White Blood Cells (WBCs)
Leucocytes

Dr.Ahmed Alsabih

Objectives;

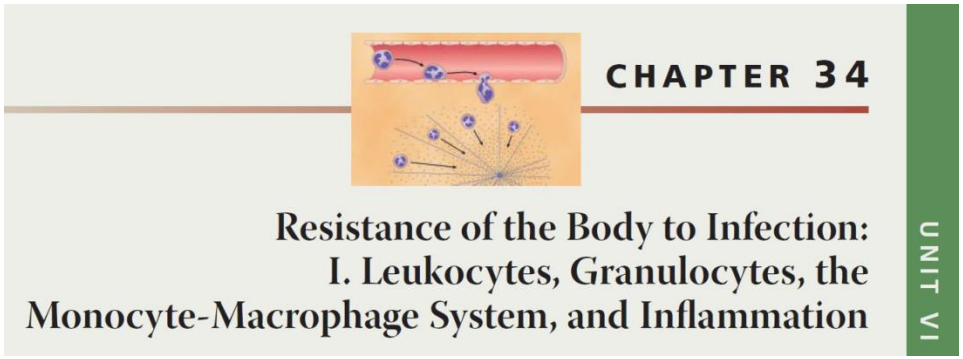
Intended learning outcomes (ILOs)

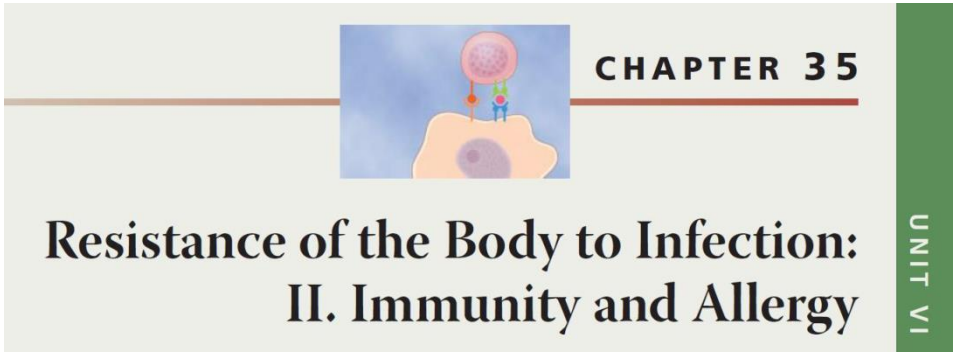
After reviewing the PowerPoint presentation and the associated learning resources, the student should be able to:

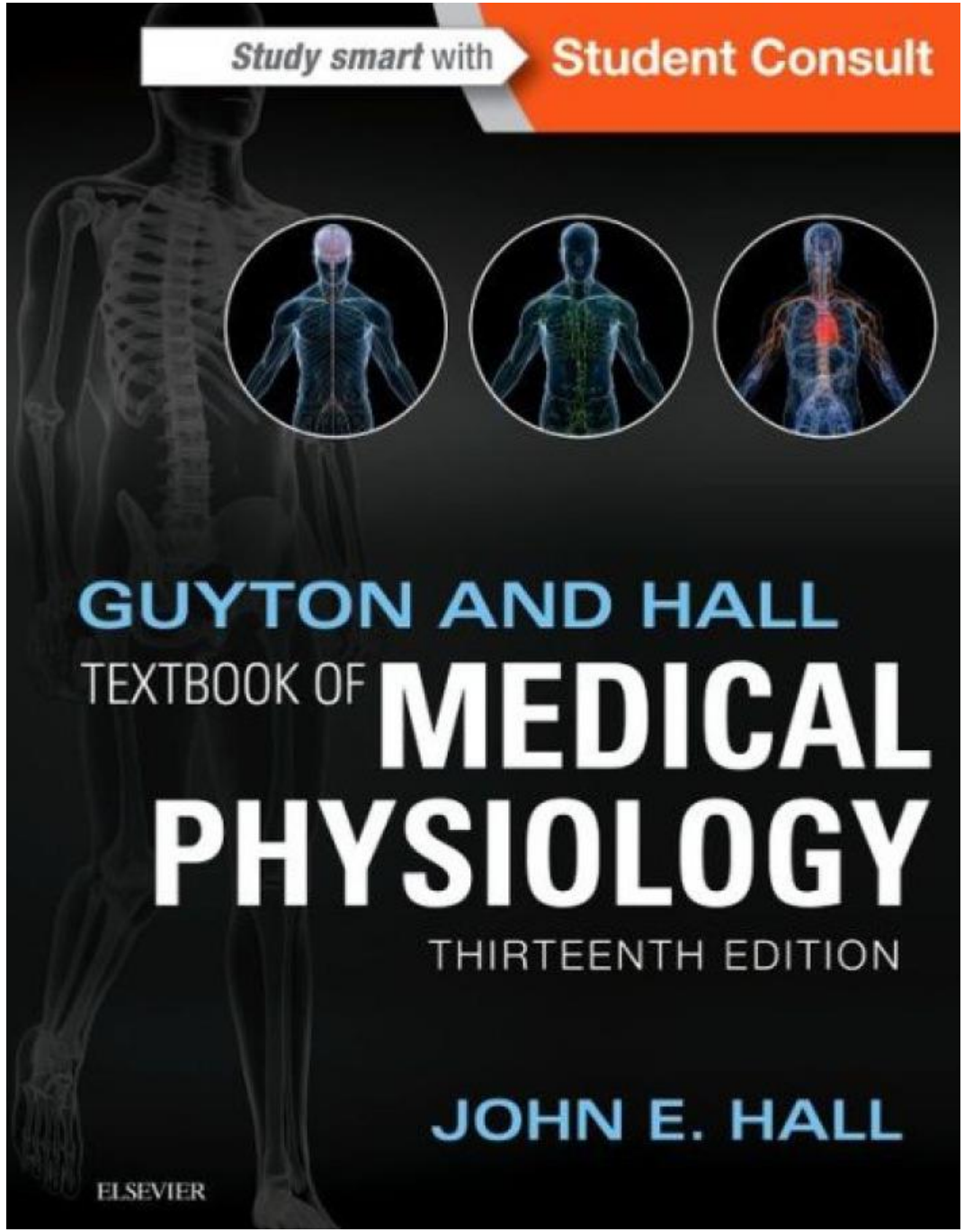
- Outline components of the immune system.
- List the types of white blood cells(WBCs).
- Describe the structure of the different types of WBCs.
- Outline differential WBCs count.
- Summarize the stages of formation of the different WBCs.
- State the functions the different types of WBCs.
- Describe the role of the WBCs in immune responses and defending against infection.
- Explain the process of phagocytosis.
- Recognize leukocytosis, leukopenia and leukemia.

Learning Resources

- Guyton and Hall, Textbook of Medical Physiology; 13th Edition; Unit VI-Chapters 34 & 35.

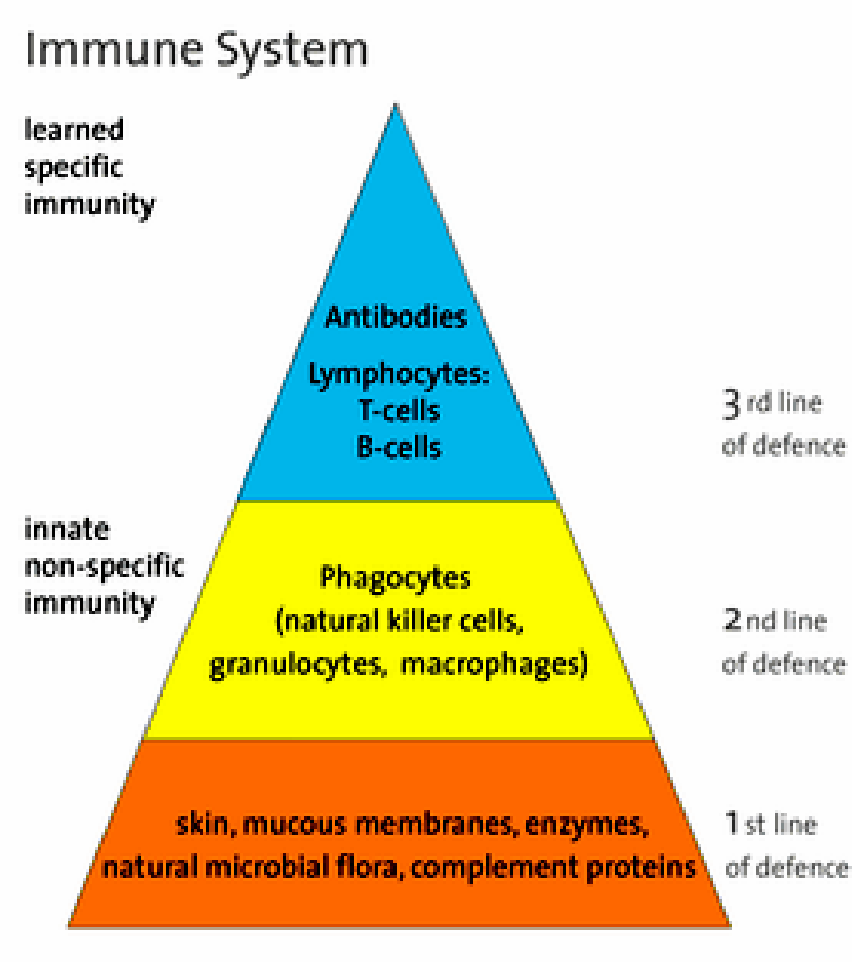




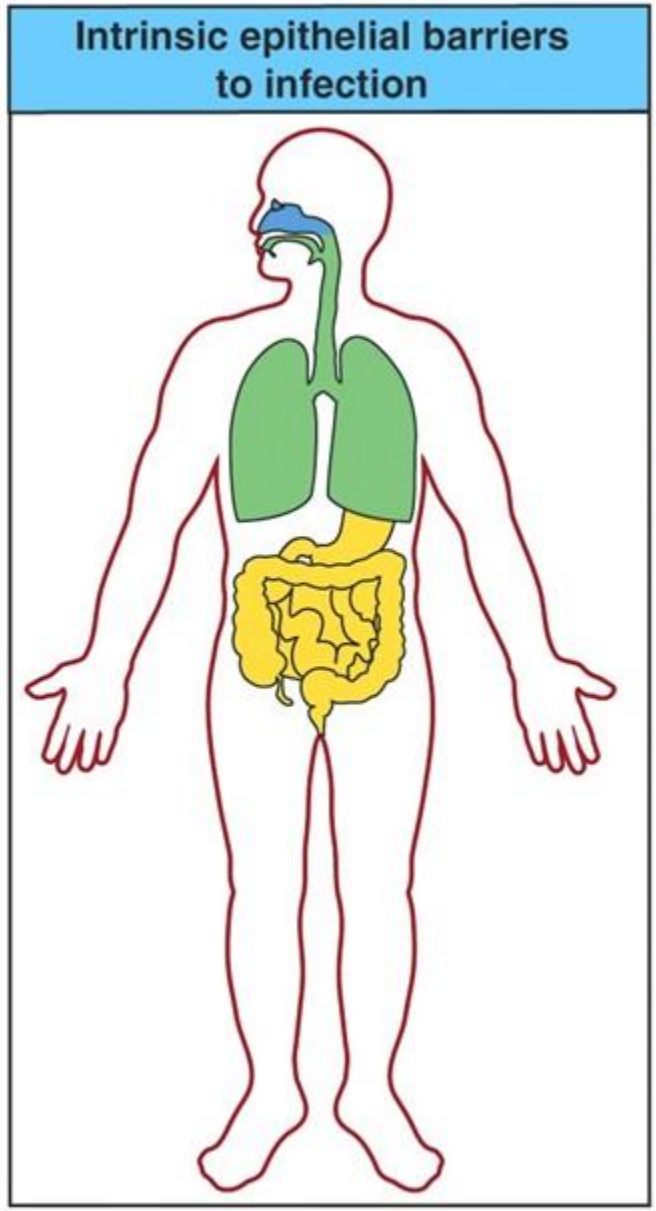


Immune System

- The immune system is a system of barriers, cells, tissues and organs that work to fight invaders.
- Another important component of the immune system is the complement system.
- The major functions of the immune system are:
  - Differentiate self from non-self.
  - Eliminate foreign substances, cells and pathogens.



