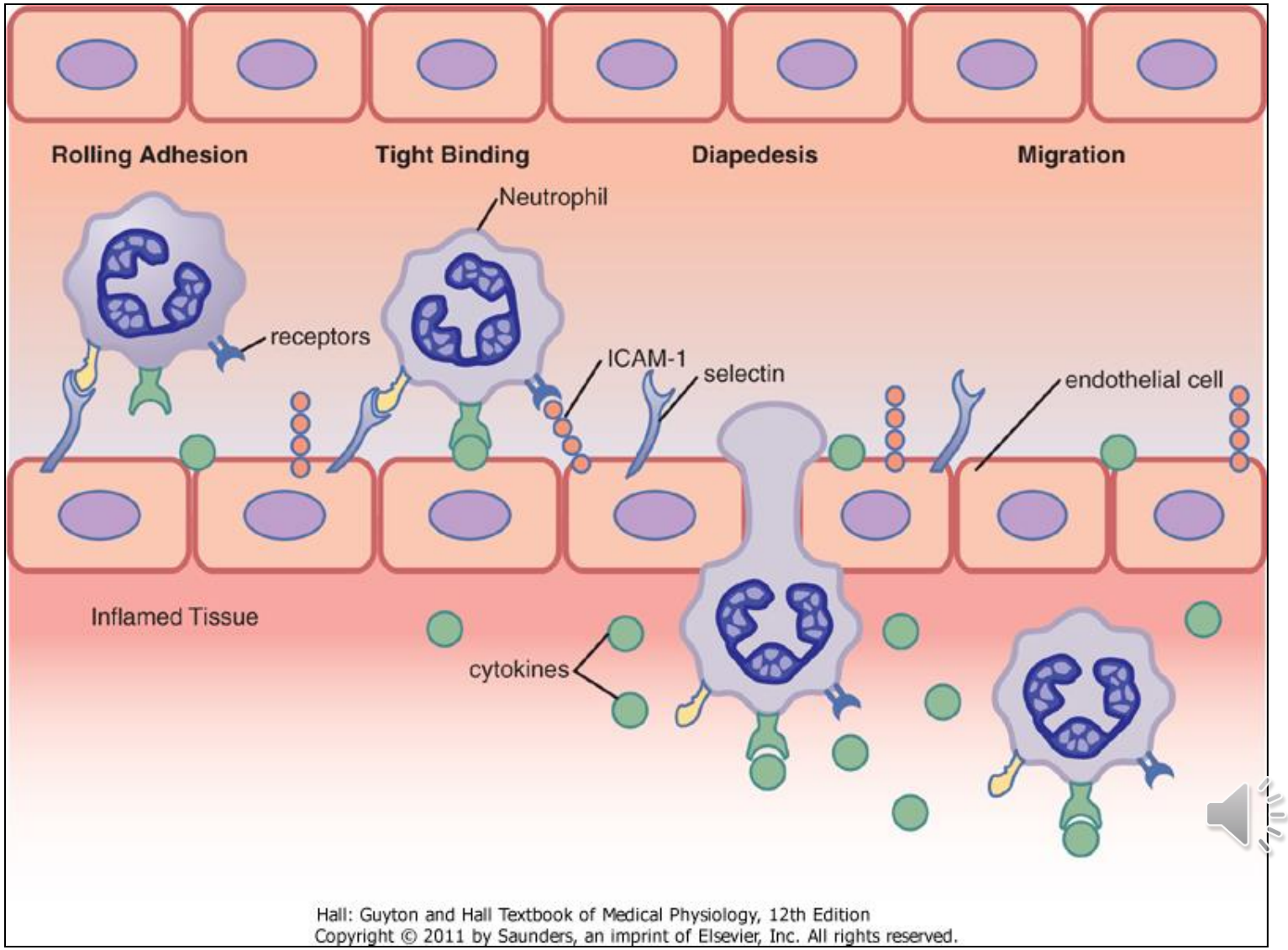
“Walling Off” Sites of Inflammation

- **Fibrinogen clots minimize fluid flow in and out of the inflamed area**
- ***Staphylococci* cause intense inflammation and are effectively “walled off”**
- ***Streptococci* induce less intense inflammation and may be more likely to spread than *staphylococci, and cause death***

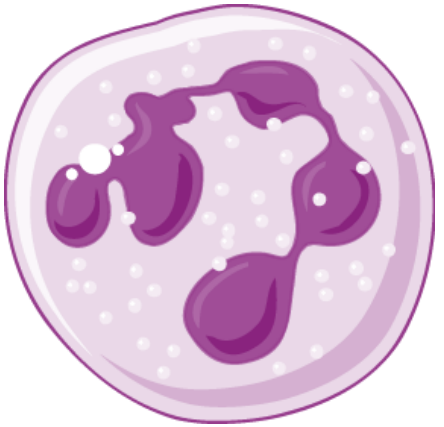
Neutrophils and Macrophages in Inflammation

