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PHYSIOLOGY

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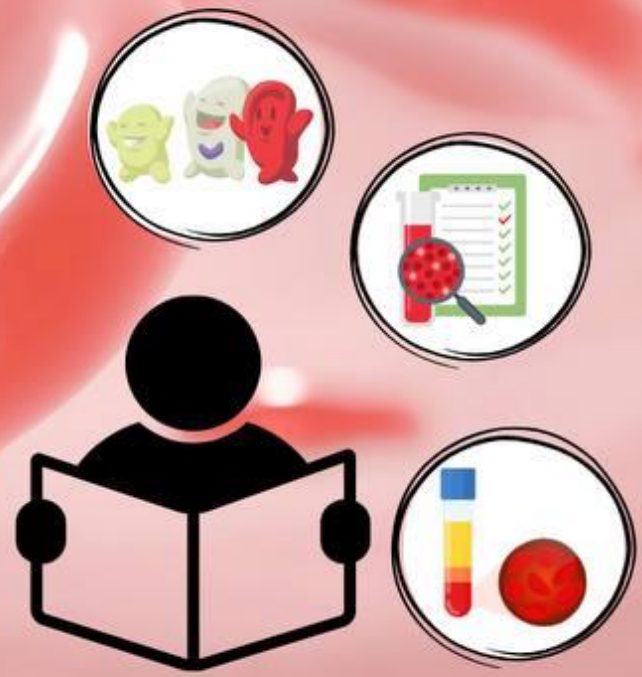

UNIT VI

Chapter 34:

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

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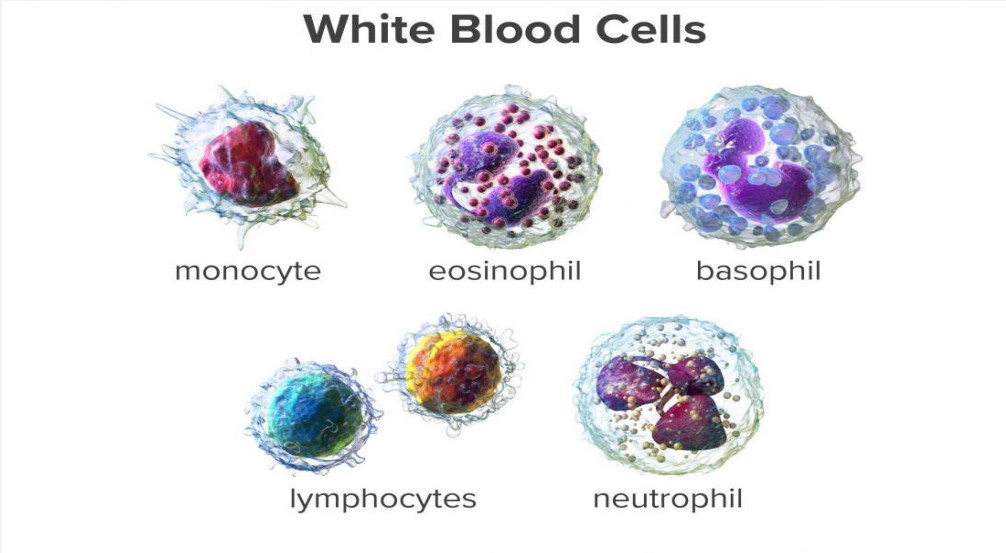
Color code
Slides
Doctor
Additional info
Important

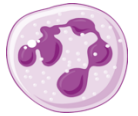
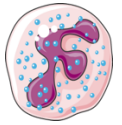
Defense Against Infection
Leukocytes

- **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.**

- Many microorganisms and bacteria are present normally in tissues such as that which are in the mouth , respiratory system as well as the lining of the intestine in the digestive tract . However, if these bacteria or microorganism invaded deeper into tissues may they cause harmful diseases or they can be directly (lethal) fatal , very harmful microorganisms like viruses and bacteria also exist in the external environment of us , so if they enter our system , they can cause lethal infections . At the same time our body has a system , which is composed of WBCs , that can defend and attack against these invading microorganisms .
- WBCs can either perform mechanisms that involve phagocytosis of these invading microorganisms or they can destroy them , by walling off the infection or by releasing substances that help to destroy these microorganisms or neutralize their toxins .
- Other WBCs such as lymphocytes , they mediate specific responses that destroy or neutralize the specific microorganisms .



White Blood Cells

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

White Blood Cell Counts

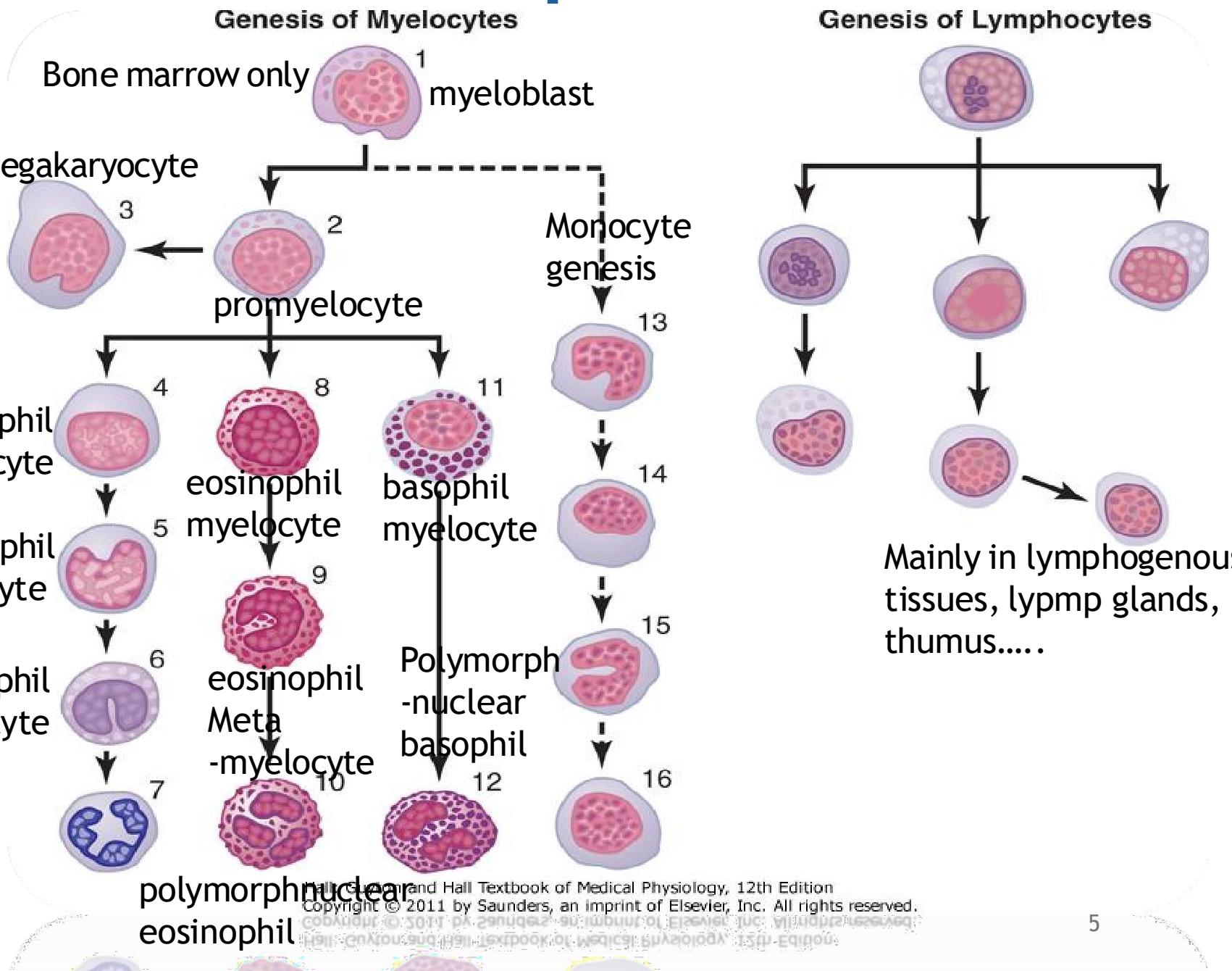
- **Total WBC ~ (7,000 – 10,000) / mm^3(almost 1,000-fold fewer than RBCs)**