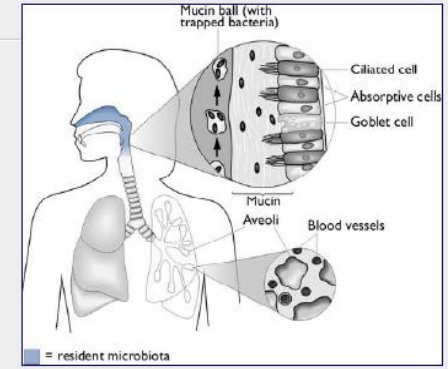
First line or defence – Epithelial Barriers

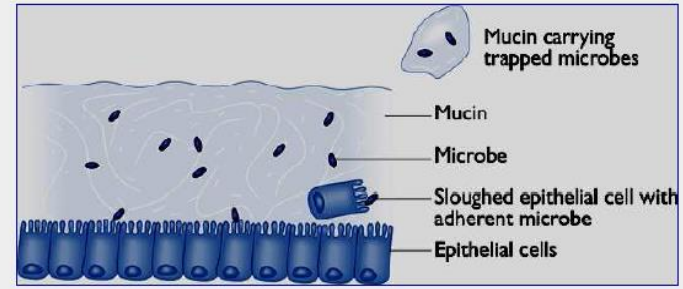


	Skin	Gut	Lungs	Eyes/nose
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	
Chemical	Fatty acids	Low pH		Salivary enzymes (lysozyme)
		Enzymes (pepsin)		
	Antibacterial peptides			
Microbiological	Normal flora			

Barriers

- Physical barrier (esp. skin)
- Mechanical action (flushing, cilia)
- Trapping of microbes in mucus
- Rapid turnover of cells
- Chemical defenses (lysozyme, defensins, lactoferrin)



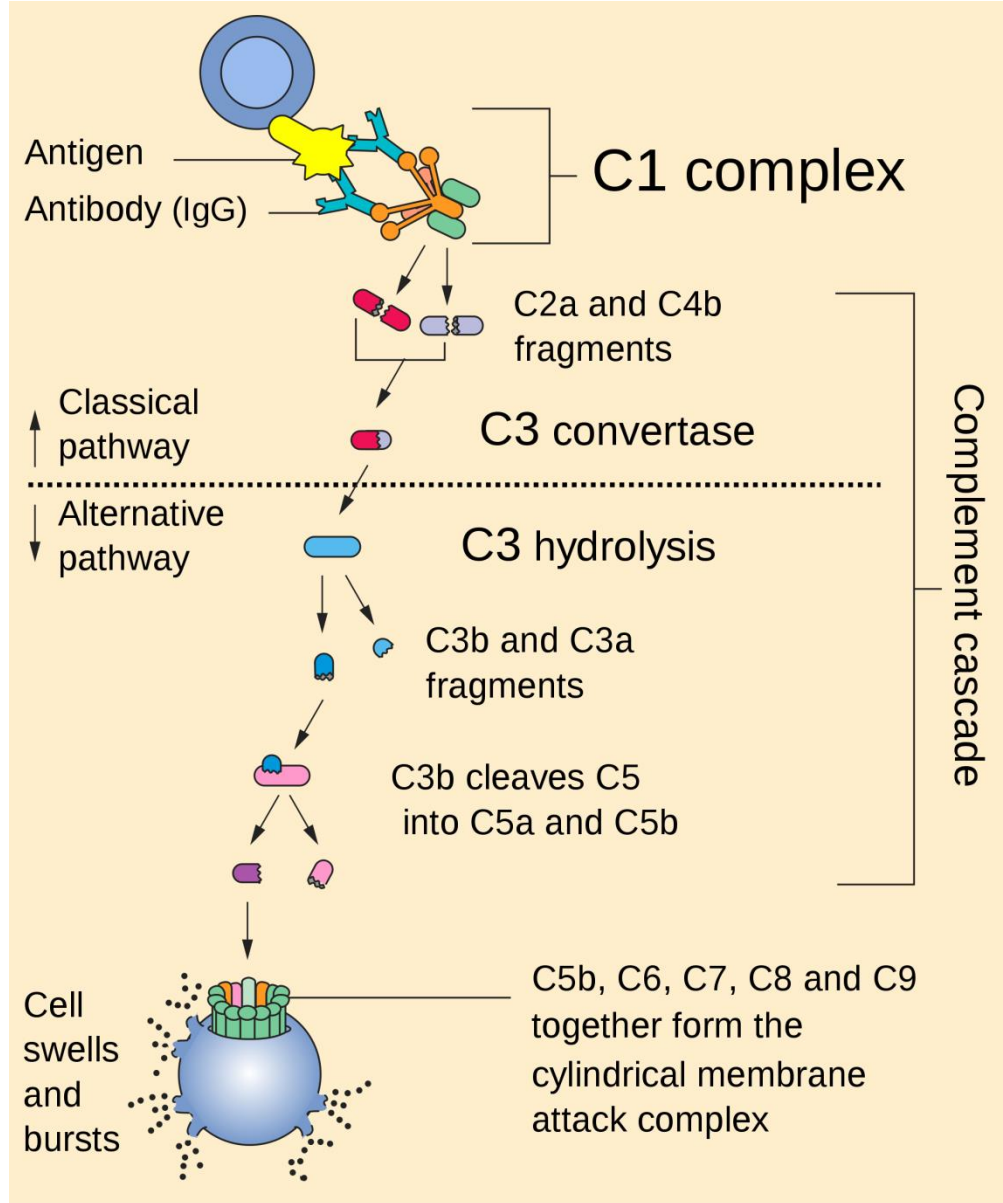


The Complement System is Part of the 1st Line of Defense

The first part of the immune system that meets invaders such as bacteria is a group of proteins called the *complement system*.

These proteins flow freely in the blood and can quickly reach the site of an invasion where they can react directly with *antigens* - molecules that the body recognizes as foreign substances. When activated, the complement proteins can:

- ❑ **Trigger inflammation.**
- ❑ **Attract eater cells such as macrophages to the area.**
- ❑ **Coat intruders so that eater cells are more likely to devour (swallow and eat) them (a process called as opsonization).**
- ❑ **Kill intruders.**



Cells of the Immune System

Phagocytes

Monocytes and macrophages

Neutrophils

Dendritic Cells

Inflammatory cells:

Mast cell

Basophils and Eosinophils

Antigen Specific cells:

B cells or B lymphocytes

T cells or T lymphocytes

The cells of the immune system work together with different proteins to seek out and destroy anything foreign or dangerous that enters our body.

Classification of White Blood Cells (WBCs)

Granulocytes

- **Polymorphonuclear leukocytes (PMNs; because of multiple nuclei)**
  - **Neutrophils (10-16 µm, 2-5 lobes of Nucleus)**
  - **Eosinophils (12-18 µm, bilobed, coarse red granules)**
  - **Basophils (10-14 µm, rarely segmented nucleus hidden by large round bluish granules)**

Agranulocytes

- **Lymphocytes(Round Nucleus, Small [5-8 µm] & large [9-15 µm])**
  - **T lymphocyte**
  - **B lymphocyte**
  - **Natural killer cells (NKCs)**
- **Monocytes (15-20 µm, Kidney shaped nucleus). The monocytes make macrophage system**

WBCs Concentrations (Normal Counts) and Life Span

Cells	Approximate Normal Range (/µL)	Percentage of Total WBCs	Life Span
Total WBCs	4000 - 11000		
Neutrophils	3000 - 6000	60 –70% (62%)	4 – 8 hours in blood and 4 – 5 days in tissues where they are needed
Eosinophils	150 - 300	1 – 4% (2.3%)	
Basophils	0 - 100	0.4% (0.4%)	
Lymphocytes	1500 - 4000	20 – 40% (30%)	Weeks - months
Monocytes (Macrophages)	300 - 600	2 – 8% (5.3%)	10 - 20 hours in blood before getting into the tissues where they can live for months