- **Tissue macrophages that encounter foreign particles enlarge and become mobile to provide a first line of defense (min)**
- **Within an hour neutrophils migrate to the area in response to inflammatory cytokines (TNF, IL-1) 2nd line of defense**
- **Upregulated *selectins* and *ICAM-1* on endothelial cells**
- **Bind to *integrins* on neutrophils, leading to *margination*, followed by *diapedesis*, and *chemotaxis* directing neutrophils into the inflamed tissues, to kill bacteria and scavenge**

Neutrophil Migration to an Inflamed Site



Neutrophilia

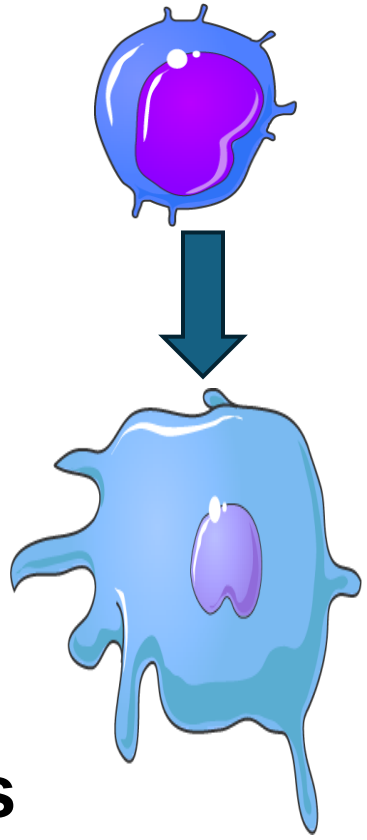


- **With intense inflammation neutrophil count can increase dramatically…**

4,000-5,000 ➡ 15,000-25,000

- **Results from mobilization of mature neutrophils from the bone marrow by inflammatory mediators**

Secondary Macrophage Invasion



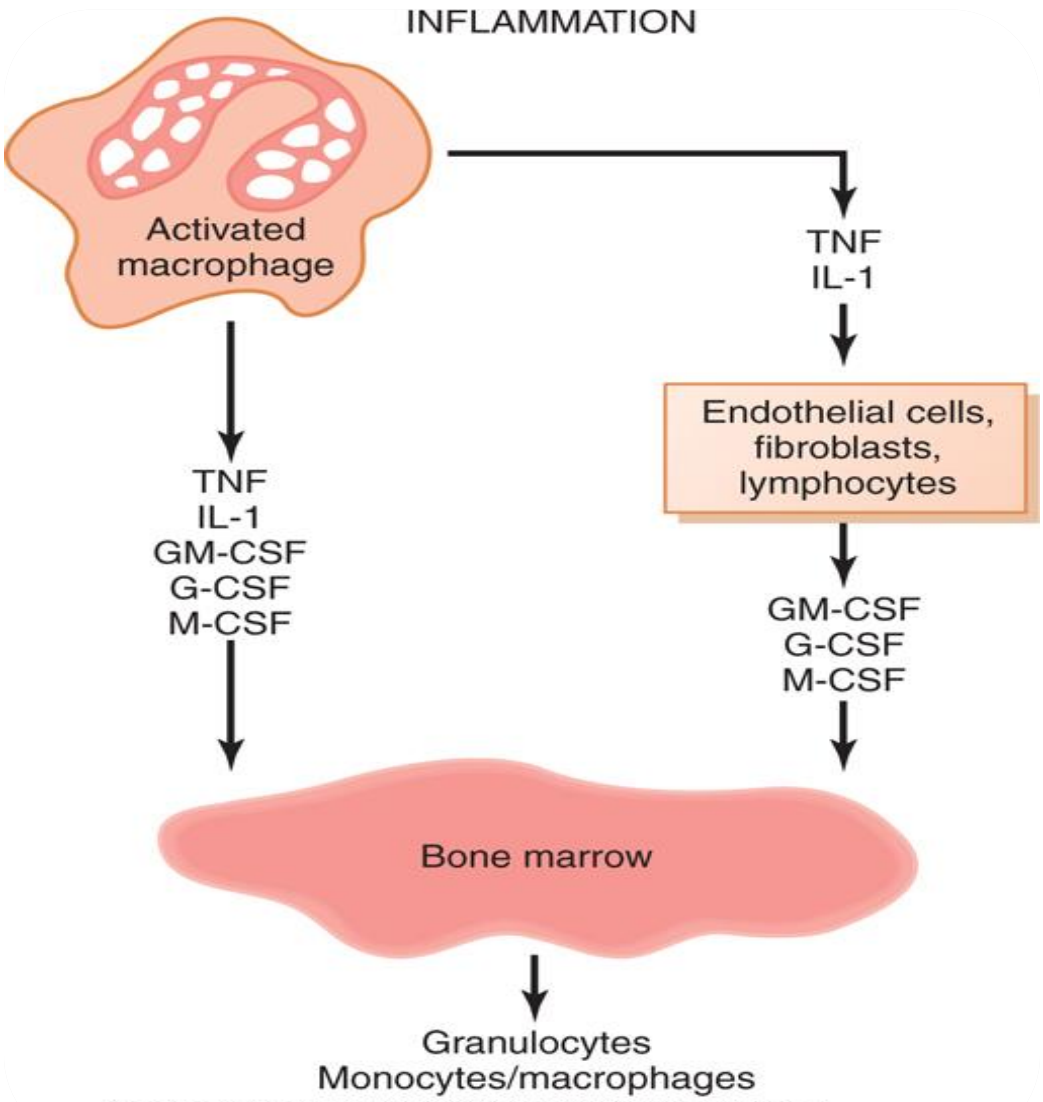
- **In response to chemoattractants, monocytes gradually accumulate (slowly) and become macrophages (after ~ 8 hours mature)**