- **Proportions:**

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

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

Leukopoiesis



•This figure is the same one in the previous slide but I think here it looks clearest

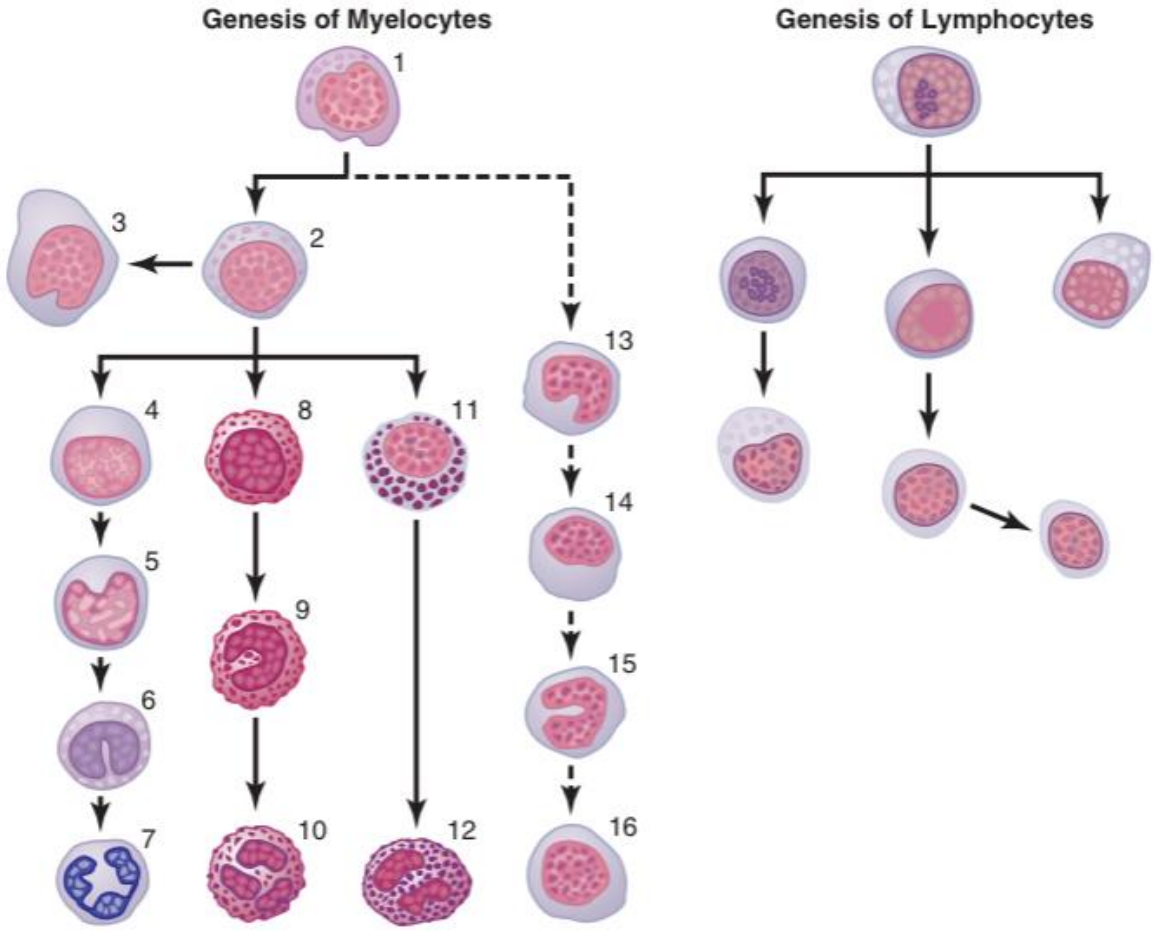


Figure 34-1. Genesis of white blood cells. The different cells of the myelocyte series are *1,* myeloblast; *2,* promyelocyte; *3,* megakaryocyte; *4,* neutrophil myelocyte; *5,* young neutrophil metamyelocyte; *6,* "band" neutrophil metamyelocyte; *7,* polymorphonuclear neutrophil; *8,* eosinophil myelocyte; *9,* eosinophil metamyelocyte; *10,* polymorphonuclear eosinophil; *11,* basophil myelocyte; *12,* polymorphonuclear basophil; *13-16,* stages of monocyte formation.

• The granulocytes and monocytes are formed only in the bone marrow. Lymphocytes and plasma cells are produced mainly in the various lymphogenous
tissues—especially the lymph glands, spleen, thymus, tonsils, and various pockets of lymphoid tissue else- where in the body, such as in the bone marrow and in
so-called Peyer's patches underneath the epithelium in the gut wall.

- The WBCs formed in the bone marrow are stored within the marrow until they are needed in the circulatory system. Then, when the need arises, various factors cause them to be released (these factors are discussed later). Normally, about three times as many WBCs are stored in the marrow as circulate in the entire blood. This quantity represents about a 6-day supply of these cells.
- The lymphocytes are mostly stored in the various lymphoid tissues, except for a small number that are temporarily being transported in the blood.
- As shown in Figure , megakaryocytes (cell 3) are also formed in the bone marrow. These megakaryocytes fragment in the bone marrow; the small fragments, known as platelets (or thrombocytes), then pass into the blood. They are very important in the initiation of blood clotting.

- The process of forming WBCs is called LEUKOPOIESIS .
- All WBCs are originated during embryogenesis from very potent hematopoietic stem cells and originally in the bone marrow , they get differentiated into either : Myeloblast or Lymphoblast .

- So the Myeloblast actually are differentiated into different types of cells that are finally give monocytes or megakaryocyte or to promyelocyte , which give granulocytes that are : Basophils , eosinophils and neutrophils . So we have different stages , for examples : neutrophils undergo the myelocyte stage then metamyelocyte stage , band neutrophil metamyelocyte stage , until it reaches the final Polymorph-nuclear neutrophil .

- Polymorph-nuclear neutrophil naming comes from the appearance of the nuclei as multilobulated . Basophils , Eosinophils also undergo the same stages .

- The monocytes also originate from myeloblast . However, the lymphoblast originates in the bone marrow but they differentiate in other tissues , some of them in the bone marrow , others differentiate in lymph nodes , glands or in the thymus , tonsils , Peyer's patches in the small intestine .

Genesis of White Blood Cells

- Basophils , Eosinophils and Neutrophils .

- **Granulocytes and monocytes develop in the bone marrow, and most remain there until needed peripherally (number in marrow ~3x blood con ; 6-day supply- storage-)**

- And upon demand , they'll be released to blood .

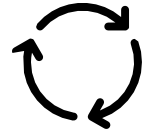
Lymphocytes develop mostly in the peripheral lymphoid organs (thymus, spleen, tonsils, lymph nodes, Peyer's patches), less are found in blood in the way as they being transported into other places .