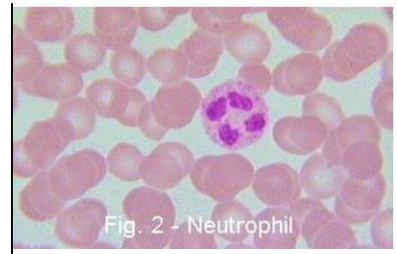


Fig. 2 - Neutrophil

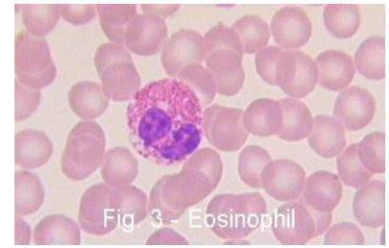


Fig. 3 - Eosinophil

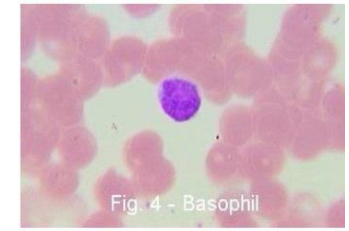


Fig. 4 - Basophil

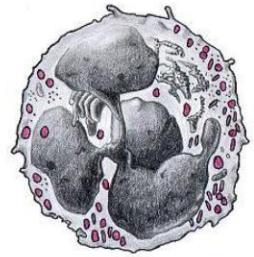


Fig. 8 - Neutrophil

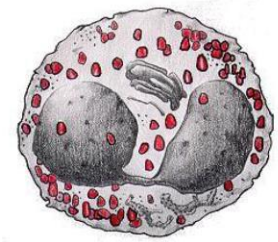


Fig. 9 - Eosinophil

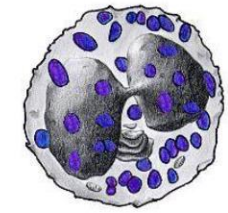


fig. 10 - Basophil

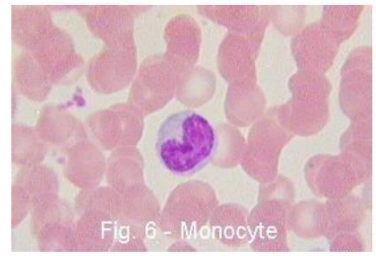


Fig. 6 - Monocyte

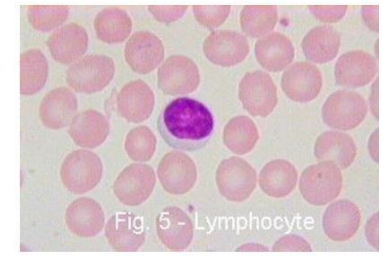


Fig. 5 - Lymphocyte

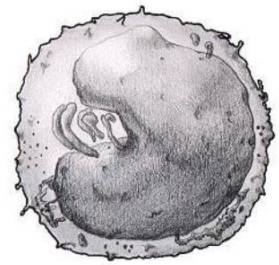


Fig. 12 - Monocyte

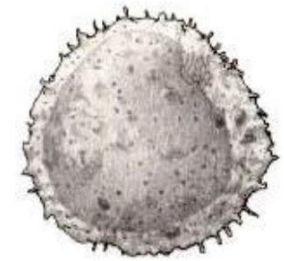


Fig. 11 - Lymphocyte

Leucopoiesis

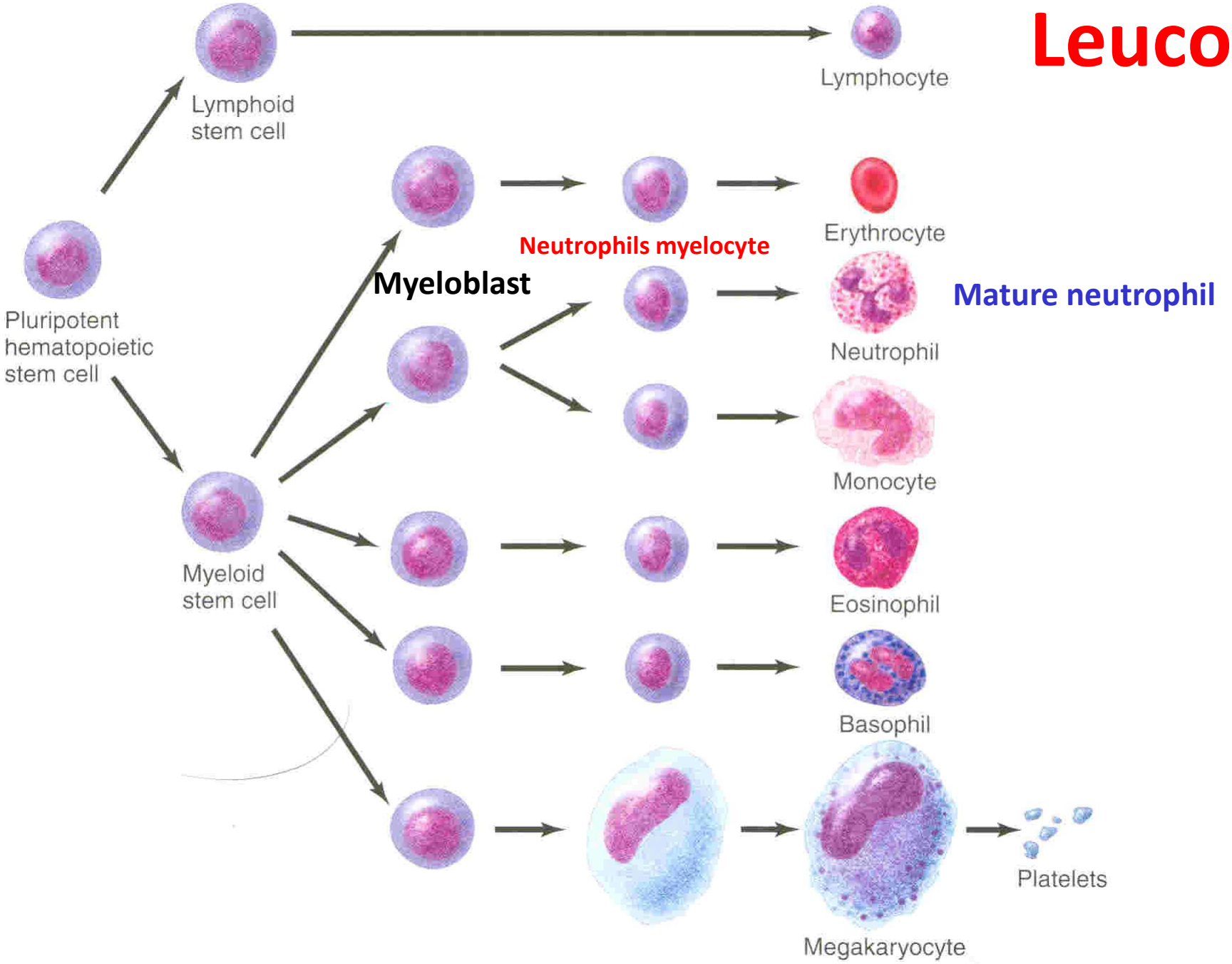
Two major lineage of WBCs are formed:

1. **Myelocytic lineage beginning with myelobast and giving rise to granular leucocytes and monocytes**
2. **Lymphocytic lineage beginning with lymphoblast and giving rise to lymphocytes**

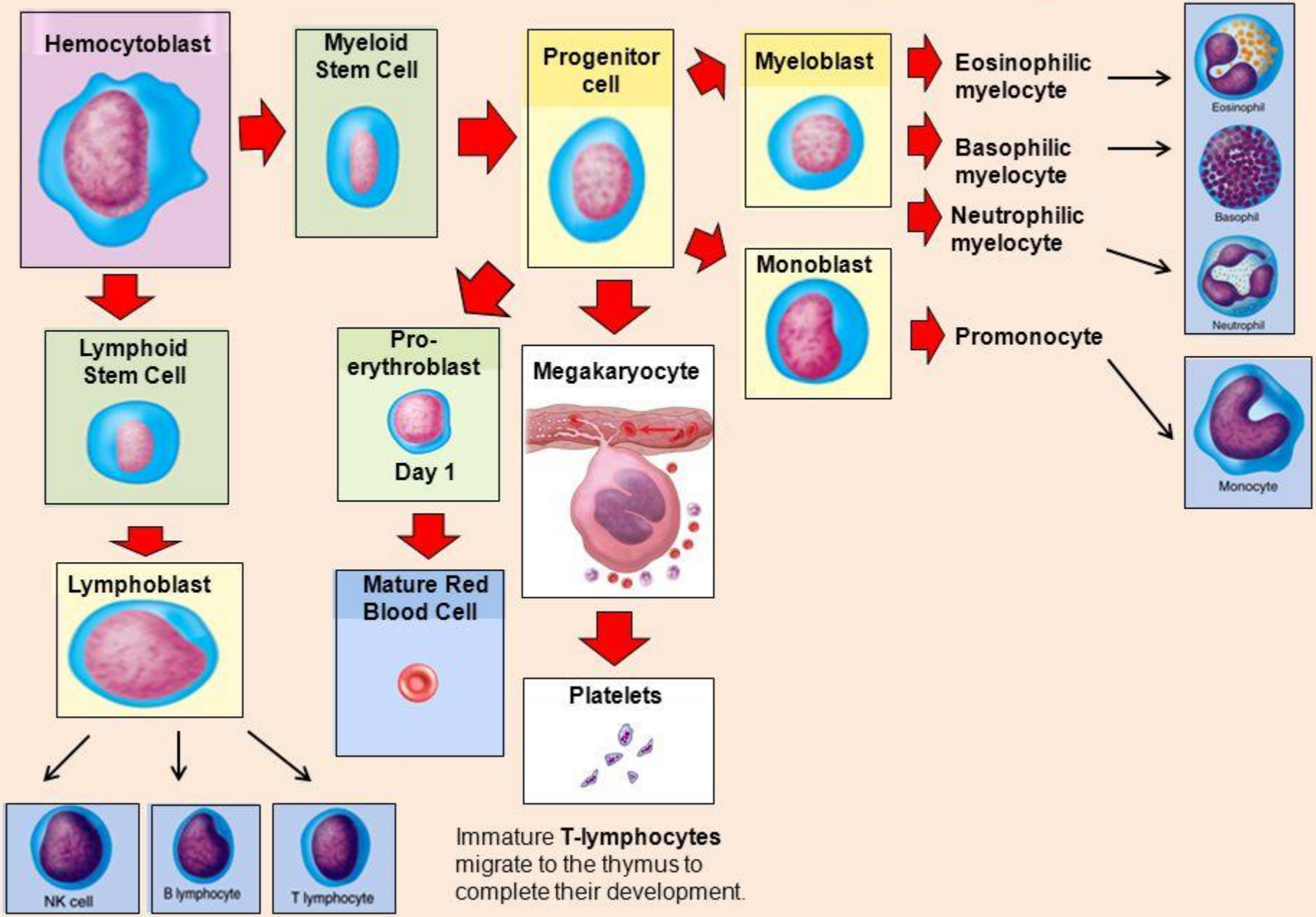
Sites of WBC Formation

- **The granulocytes and monocytes are formed only in the bone marrow.**
- **Lymphocytes are produced in the bone marrow and the various lymphoid tissues especially the lymph glands, spleen, thymus, tonsils, and Peyer's patches (small intestine).**
- **WBCs formed in the bone marrow are stored within the marrow until they are needed in the circulatory system. Various factors cause them to be released. Normally, about three times as many white blood cells are stored in the marrow as circulate in the entire blood.**
- **The lymphocytes are mostly stored in the various lymphoid tissues, except for a small number that are temporarily being transported in the blood.**

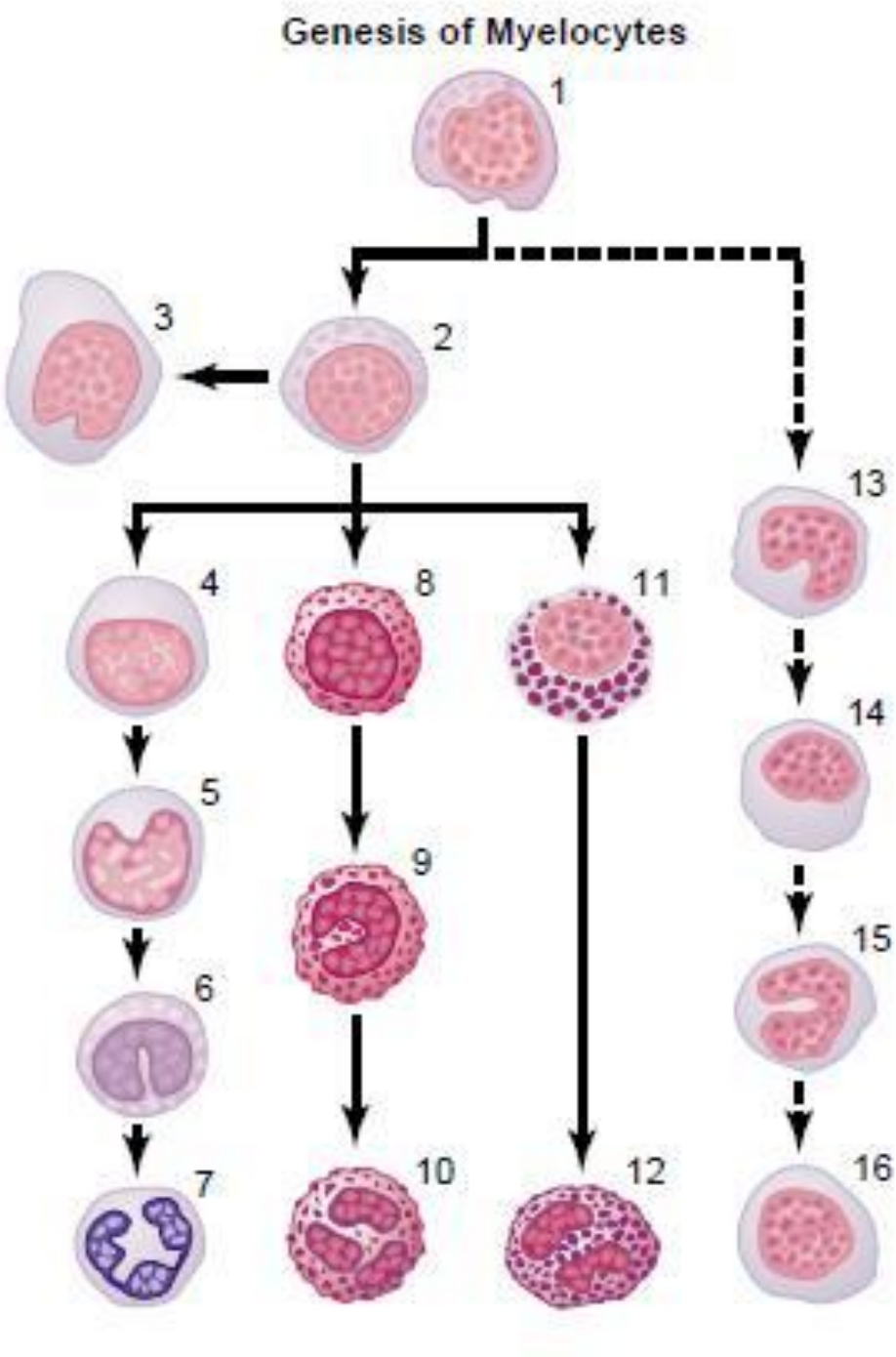
Leucopoiesis



WBC Production (leucopoiesis).



Immature **T-lymphocytes** migrate to the thymus to complete their development.