- **In part due to increased bone marrow production (store is low), macrophages become the dominant inflammatory cell over several weeks, cleaning up remaining bacteria, necrotic tissue, and directing tissue remodeling. Third line of defense**

Bone Marrow Responses

- **Growth factors produced in response to infection and inflammation drive proliferation and differentiation of leukocyte precursors in the marrow**
- **First mature cells released after 3 – 4 days**
- **The bone marrow can increase production of granulocytes and monocytes by 20 – 50- fold and maintain this for months or years**
- **Fourth line of defense**

Bone Marrow Response to Inflammation

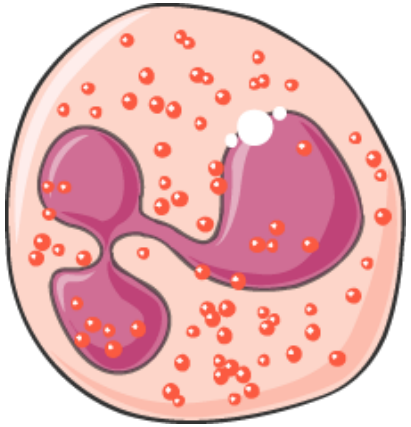


Formation of Pus

- **Pus is composed of dead bacteria and neutrophils, many dead macrophages, necrotic tissue that has been degraded by proteases, and tissue fluid, often in a cavity formed at the inflammatory site**

- **Over days and weeks it is absorbed into the surrounding tissue and lymph and disappears**

Eosinophils



- **Eosinophils are weak phagocytes**

and exhibit chemotaxis

- **Particularly important in defense against parasites, Ex: schistosomiases and trichinosis**

- **Can adhere to parasites and release substances that kill them (hydrolases, reactive oxygen species, major basic protein(larvacidal).**
- **Also accumulate in tissues affected by allergies, perhaps in response to eosinophil chemotactic factor from basophils (eosinophils may detoxify some products of basophils)**

Basophils

- **Similar to *mast cells* adjacent to Capillaries, both cell types release heparin**
- **Basophils and mast cells both release histamine, bradykinin, and serotonin**
- **When IgE bound to receptors on their surfaces is cross-linked by its specific antigen, mast cells and basophils *degranulate*, releasing…**
  - ***histamine, bradykinin, serotonin, heparin, leukotrienes,* and several *lysosomal enzymes***

Clinical Perspective

Leukopenia

- ***Leukopenia*, or low white blood cell count, is usually the result of reduced production of cells by the bone marrow**
- **It can allow clinically severe infections with organisms that are not usually pathogenic**
- **Within two days of bone marrow shutdown mucous membrane ulcers or respiratory infection may occur**
- **<u>Causes</u>: radiation, chemical toxins, some medicines**
- **In most cases marrow precursors can reconstitute normal blood cell counts with proper support**

Clinical Perspective

Leukemias

- **Uncontrolled production of abnormal white blood cells due to a genetic mutation**
- **Clonal, lineage-specific, often immature cells**
- **Leukemias are…**
  - **Lymphocytic vs. myelogenous**
  - **Acute vs. chronic (sometimes up to 10-20 years)**
- **Leukemias with partially differentiated cells may be classified as *neutrophilic, eosinophilic, basophilic, or monocytic leukemias***

Clinical Perspective

Clinical Effects of Leukemias

- **Growth of leukemic cells in abnormal sites**
- **Invasion of bone from the marrow, with pathologic fractures**
- **Eventually spreads to vascular and lymphatic "filters"… spleen, lymph nodes, liver, other organs**
- **Replacement of normal bone marrow, resulting in infection, and bleeding**
- **Wasting because of metabolic demands**