- **Megakaryocytes develop and reside in the marrow, fragment to release platelets**

Life Span of White Blood Cells

- **Granulocytes**:
  - Circulating, life span -> 4 – 8 hours in blood
  - In the tissues, 4 – 5 days

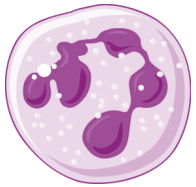
    (shorter timelines- hours- with infection, inflammation because they get destroyed while combating during that cases)

- **Monocytes / Macrophages**:
  - Circulating, 10 – 20 hours then , they
  - As tissue macrophages, months or longer, they swell and become larger in size , in their maturation they need specific enzymes .
  - **Lymphocytes**:
    - Continuously re-circulate (they circulate in the body all the time): 

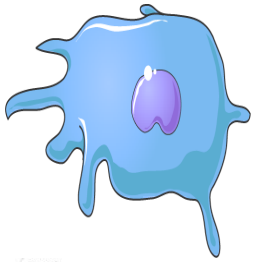
      lymph…nodes…blood.. tissues (diapedesis)

      ## Long-lived… weeks, months, longer

- **Platelets**: ~ Replaced every ten days because their life span is from 10-12 days ~ 30K each day are formed



Neutrophils and Macrophages



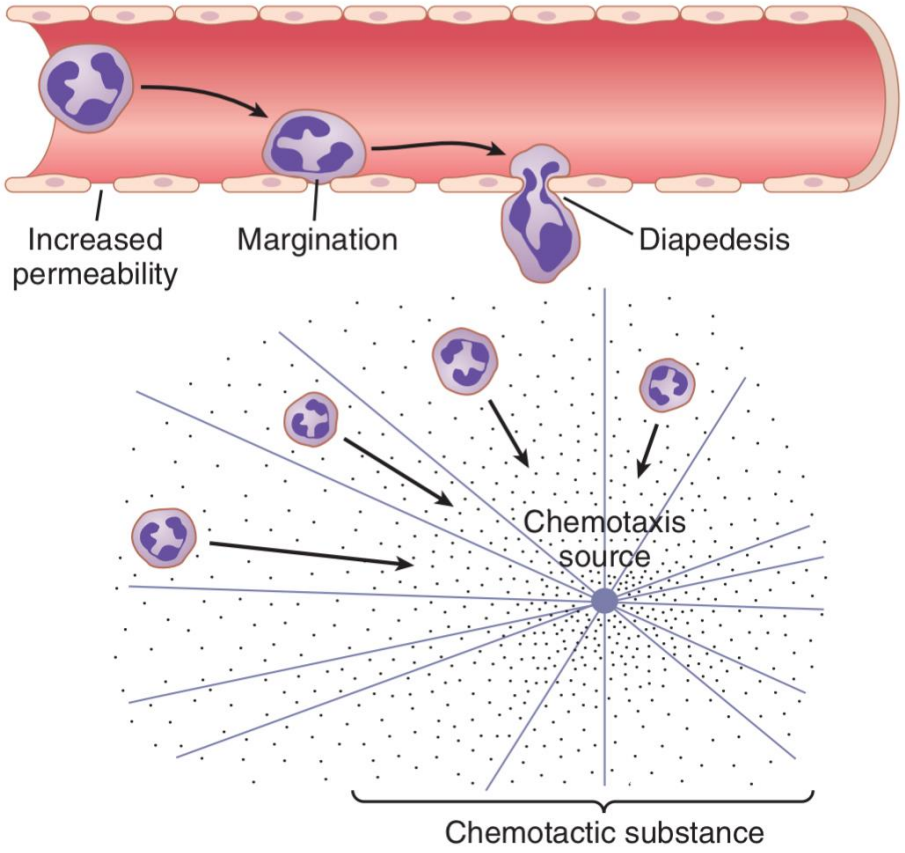
- Neutrophils are mature cells that can respond immediately to infection while being inside the blood stream mainly .
- Monocytes (they're immature in blood) but mature in the tissues to become macrophages and they'll be active against microorganisms (monocytes in blood little ability)

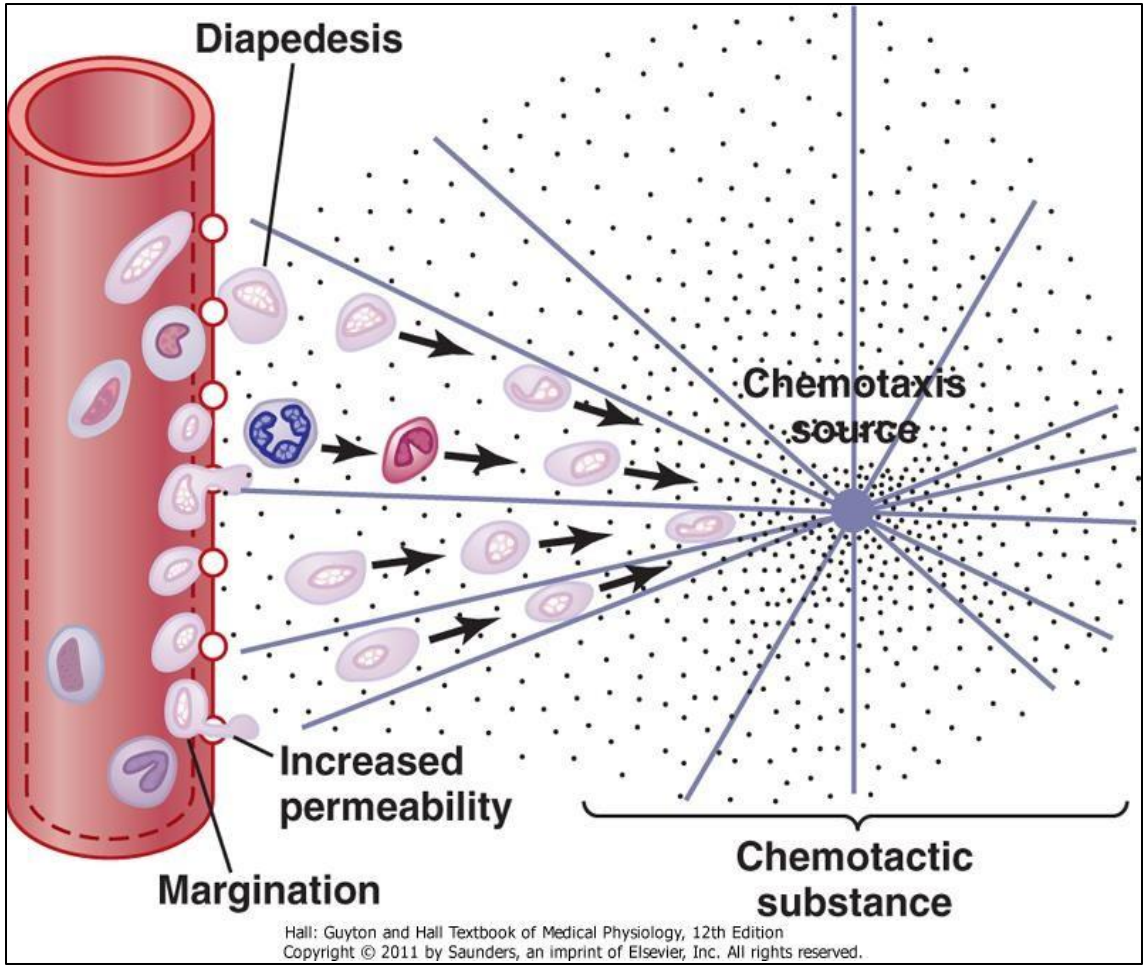
- Both exhibit motility:
  - Diapedesis is a process where pseudopods are formed in order to get outside the blood vessel endothelial cells , they keep move until they exist .

Diapedesis - Medical Animation by Arc Solutions - YouTube

  - Ameboid motion
  - Chemotaxis (Chemoattractants: bacterial or tissue degradation products, complement fragments, other chemical mediators) in the infection site .

Neutrophil Margination & Migration





Movement of neutrophils by diapedesis through capillary pores and by chemotaxis toward an area of tissue damage.

- So the way by which neutrophil or macrophages can get close to the site of infection is firstly by exiting the blood vessels by a process called (Margination and Diapedesis as well) , then the permeability of the blood vessels enhance the process of Diapedesis to exist it .
- Then these WBCs will be directed to the chemoattractant sources which is called Chemotaxis by an ameboid motion .
- Ameboid movement is movement of an entire cell in relation to its surroundings, such as movement of white blood cells through tissues. It receives its name from the fact that amebae move in this manner, and amebae have provided an excellent tool for studying the phenomenon.