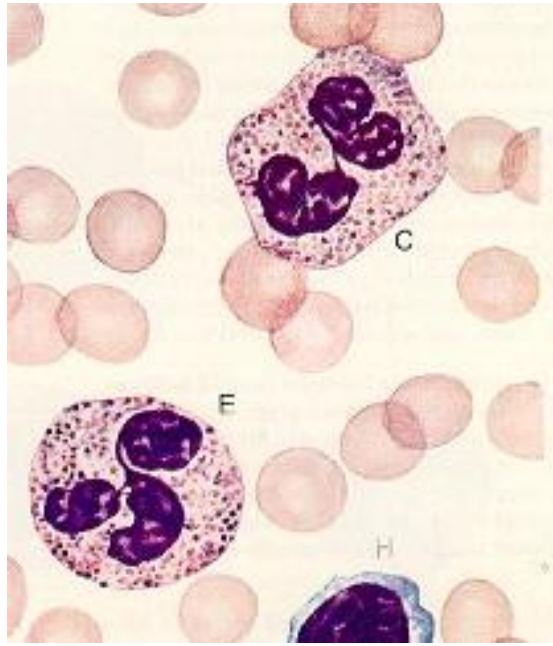


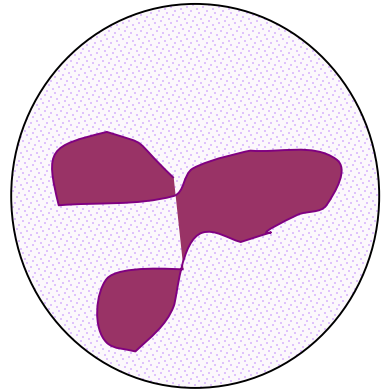
Leucopoiesis

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.

Neutrophils

- Granulocyte
  - They constitute 60-75% of WBCs.
  - They have cytoplasmic granules.
- Polymorphonuclear.
- They contain small granules of both acidic and basic.
- They are phagocytic cells (Phagocytosis); Microphages.
- Short life span (4-8 hours in the blood).
- They constitute the first line of defence against bacterial infection.
- Very important at “clearing” bacterial infections.

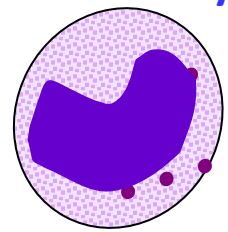




Monocytes/Macrophage

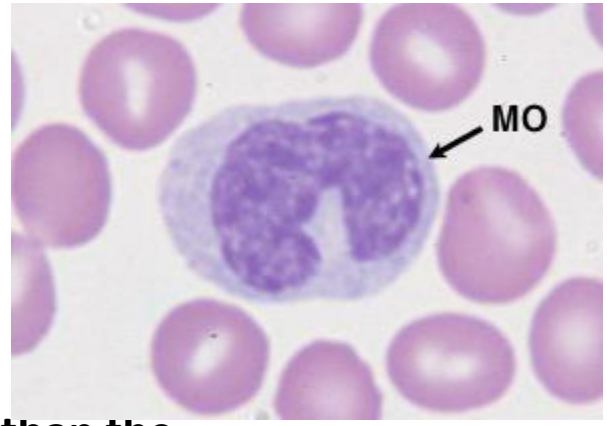
- Monocyte is a young macrophage in the blood.
- They are formed in the bone marrow: stem cell → monoblast → promonocyte → mature monocyte released into blood.
- Monocytes which leave the blood stream turn into macrophages.
- Monocytes contain agranular cytoplasm but when they enter the tissues and converted into macrophages, they swell and their cytoplasm become filled by large number of lysosomes and then they are called macrophages.

Monocyte



Macrophage Phagocytosing E coli

- The momocytes are big eaters
  - 15-20 µm
  - active cells 60-80 µm.



- Life span hours to days.
- They are slower to respond to invaders than the neutrophils, but they are larger, live longer, and have far greater capacities.

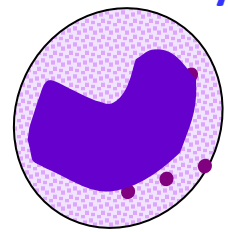
Monocytes/ Macrophage

- There are two types of macrophages; motile and fixed.

- Functions of monocytes/macrophages:
  - Phagocytosis and killing of microorganisms. They are more Efficient than Neutrophils (100 bacteria vs 3-20 by Neutrphil, larger particles like old RBCs & malarial parasites).
  - Activation of T cells and initiation of the immune response by presenting the antigen to these cells.
  - Monocytes secrete:
    - Interleukin-1 (IL-1).
    - Colony stimulating factor (M-CSF).
    - Platelet-activating factor (PAF).

- There are tissue-specific macrophages; fixed macrophages (monocyte-macrophage system; reticulo-endothelial system)
  - Alveolar macrophage
  - Peritoneal macrophage
  - Kuppfer cells in liver sinuses
  - Osteoclasts in bone
  - Microglial cells in brain
  - Histiocytes in skin and subcutaneous tissue
  - Mesengial cells in the kidneys
  - Few specialized endothelial cells in the bone marrow, spleen and lymph nodes

Monocyte



Macrophage Phagocytosing E coli

Functions of the Reticulo-endothelial System

- Phagocytosis of bacterial, dead cells and foreign particles
- Breakdown of Hb
- Immune function
- Storage of iron

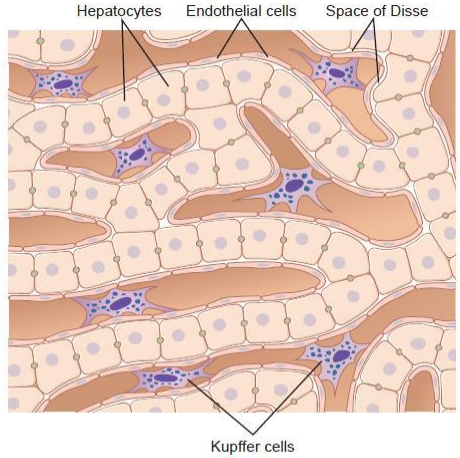


Figure 34-4. Kupffer cells lining the liver sinusoids, showing phagocytosis of India ink particles into the cytoplasm of the Kupffer cells.

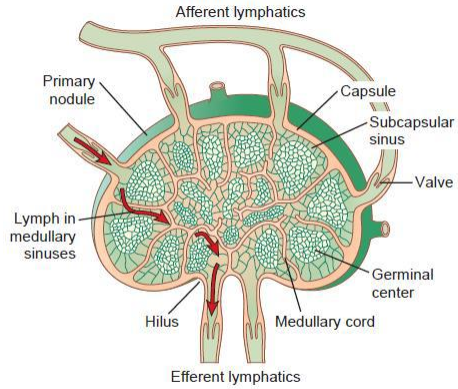
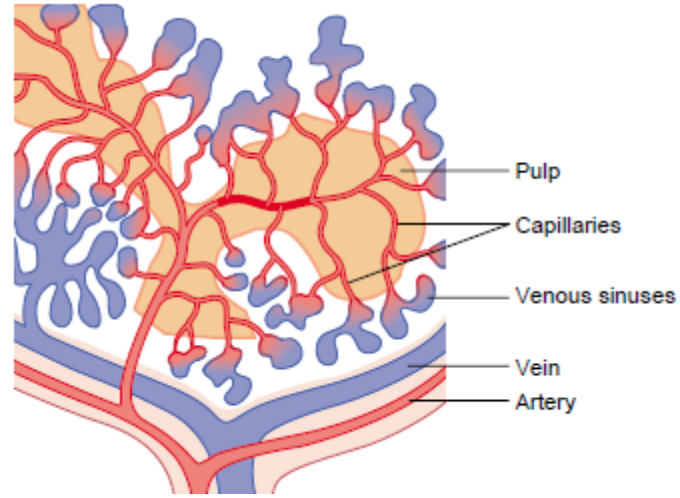
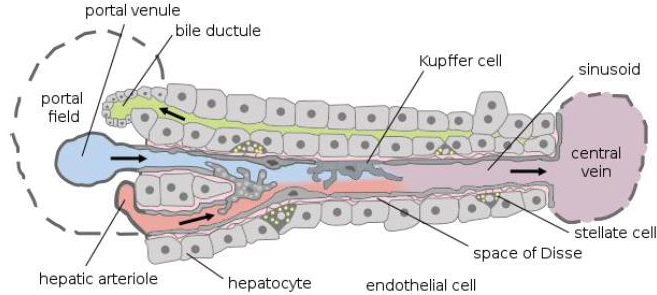
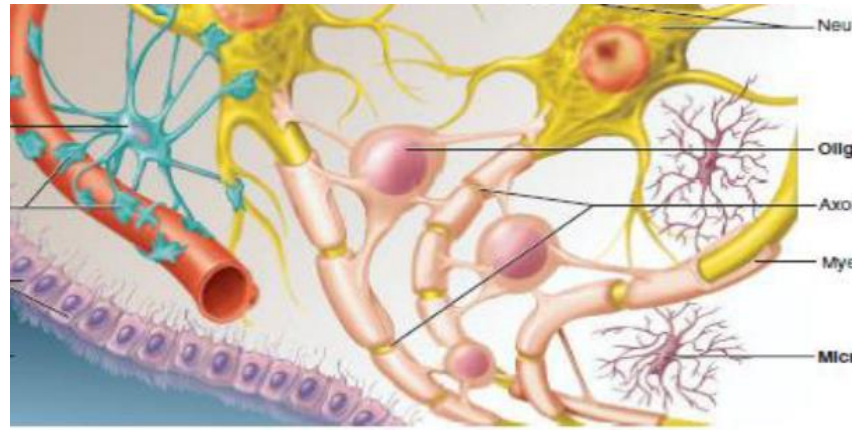
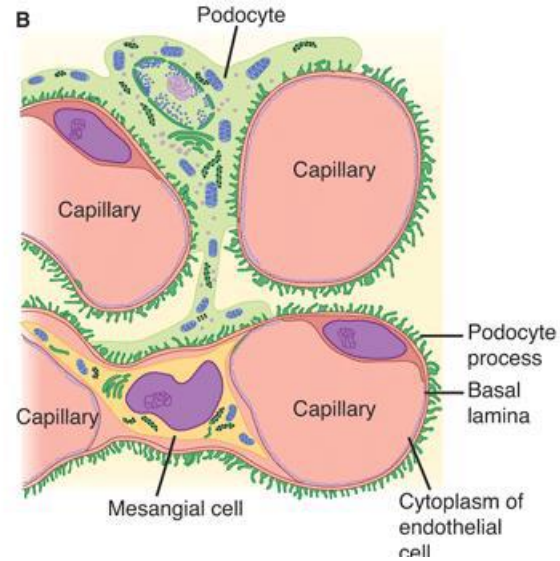


Figure 34-3. Functional diagram of a lymph node.









Macrophage and Neutrophil Responses During Inflammation

- 1st line of defense –Tissue macrophages, barriers and complement system.
- 2nd line of defense –Neutrophil invasion of the inflamed area.
- 3rd line of defense –Monocytes–macrophage invasion of inflamed area.
- 4th line of defense –Increased production of granulocytes and monocytes by the bone marrow.

Defensive Properties of Neutrophils and Macrophages

Invasion of the body by bacteria triggers the inflammatory response.

- **Margination:** The Neutrophils and monocytes aggregate and stick along the walls of blood capillary.
- **Chemotaxis:** Many different chemical substances in the tissues cause neutrophils and monocytes to move toward the source of the chemical. This phenomenon is known as chemotaxis.. The chemotactic agents include a component of the complement system (C5a); leukotrienes; and polypeptides from lymphocytes, mast cells, and basophils.
- **Diapedesis:** Neutrophils and monocytes can squeeze through the pores of the blood capillaries by diapedesis. To enter the tissue spaces
- **Ameboid movement:** Both neutrophils and macrophages can move through the tissues by amoeboid motion, It is a crawling-like type of movement .
- **Phagocytosis:** The most important function of the neutrophils and macrophages is phagocytosis, which means cellular ingestion of the offending agent.
- **Opsonization:** Some plasma factors act on the bacteria to make them “tasty” to the phagocytes (opsonization). The principal opsonins that coat the bacteria are immunoglobulins of a particular class (IgG) and complement proteins.