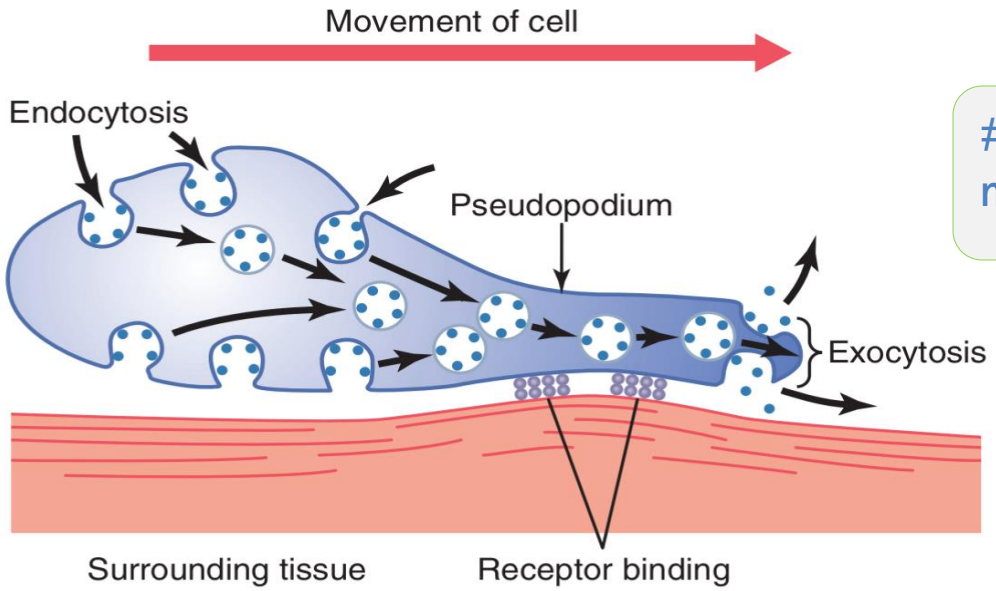
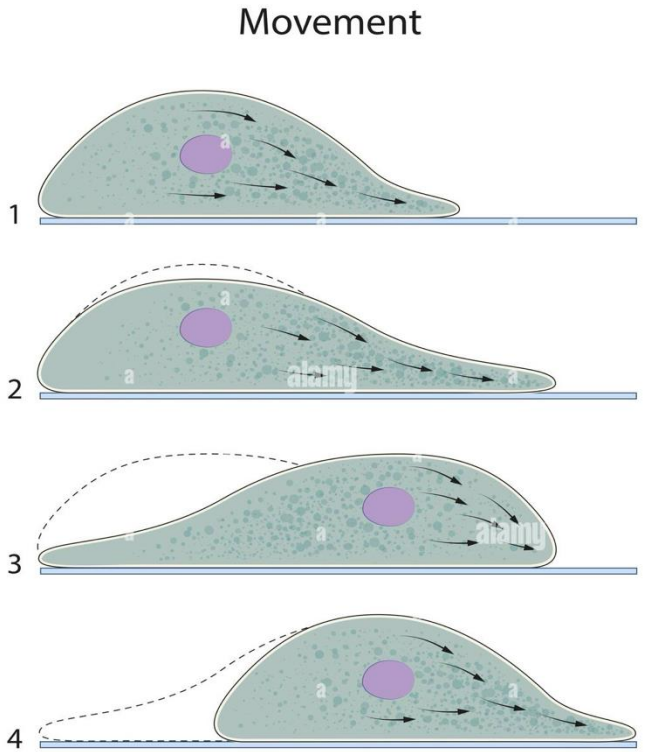


Figure 2-17. Ameboid motion by a cell.

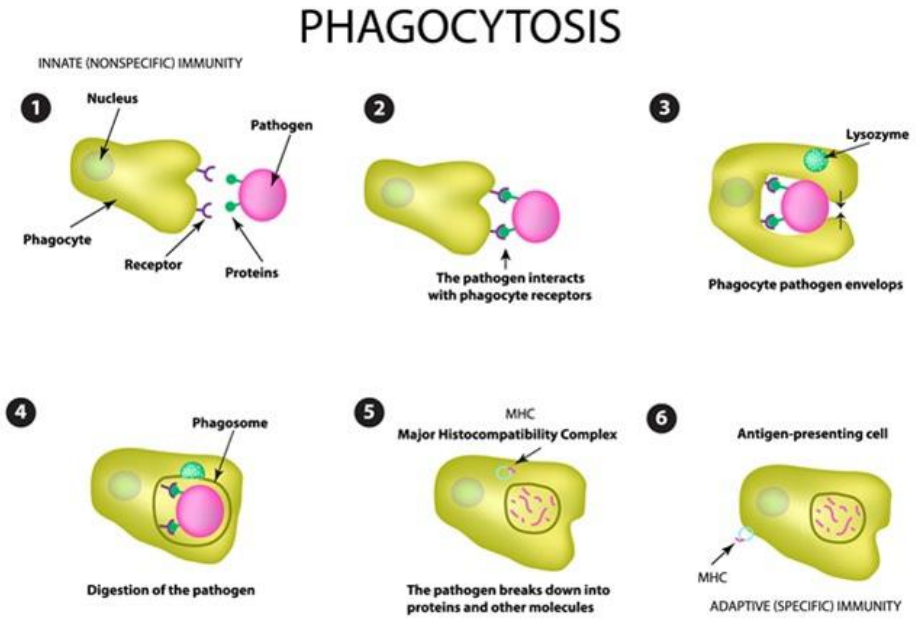
#An extra pictures for more understanding!!



Phagocytosis

- **"Phagocytosis" is the ingestion of particles by neutrophils and macrophages .**
- **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"



An extra picture for more understanding!!

Phagocytosis

- **Neutrophils: can ingest 3-20 bacteria**

- **Macrophages: After being activated in the tissues, are extremely effective phagocytes (up to ~100 bacteria)**
  they're more efficient in ingesting the tissue's bacteria .

- **Macrophages can ingest larger particles** than neutrophils
  - **Damaged RBCs**
  - **Malarial parasites**

- **Macrophages can extrude digestion products and survive and function for many months** on the other hand , neutrophils aren't going to live after they had ingested the bacteria.

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) as you'll know them in microbiology.**

Note:Lipases aren't found in neutrophils

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**

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

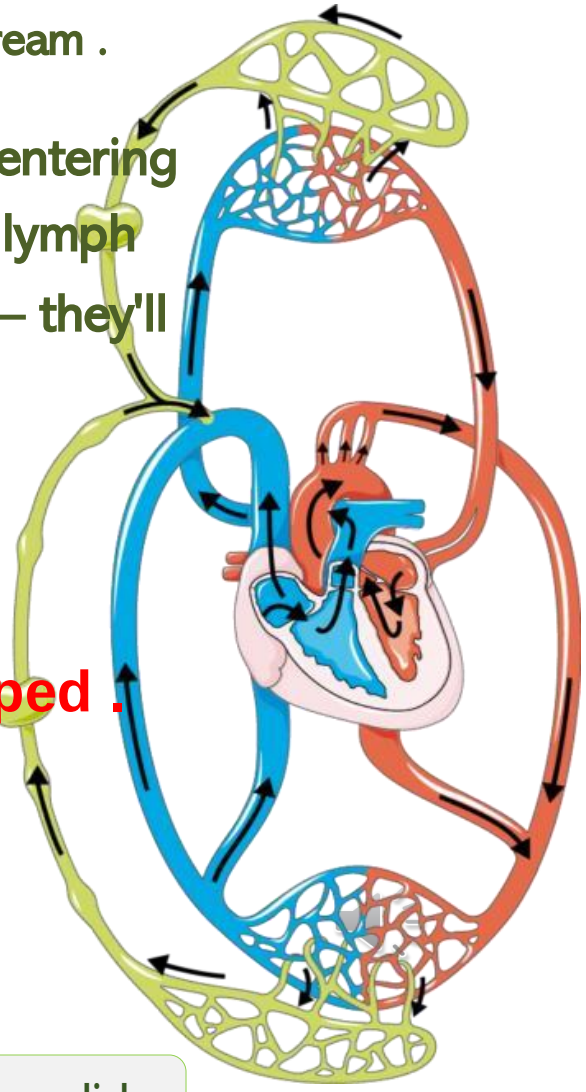
- Also, one of the lysosomal enzymes, myeloperoxidase, catalyses the reaction between H2O2 and chloride ions to form hypochlorite, which is exceedingly bactericidal .

The Reticuloendothelial System

- **After entering the tissues, macrophages become fixed and may be resident for years until they're called for invading microorganisms**
- **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

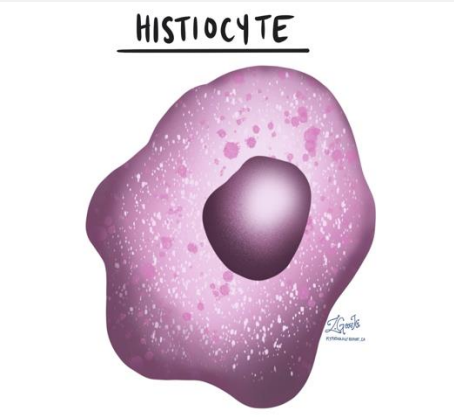
- **Skin, subcutaneous (histiocytes)** when the skin has a cut in it , and some bacteria get into the deeper part of the skin then the histiocytes will divide and will give macrophages that are going to digest microorganisms preventing them from succeeding in entering the blood stream .
- **Lymph nodes** (they play an important role in preventing microorganisms form entering the general circulation , any particle in tissues will actually be taken by lymph into the lymph nodes and then they'll be cleared by the macrophages which residing in lymph nodes – they'll be digested).
  - Ingest / sample particles arriving through the lymph
- **Alveolar macrophages**
  - Digest or entrap inhaled particles and microorganisms like silica, tuberculosis bacilli --> they're entrapped .
- **Kupffer cells**
  - Lining sinusoids, Surveillance of the portal circulation.
- **Macrophages in the spleen and bone marrow**
  - Surveillance of the general circulation



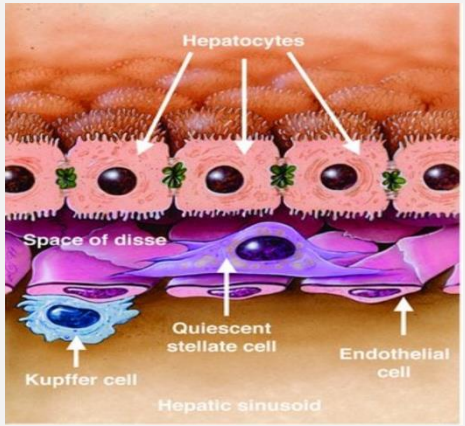
• Further Explanation in the following slide

1- **Tissue Macrophages in the Skin and Subcutaneous Tissues (Histiocytes).** Although the skin is mainly impregnable to infectious agents, this is no longer true when the skin is broken. When infection begins in a sub-cutaneous tissue and local inflammation ensues, local tissue macrophages can divide in situ and form still more macrophages. Then they perform the usual functions of attacking and destroying the infectious agents .

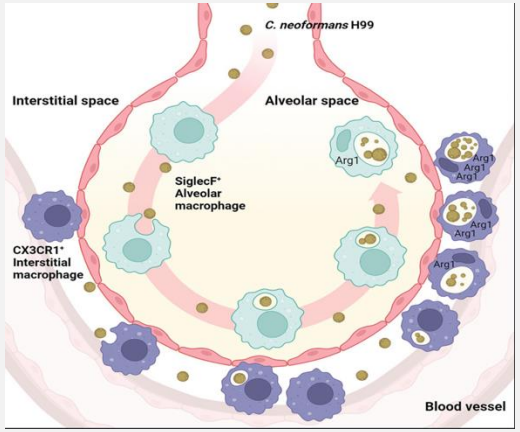
2- **Macrophages in the Lymph Nodes.** Essentially no particulate matter that enters the tissues, such as bacteria, can be absorbed directly through the capillary membranes into the blood. Instead, if the particles are not destroyed locally in the tissues, they enter the lymph and
flow to the lymph nodes located intermittently along the course of the lymph flow. The foreign particles are then trapped in these nodes in a meshwork of sinuses lined by tissue macrophages.
Large numbers of macrophages line the lymph sinuses, and if any particles enter the sinuses by way of the lymph, the macrophages phagocytise them and prevent general dissemination throughout the body.



Histiocytes



Kupffer Cells



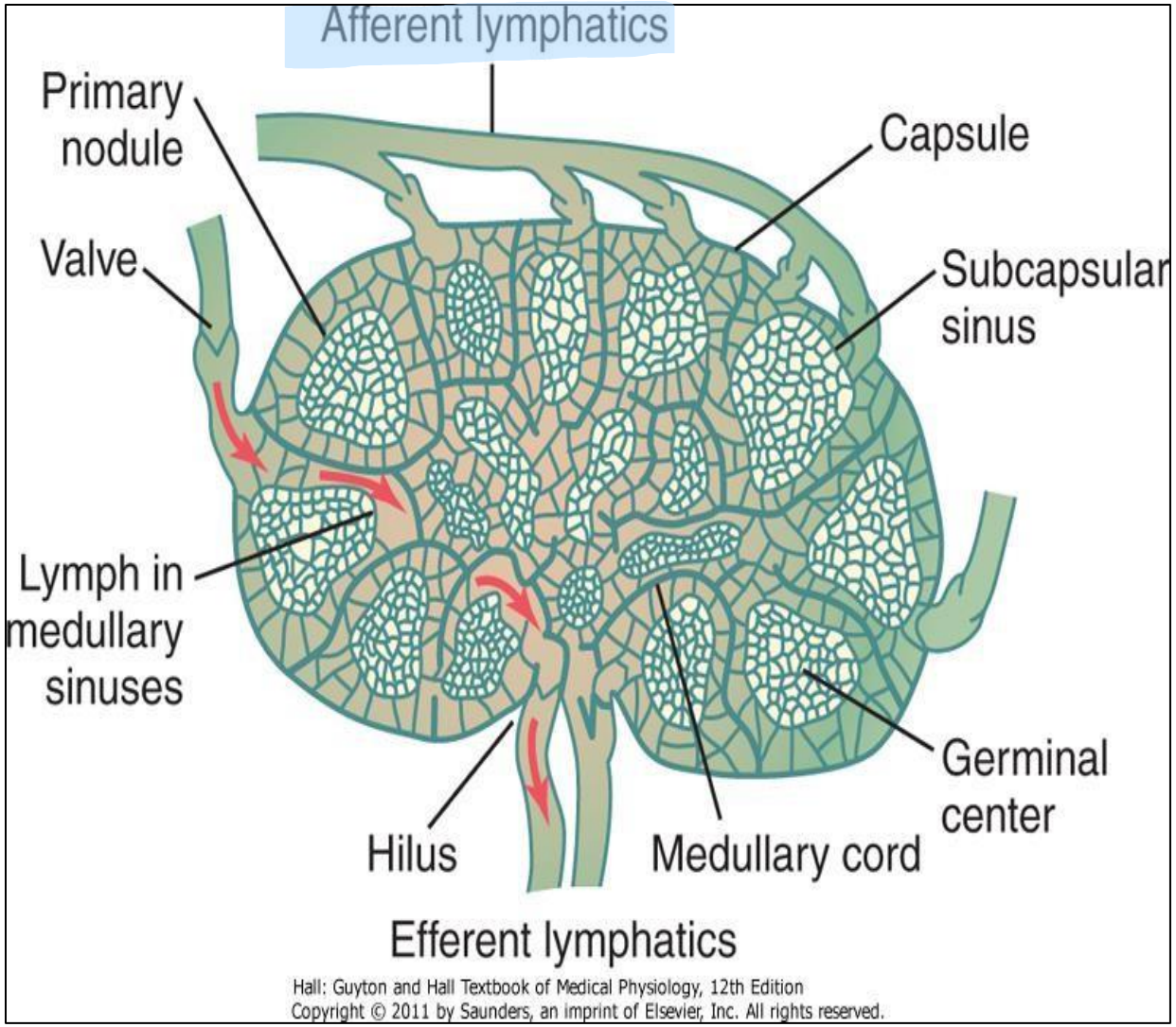
Alveolar Macrophages in the Lungs

3- **Alveolar Macrophages in the Lungs.** Another route by which invading organisms frequently enter the body is through the lungs. Large numbers of tissue macrophages are present as integral components of the alveolar walls. They can phagocytize particles that become entrapped in the alveoli. If the particles are digestible, the macrophages can also digest them and release the digestive products into the lymph. If the particle is not digestible, the macrophages often form a "giant cell" capsule around the particle until such time—if ever—that it can be slowly dissolved. Such capsules are frequently formed around tuberculosis bacilli, silica dust particles, and even carbon particles.