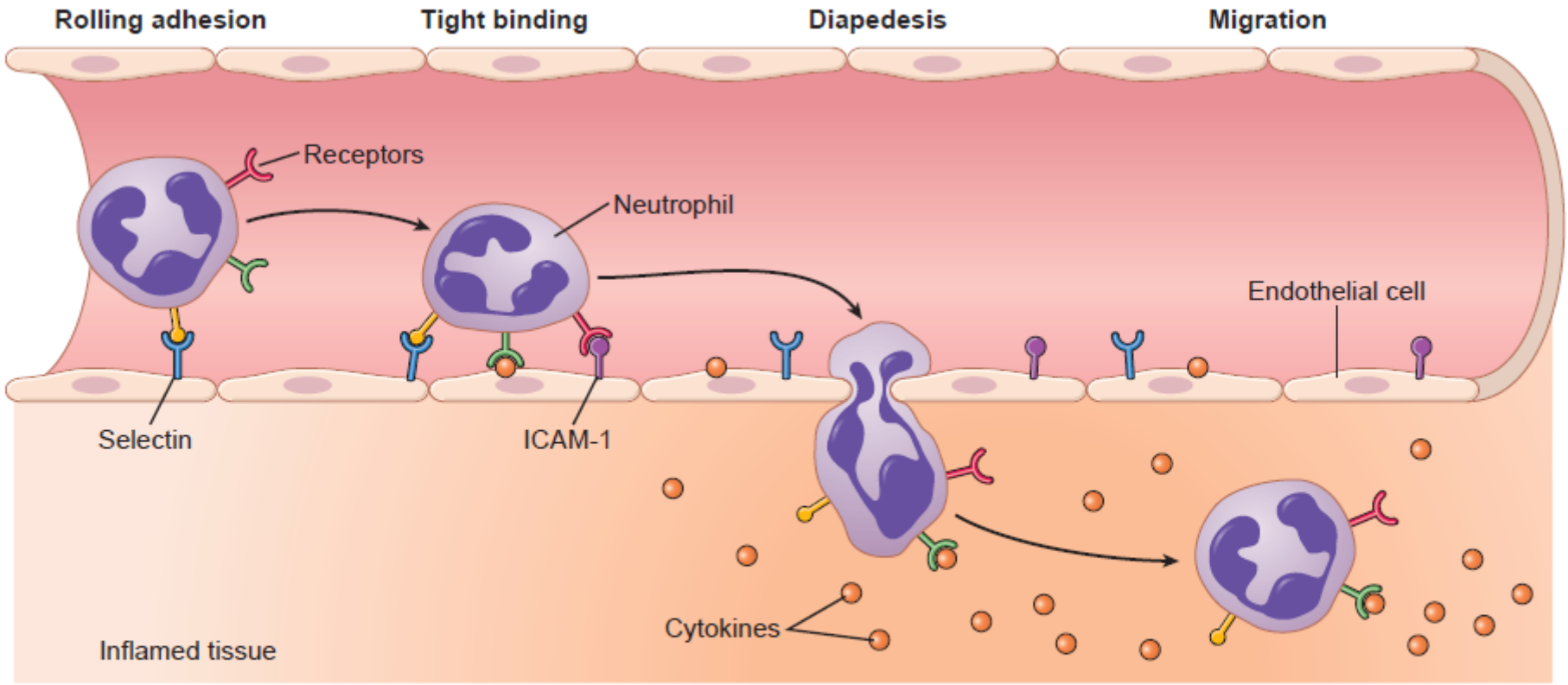


Figure 34-6. Migration of neutrophils from the blood into inflamed tissue. Cytokines and other biochemical products of the inflamed tissue cause increased expression of selectins and intercellular adhesion molecule-1 *(ICAM-1)* in the surface of endothelial cells. These adhesion molecules bind to complementary molecules/receptors on the neutrophil, causing it to adhere to the wall of the capillary or venule. The neutrophil then migrates through the vessel wall by diapedesis toward the site of tissue injury.

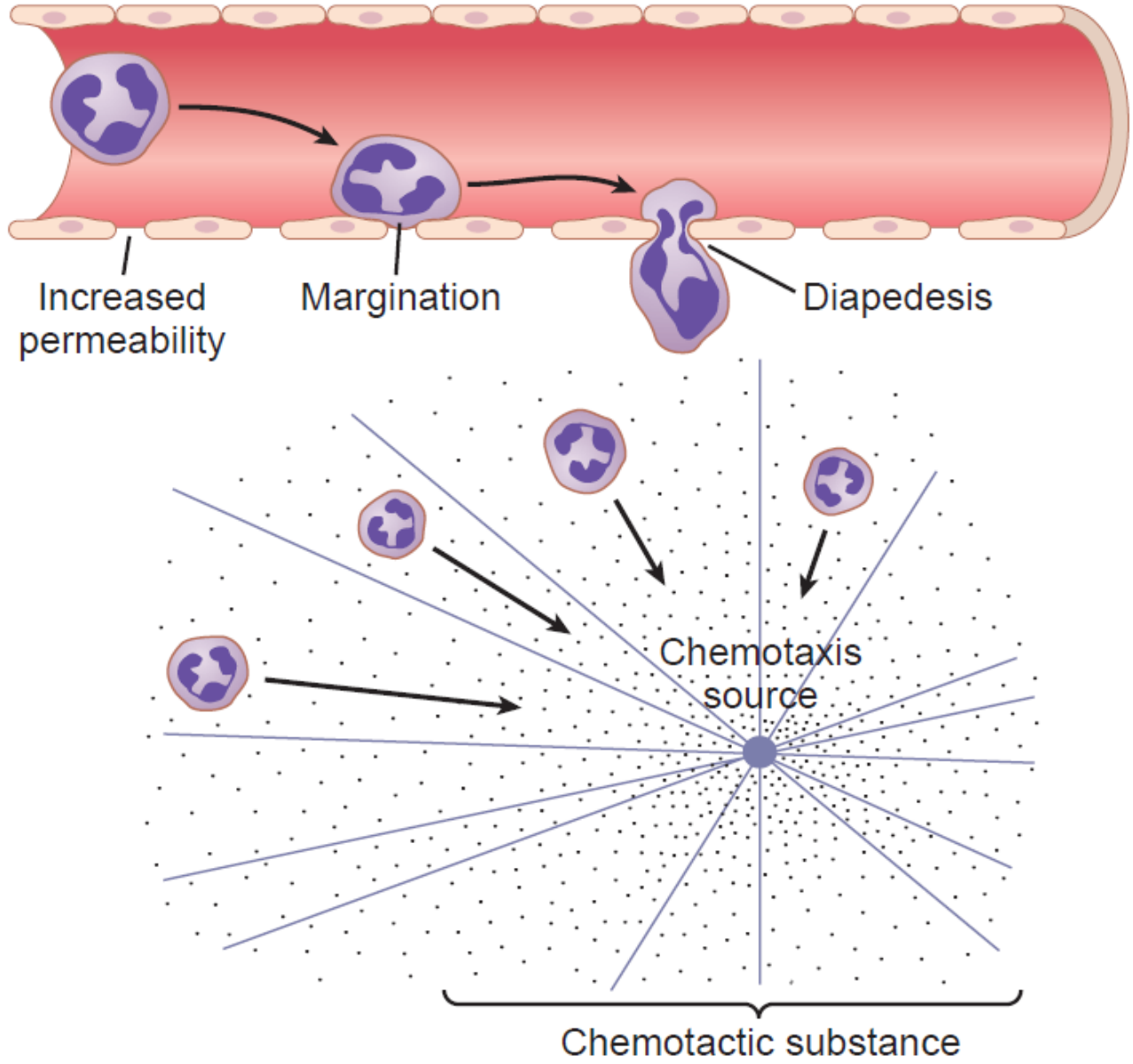
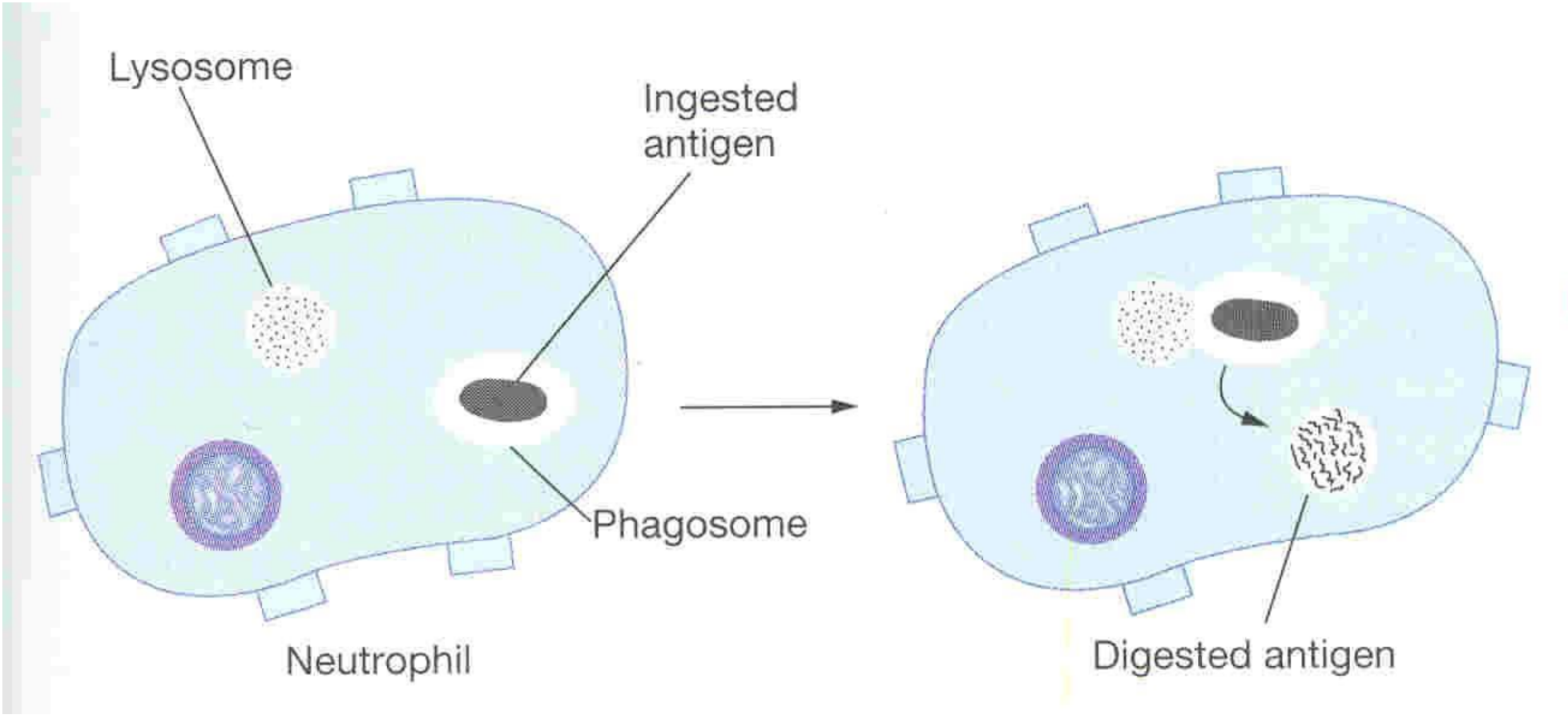


Figure 34-2. Movement of neutrophils by *diapedesis* through capillary pores and by *chemotaxis* toward an area of tissue damage.