4- **Macrophages (Kupffer Cells) in the Liver Sinusoid.** Another route by which bacteria invade the body is through the gastrointestinal tract. Large numbers of bacteria from ingested food constantly pass through the gastrointestinal mucosa into the portal blood. Before this blood enters the general circulation, it passes through the liver sinusoids, which are lined with tissue macrophages called Kupffer cells . These cells form such an effective particulate filtration system that almost none of the bacteria from the gastrointestinal tract pass from the portal blood into the general systemic circulation. Indeed, motion pictures of phagocytosis by Kupffer cells have demonstrated phagocytosis of a single bacterium in less than 0.01 second.

5- **Macrophages of the Spleen and Bone Marrow.** If an invading organism succeeds in entering the general circulation, there are other lines of defense by the tissue macrophage system, especially by macrophages of the spleen and bone marrow. In both these tissues, macrophages become entrapped by the reticular meshwork of the two organs and when foreign particles come in contact with these macrophages, they are phagocytized.

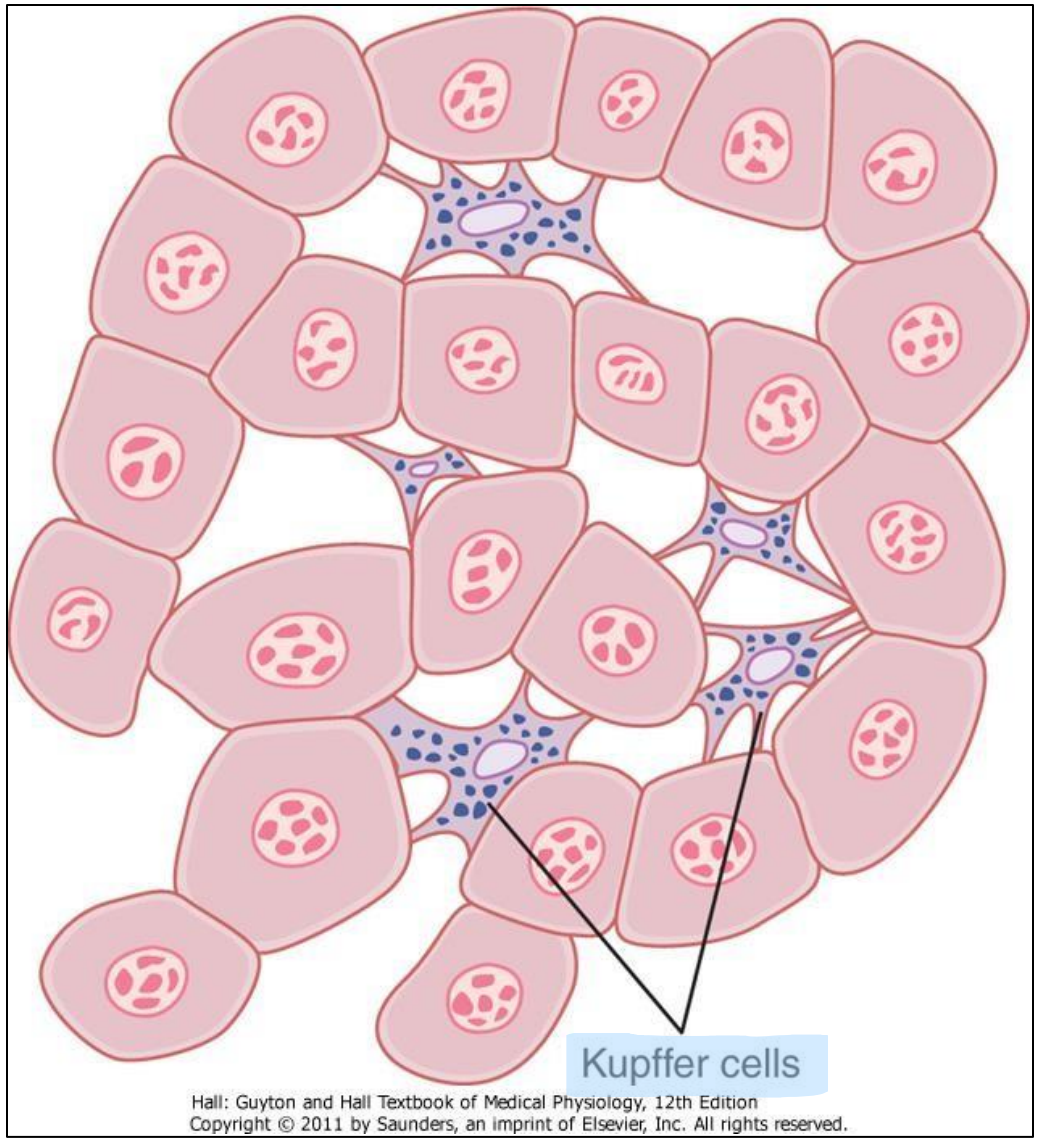
Structure of a Lymph Node



Explanation for the picture !

- Particles through the lymph pass from the afferent lymphatics and enter the capsule of the lymph node then invade the sinus (which are lined by macrophages) , continue this process and pass all the general circulation until cleared or trapped inside the lymph node !

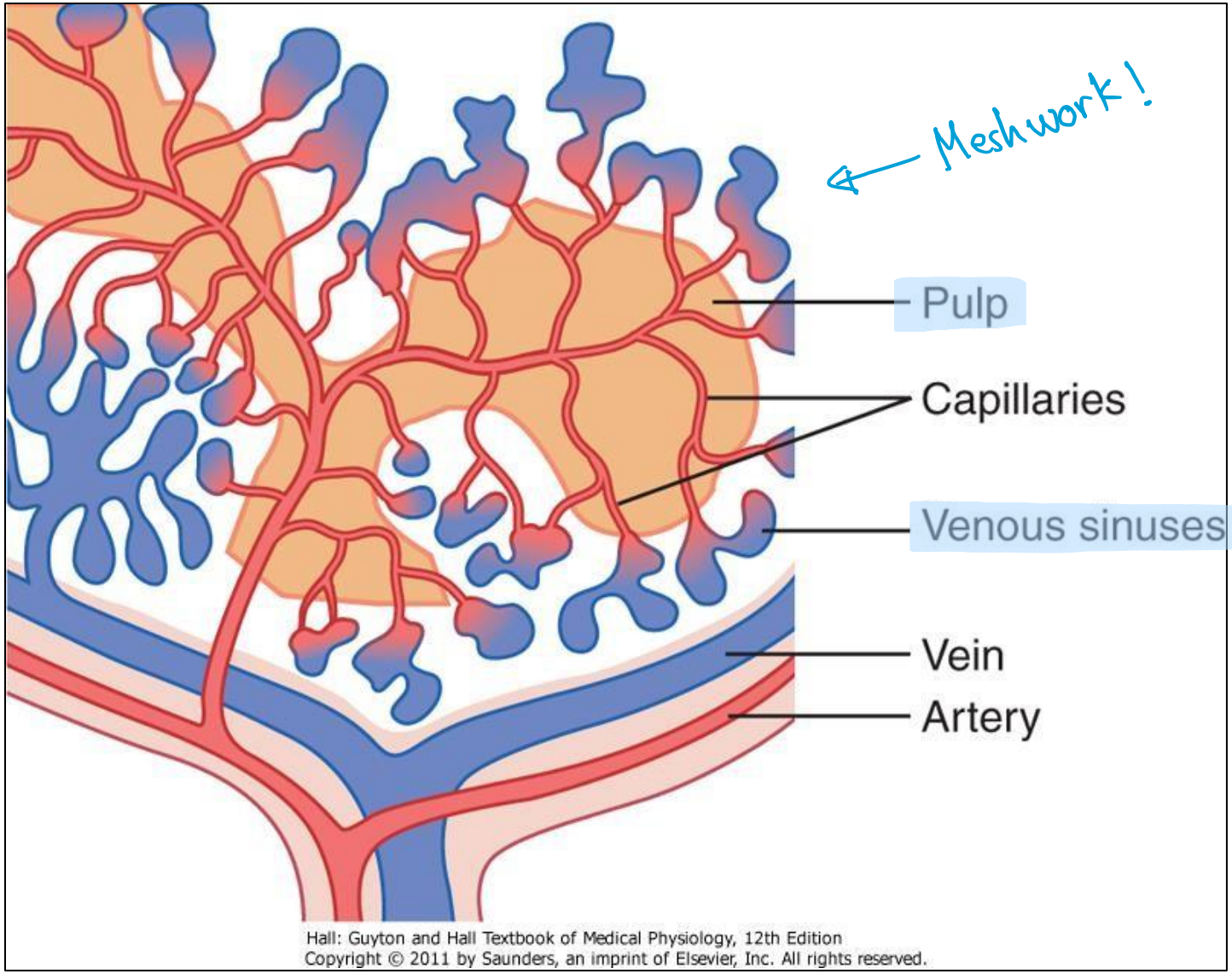
Kupffer Cells in the Liver Sinusoids



Explanation of the picture !!

- It's Demonstrating the kupffer cells in the liver sinusoids which act very efficient role in clearing particles of microorganisms that can pass GI system to liver by its portal circulation .

Structure of the Spleen



Explanation of the picture !!!

- The meshwork in spleen will trapped the foreign particles and then they will come and contact with macrophages lining these meshwork and get phagocytes.

Neutrophils, Macrophages & Inflammation

- **Inflammation is driven by chemical mediators** that are released during the fight against the microorganisms and from toxins of the particles or from necrotic tissue **and characterized by heat, redness, swelling, and pain**

- **Physiologically, it involves…**
  - **Vasodilatation and increased blood flow**
  - **Increased capillary permeability**
  - **Coagulation of interstitial fluids** that will occur by fibrinogen that released into tissue spaces .
  - **Accumulation of granulocytes and monocytes**
  - **Swelling of tissue cells** (increase the fluid)

- **Mediators:** ***histamine, bradykinin, serotonin, prostaglandins, complement products, clotting components, lymphokines*** (that are released from lymphocytes)

“Walling Off” Sites of Inflammation

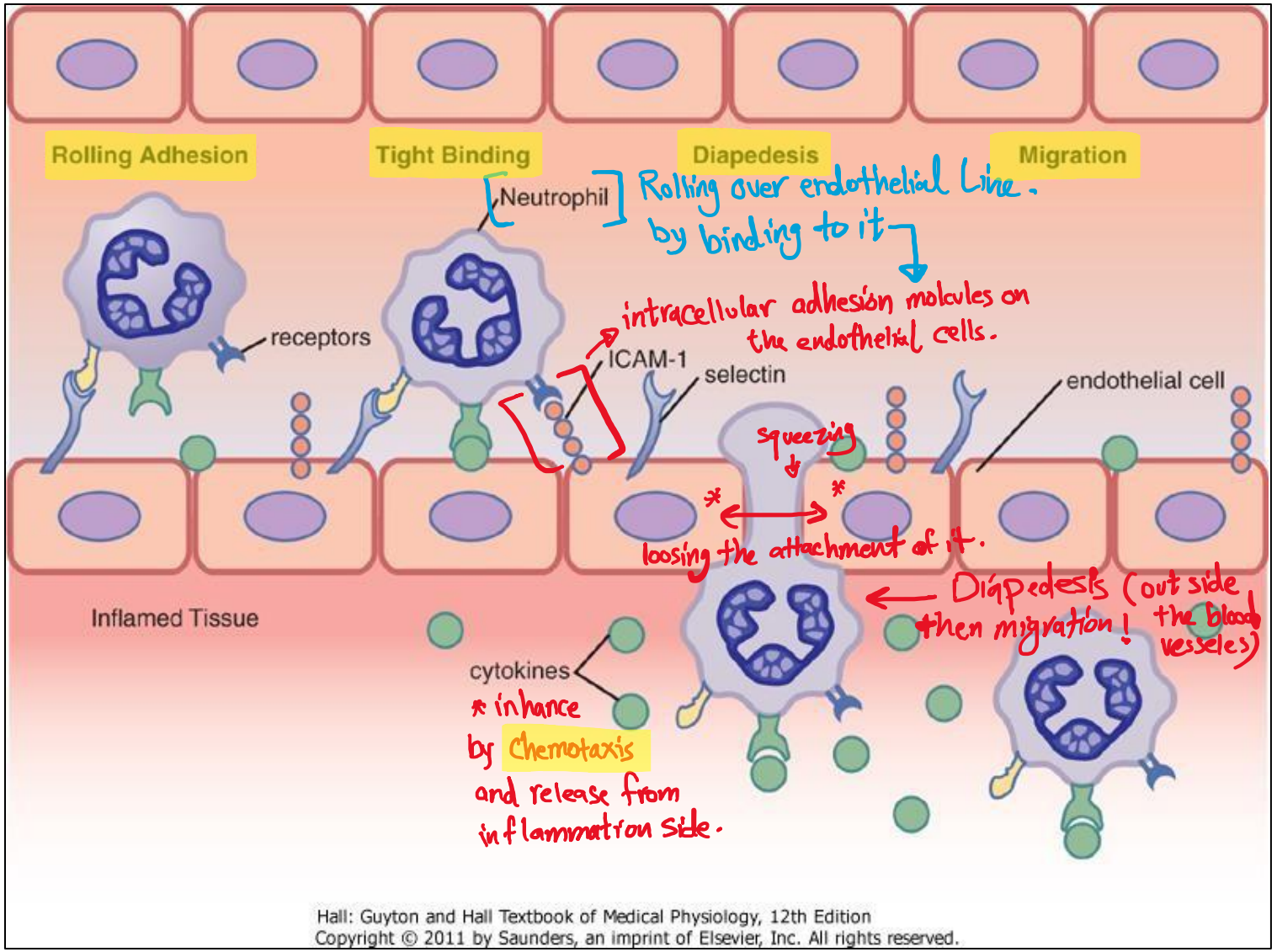
- **Fibrinogen clots which may form during inflammation and make like a wall that minimizes fluid flow as well as spread of microorganism and inflammation in and out of the inflamed area**
- The intensity or the degree of “walling off” depends on the intensity or the degree of tissue injury . Like:
- ***Staphylococci release very harmful and toxic cellular toxins* cause intense inflammation and are effectively “walled off”**

- ***Streptococci* induce less intense (less walling off, more proliferation) inflammation and may be more likely to spread than *staphylococci, and cause death***

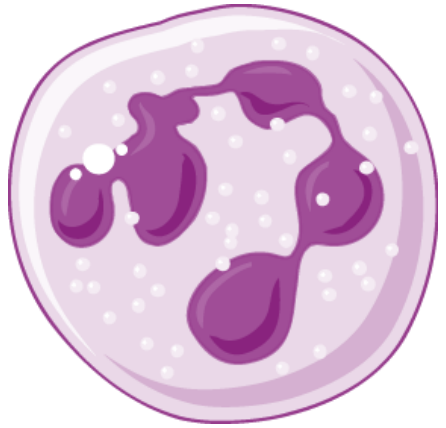
Neutrophils and Macrophages in Inflammation

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

Neutrophil Migration to an Inflamed Site



Neutrophilia

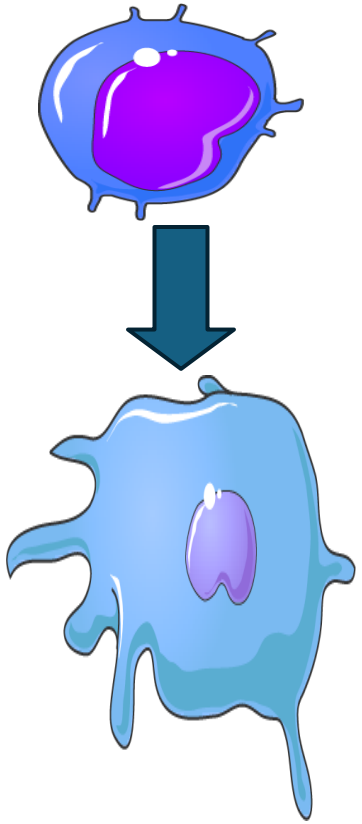


- **With intense inflammation after few hours , neutrophil count can increase dramatically…**

4,000-5,000 ➡ 15,000-25,000

- **Results from mobilization of mature neutrophils from the bone marrow by inflammatory mediators** HOW!? By entering the blood stream then they get transported into bone marrow and act on the stored neutrophils in bone marrow and mobilize them into circulation

Secondary Macrophage Invasion



- **In response to chemoattractants, monocytes gradually accumulate from circulation and (slowly) increase in number in tissues after that they 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**

For more understanding

And because the number in circulation is not high , the store of macrophages is low , the bone marrow need to be stimulated ti increase production of monocytes , so from days to weeks the number of induced monocytes will increase and accumulate in tissues then inflamed and clean it up ! Nice story🧠.