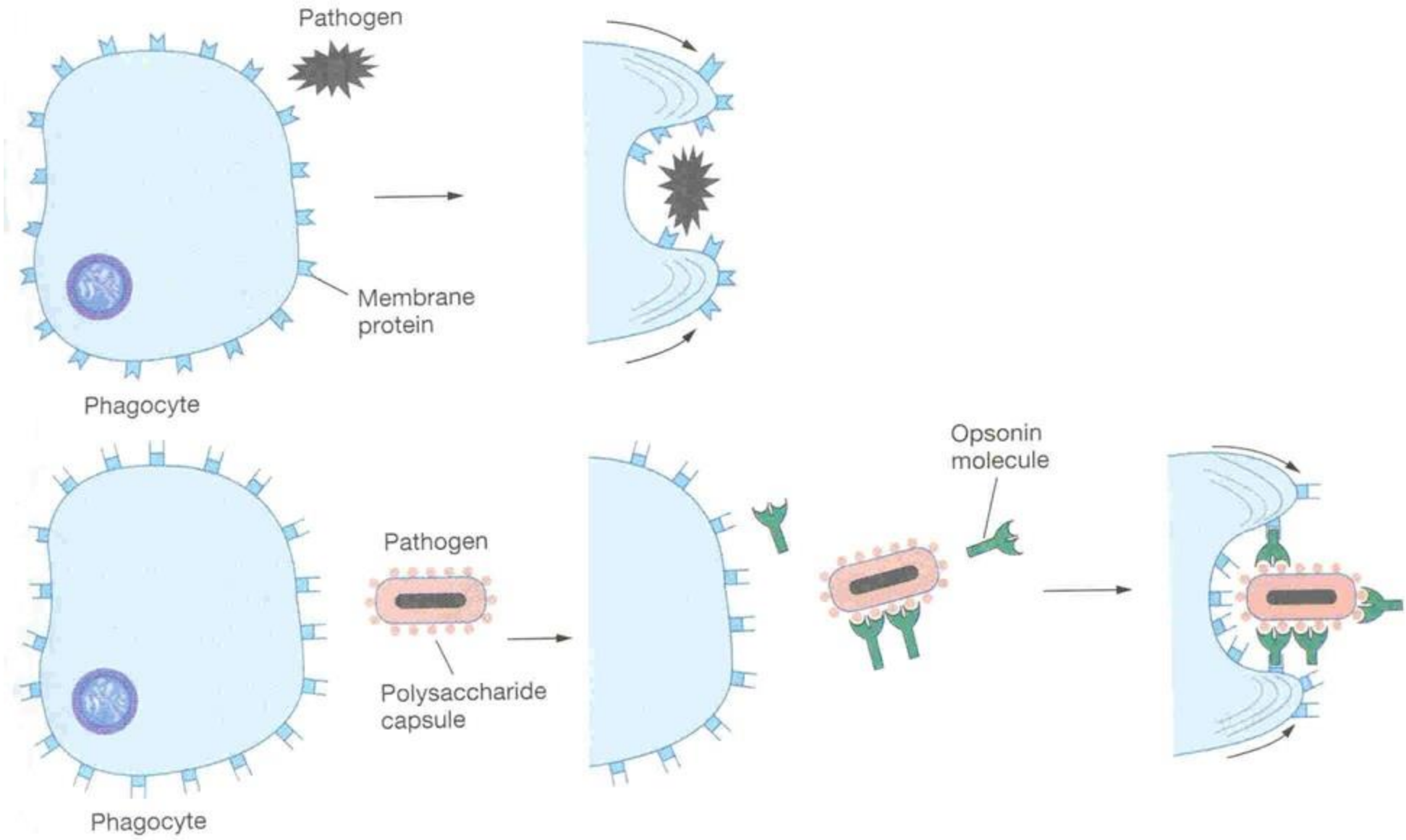
Phagocytosis and Digestion



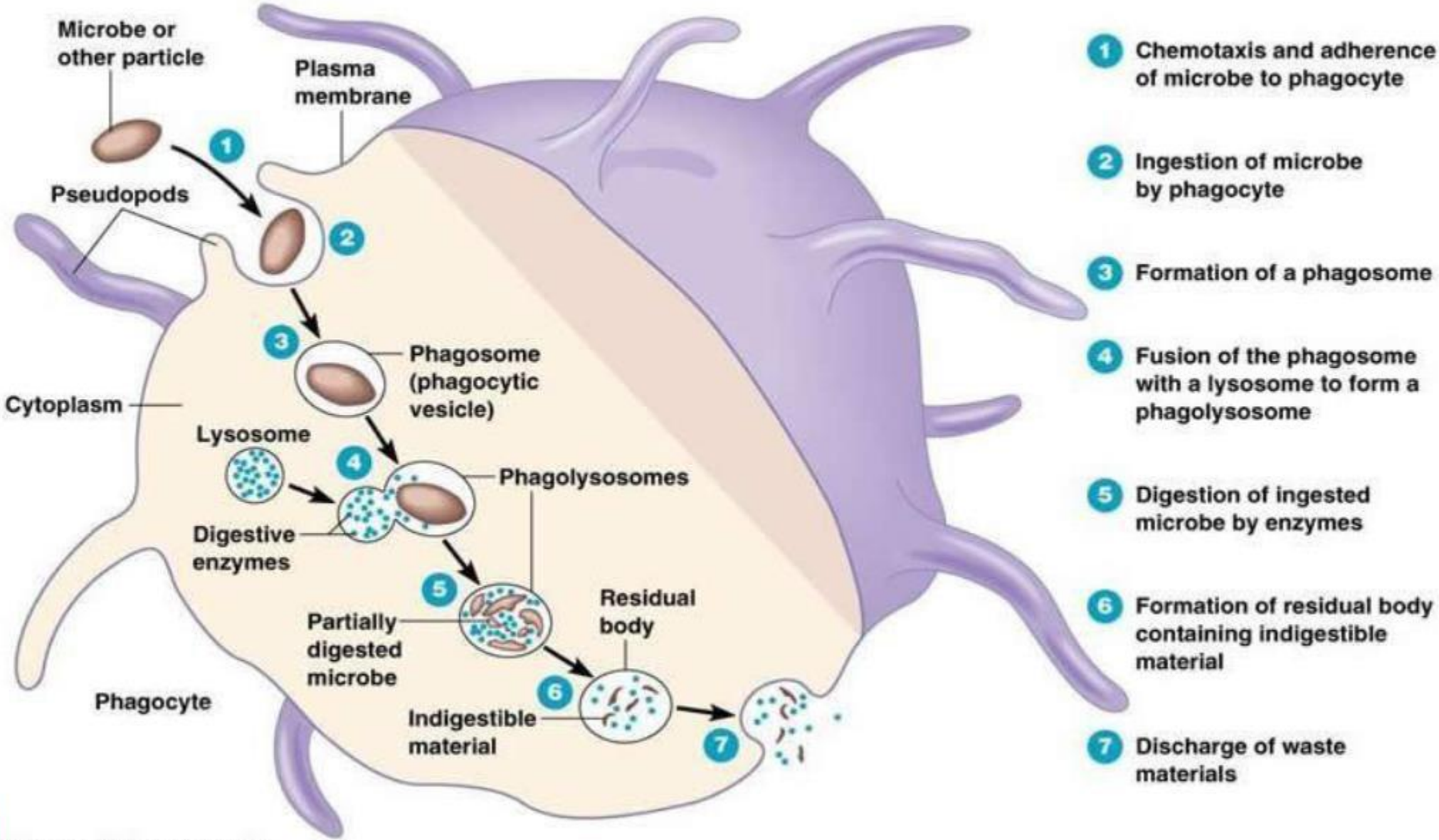
Complement 3b or antibodies like IgG making them ready for killing a process known as opsonization.

Neutrophils encircle the bacteria with pseudopodia and engulf it inside into a vacuole (phagosome), can kill 3-20 bacteria

Opsonization and Phagocytosis

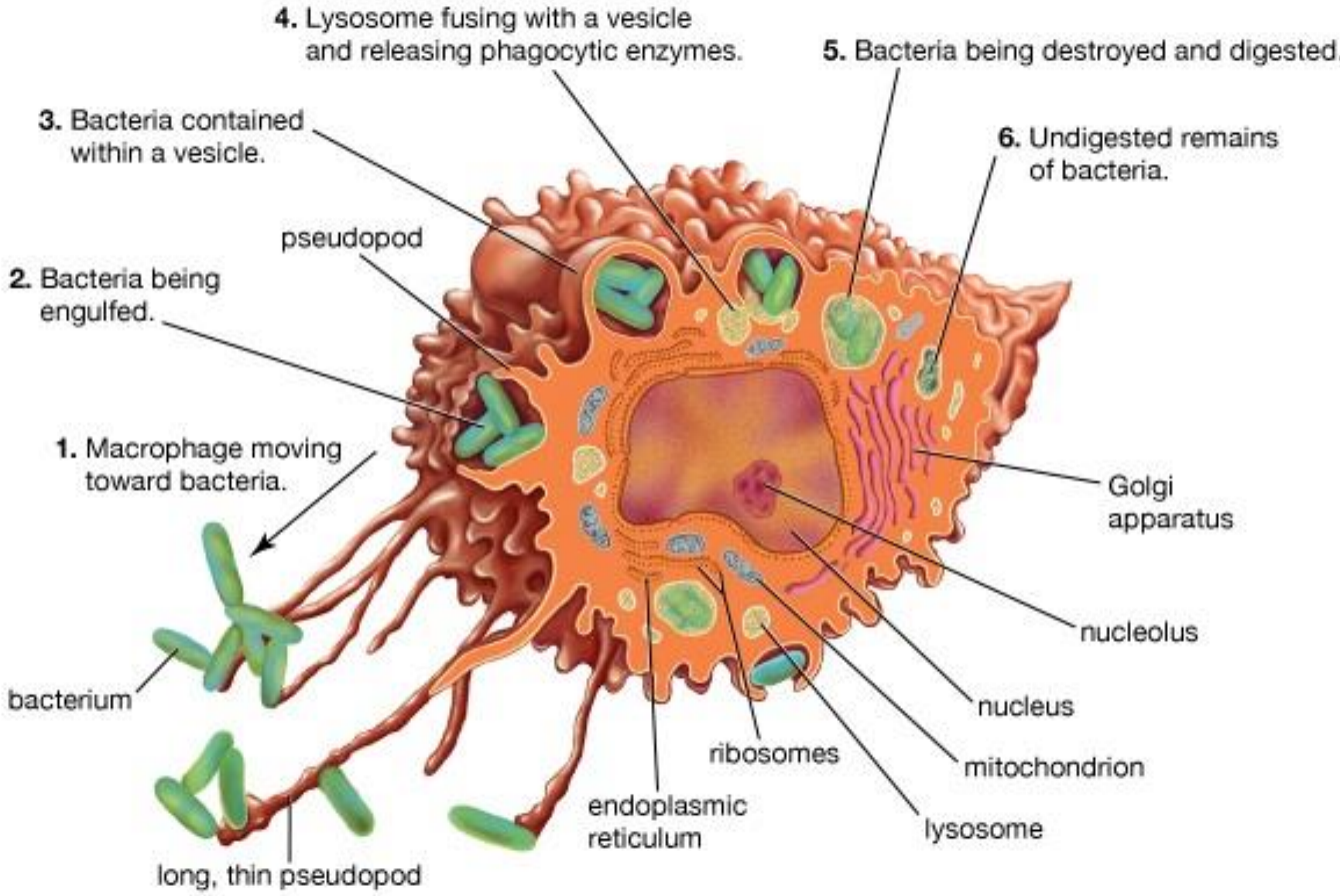


Microbial Killing



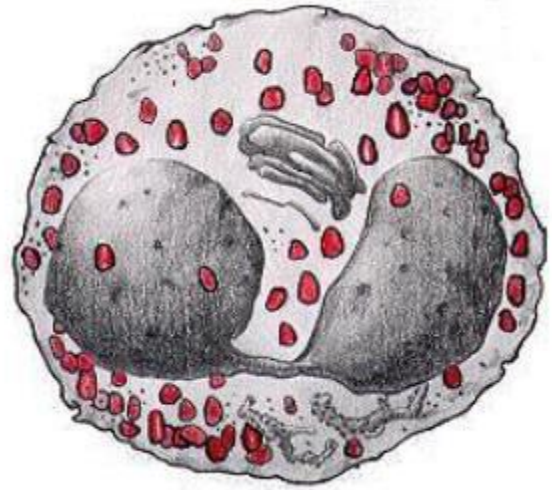
Phases of phagocytosis

Microbial Killing

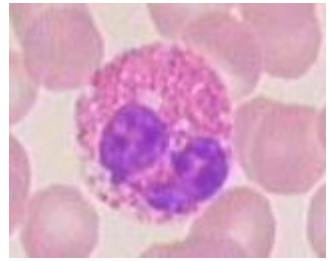


Eosinophils

- Eosinophils are formed in the bone marrow: Stem cell → myeloblast → promyelocyte → eosinophil myelocyte → eosinophil metamyelocyte → mature eosinophil released into the blood. The normally constitute ~2% of all the blood leucocytes.
- Size: 12-18 µm in diam.
- Life span: 4-5 hours in the circulation.
- They have bilobed nucleus
- The cytoplasm contains granules, which are arginine rich and take acid dye (eosin).