Bone Marrow Responses

They will be stimulation of the bone marrow stem cells

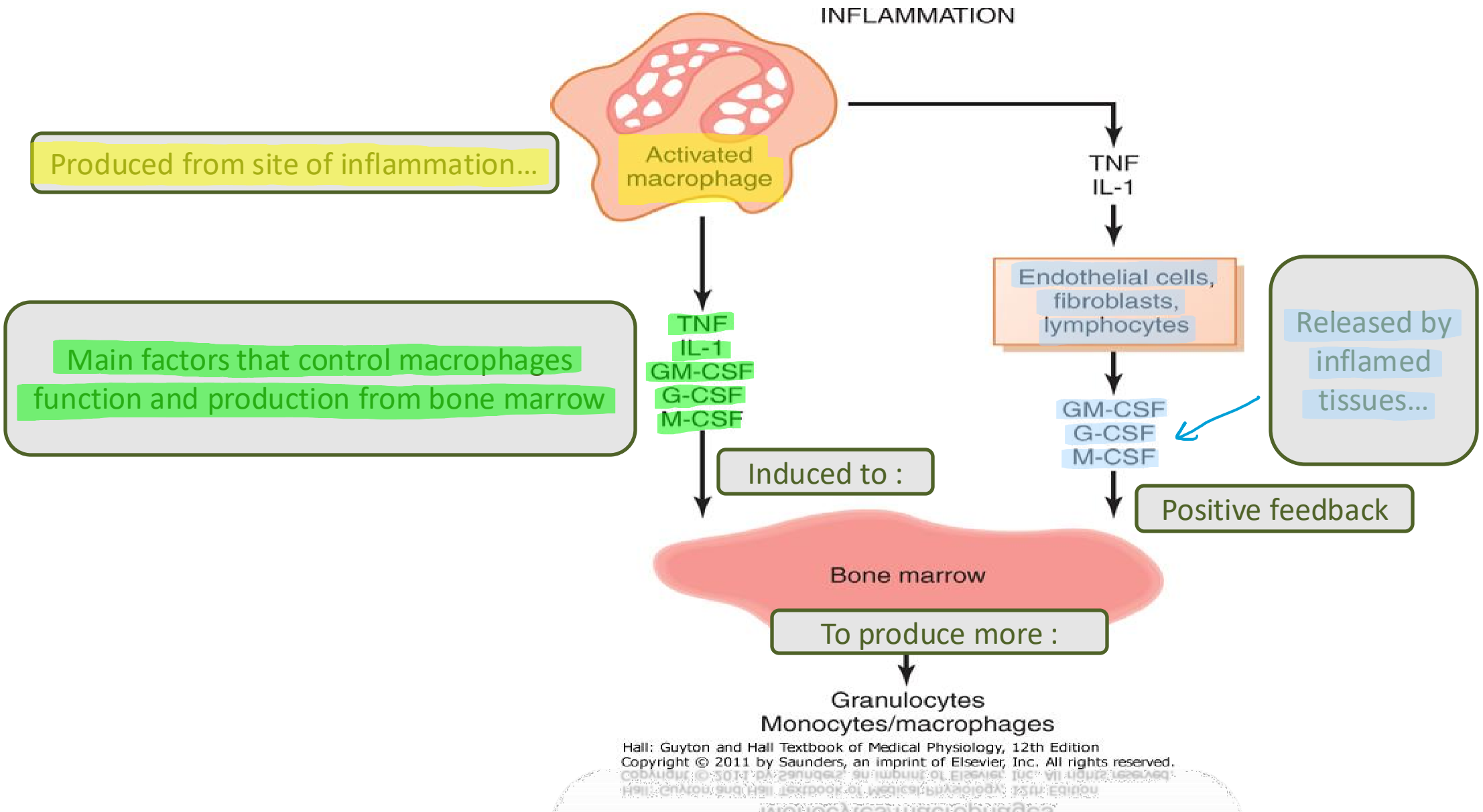
- **Growth factors produced in response to infection and inflammation drive proliferation and differentiation of leukocyte precursors in the marrow**

And those cells can be granulocytes or monocytes

- **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



Produced from site of inflammation…

Main factors that control macrophages function and production from bone marrow

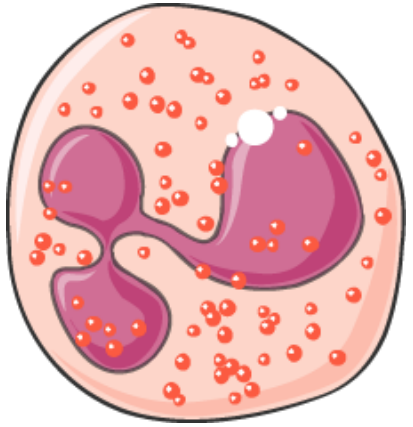
Released by inflamed tissues…

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 with help of lymph it will finally disappears !**

Eosinophils

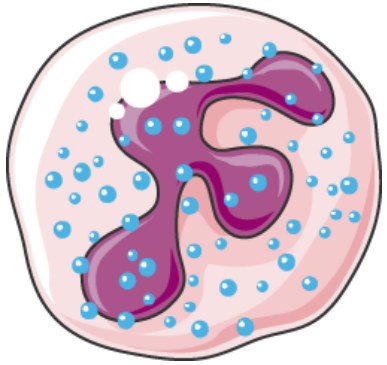


- **Eosinophils are weak phagocytes**

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)** like antihistamine

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*** when IgE bound on their receptors **, releasing…**
  - ***histamine, bradykinin, serotonin, heparin, leukotrienes,* and several *lysosomal enzymes*** vascular and tissue reactions that are manifested in the allergic reactions .

Leukopenia

- ***Leukopenia*, or low white blood cell count , is usually the result of reduced production of cells by the bone marrow** *it's NEVER beneficial !*
- **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**
- **Causes: radiation, chemical toxins, some medicines** damaged of bone marrow cells .
- **In most cases marrow precursors can reconstitute normal blood cell counts with proper support** after acute phase

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** (depending on its origin !)
  - **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 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** (low number of MATURE RBCs ,WBCs and platelets resulting in it !)
- **Wasting because of metabolic demands**

وَلَا تَحْسَبَنَّ الَّذِينَ قُتِلُوا فِي سَبِيلِ اللَّهِ أَمْوَاتًا ۚ بَلْ أَحْيَاءٌ عِندَ رَبِّهِمْ يُرْزَقُونَ

الآن جاء الموعد يا أماه، فلقد رأيت نفسي أقتحم عليهم موقعهم، أقتلهم كالنعاج ثم استشهد، ورأيتني بين يدي رسول الله ﷺ في جنات النعيم، وهو يهتف بي مرحى بك مرحى بك.

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Additional sources

1. Guyton and Hall , Textbook of Medical Physiology
2. https://youtu.be/B9Qi7we0Ynk?si=xzDkhKDluhKGeOye
3. https://youtu.be/ZQSzIOMRZMQ?si=-z-u1nuYqLZFznpM

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!