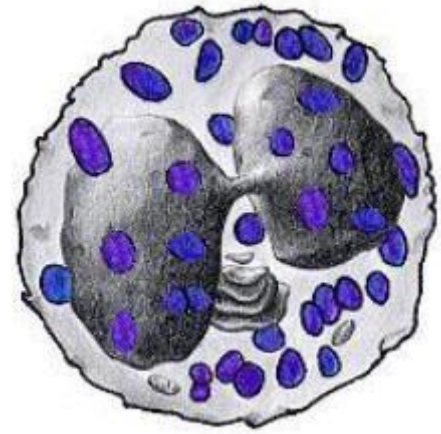


- Functions:
  1) They are weak phagocytes.
  2) They are often produced in large numbers in people with parasitic infections, and they migrate in large numbers into tissues diseased by parasites., e.g., ascaris. Eosinophils attach themselves to the parasites by way of special surface molecules and release substances that kill many of the parasites
  3) They are increased in allergic conditions by the release of eosinophil chemotactic factor released from the mast cells and basophiles. Eosinophils phagocytose the antigen-antibody complexes and release substances to neutralize the histamine.
  4) They may produce profibrinolysin → fibrinolysin which digest fibrin clot.

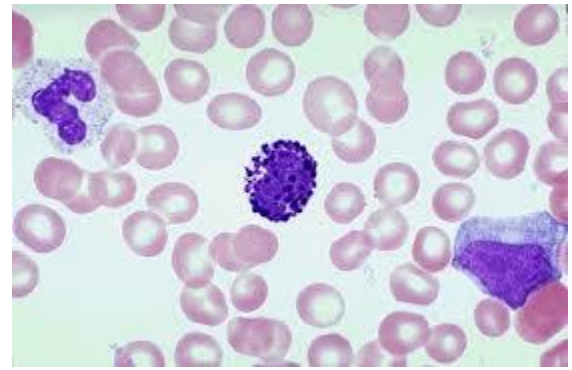


Basophils

- Basophils are formed in the bone marrow: Stem cell → myeloblast → promyelocyte → basophil myelocyte → basoophil metamyelocyte → maturebasophil released into the blood. The normally constitute less than 1% of all the blood leucocytes.
- Size: 10-14 µm in diam.
- Rarely segmented nucleus hidden by large round cytoplasmic polysaccharide granules, which take base dye (methylene blue) and stain blue in color.



- Functions:



1) Both mast cells and basophils liberate histamine, heparin, bradykinin, Serotonin (5HT) , slow-reacting substance of anaphylaxis (a mixture of three leukotrienes) and a number of lysosomal enzymes.

2) They are increased in allergic reaction: immediate-type hypersensitivity (allergic) reactions.

Cellular Elements of the Innate Immune System
Lymphocytes – T and B cells

- Make up 20–40% of circulating leukocytes

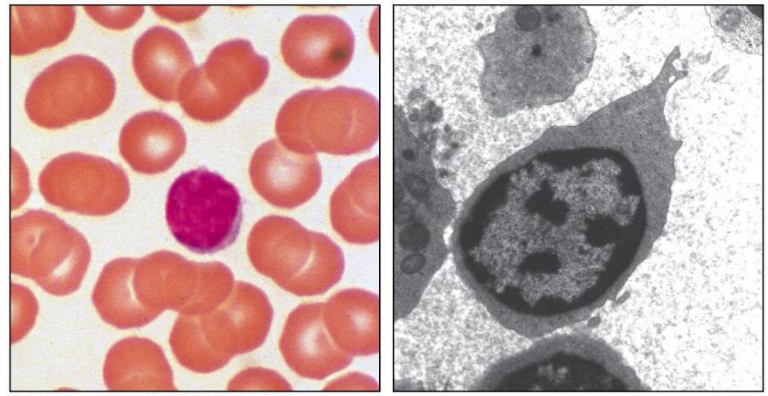


Figure 1-5 Immunobiology, 6/e. (© Garland Science 2005)

3 Classes of circulating Lymphocytes

- T cells: thymus-dependent
- B cells: thymus-independent

Lymphocytes – T and B cells

- Both types of lymphocytes are derived in the embryo from *pluripotent hematopoietic stem cells* that form *common lymphoid progenitor cells.*

- All of the lymphocytes formed end up in the lymphoid tissue, but before doing so, they are further differentiated or "preprocessed":

  - The lymphoid progenitor cells that are destined to eventually form activated T lymphocytes first migrate to and are preprocessed in the thymus gland, and thus they are called "T" lymphocytes. They are responsible for cellular or cell-mediated immunity

  - The B lymphocytes are preprocessed in the liver during mid–fetal life and in the bone marrow in late fetal life and after birth. They are changed to plasma cells and are responsible for humeral immunity or antibody- mediated immunity.

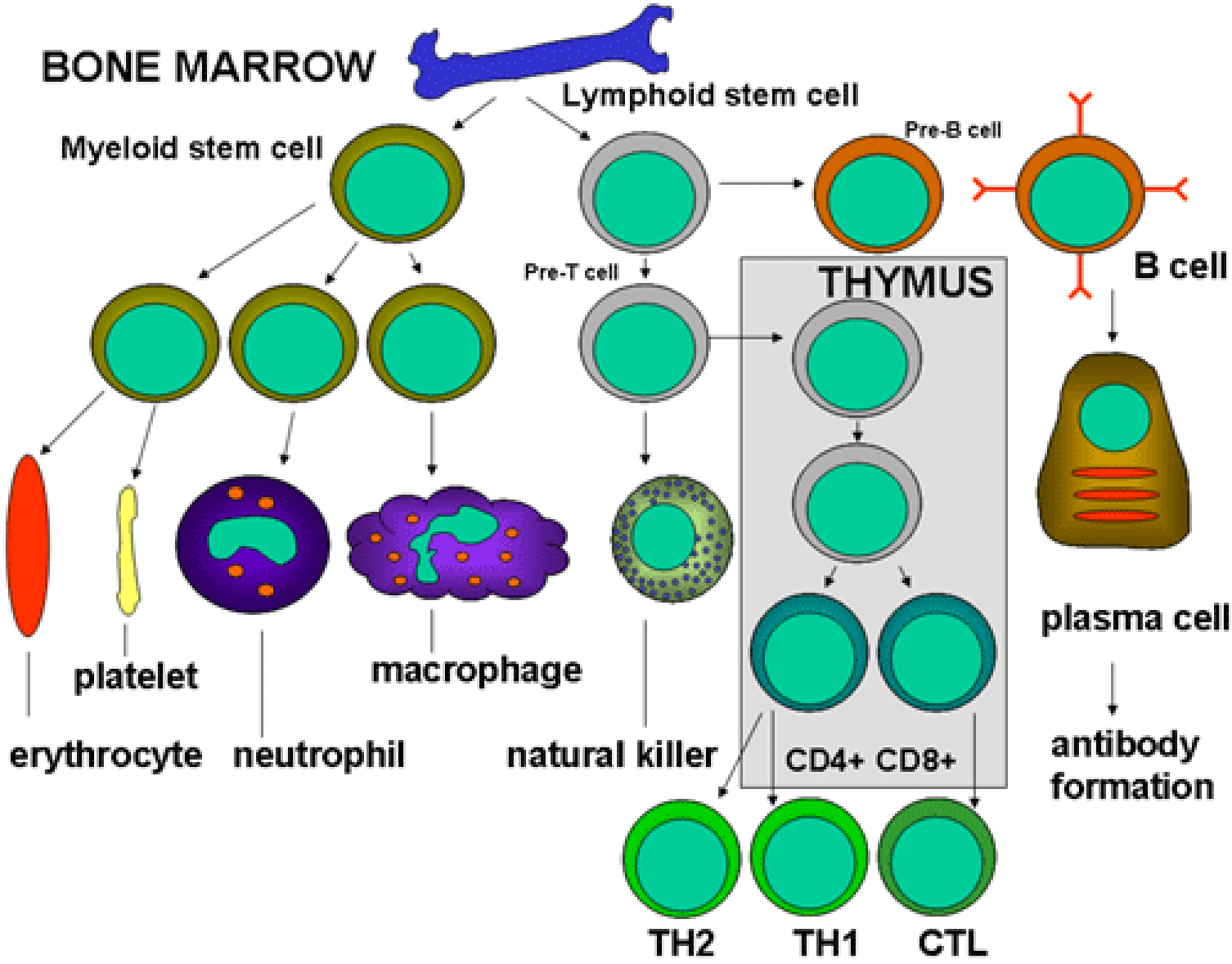
Lymphocytes – T and B cells

- Lymphocytes migrate to the lymphoid organs.

- On the surface of each lymphocyte are receptors that enable them to recognize foreign substances. These receptors are very specialized - each can match only one specific antigen.

- It might seem limiting that the receptors of each lymphocyte cell can only match one specific type of antigen, but the body makes up for this by producing so many different lymphocyte cells that the immune system can recognize nearly all invaders.

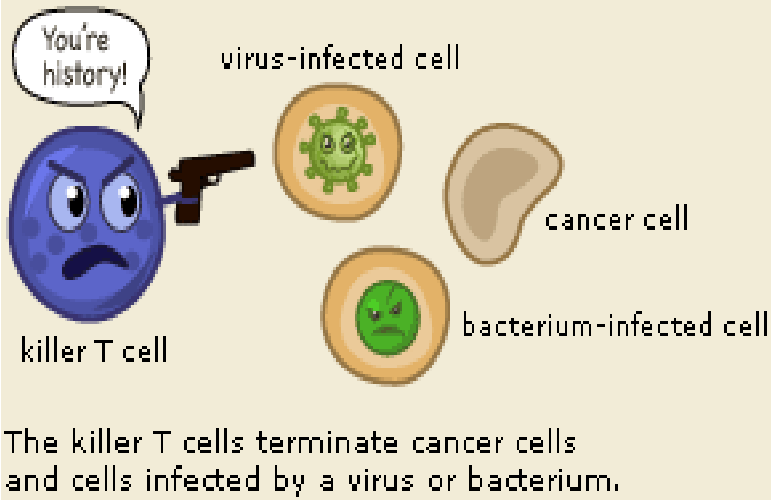
Lymphocytes – T and B cells



T cells

T cells are produced in the bone marrow and later move to the thymus where they mature, hence these lymphocytes are called T cells.

T cells come in two different types, helper cells and killer cells.



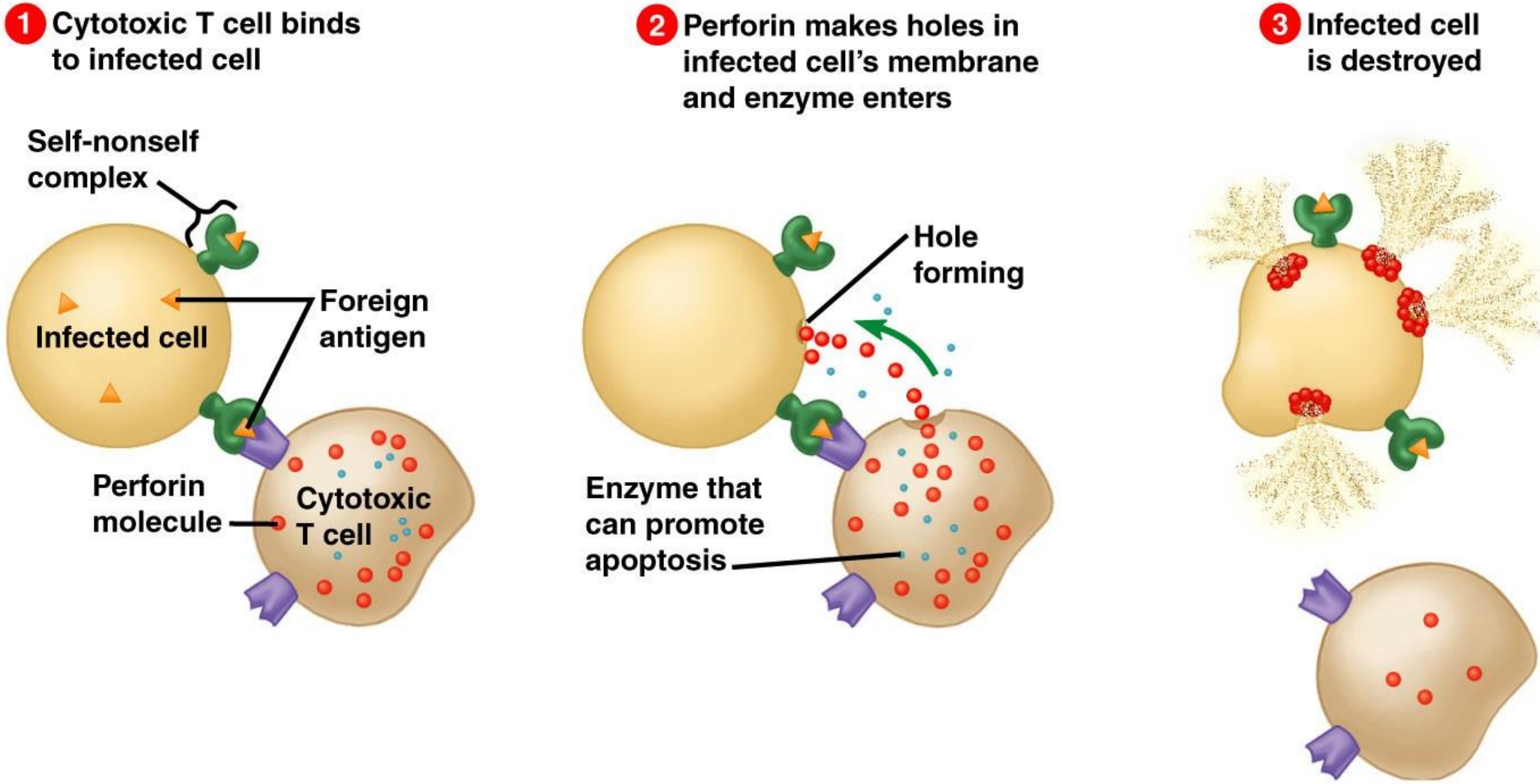
The killer T cells terminate cancer cells and cells infected by a virus or bacterium.

Killer T cells

A **cytotoxic T cell** (also known as T_C, **cytotoxic T**lymphocyte, CTL, **T-killer cell**, cytolytic **T cell**, CD8+**T-cell** or **killer T cell**)

- **The killer T cell** is specialized in attacking cells of the body infected by viruses and sometimes also by bacteria. It can also attack cancer cells.
- **The killer T cell has receptors** that are used to search each cell that it meets. If a cell is infected, it is swiftly killed.
- Infected cells are recognized because tiny traces of the intruder, antigen, can be found on their surface.

Killer T cells

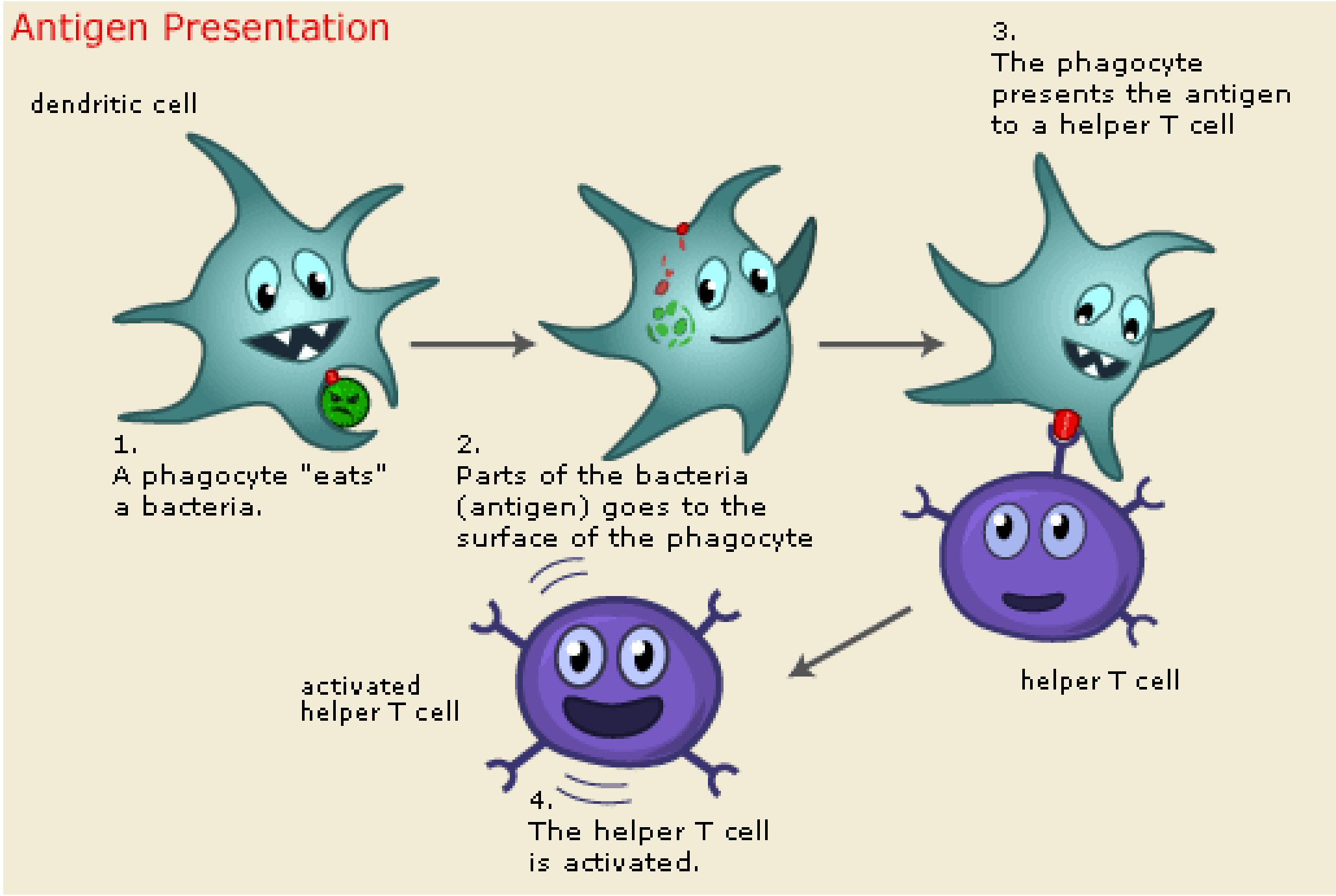


Helper T cells

- **Helper T cells** are the major driving force and the main regulators of the immune defense.

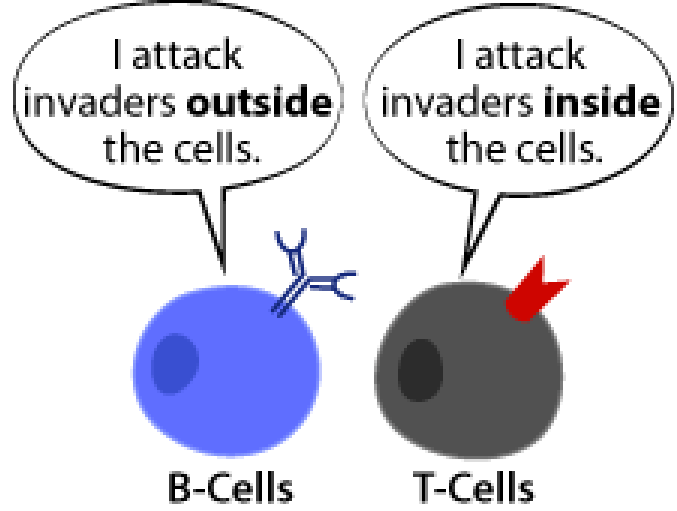
- Their primary task is to **activate B cells and killer T cells**. However, the helper T cells themselves must be activated. This happens when a **macrophage or dendritic cell (antigen-presenting cell (APC) that form an important role in the adaptive immune system),** which has eaten an invader, travels to the nearest lymph node to present information about the captured pathogen. The phagocyte displays an antigen fragment from the invader on its own surface**, a process called *antigen presentation*.**
- When the receptor of a helper T cell recognizes the antigen, the T cell is activated. Once activated, helper T cells start to divide and to produce proteins that activate B and T cells as well as other immune cells.

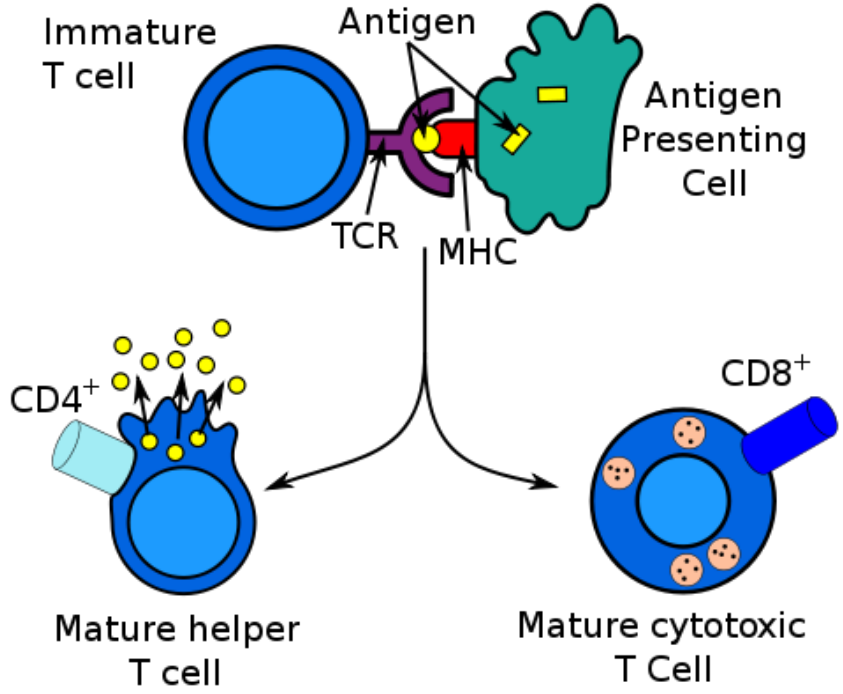
Antigen Presentation



B cells

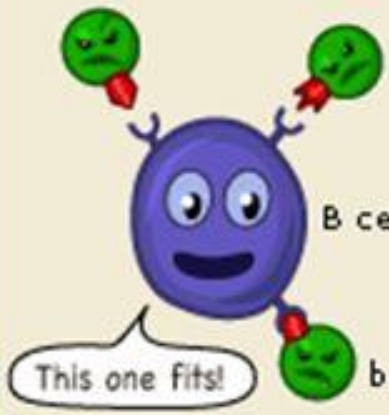
- The B lymphocyte searches for antigen matching its receptors.
- If it finds such antigen it connects to it, and inside the B cell a triggering signal is set off.
- The B cell now needs proteins produced by helper T cells to become fully activated. When this happens, the B cell starts to divide to produce clones of itself.
- During this process, two new cell types are created, plasma cells and B memory cells.
- The plasma cell is specialized in producing a specific protein, called an *antibody*
- The memory Cells are the second cell type produced by the division of B cells. These cells have a prolonged life span and can thereby "remember" specific intruders.
- T cells can also produce memory cells with an even longer life span than B memory cells. The second time an intruder tries to invade the body, B and T memory cells help the immune system to activate much faster.
- The invaders are wiped out before the infected human feels any symptoms. The body has achieved immunity against the invader.



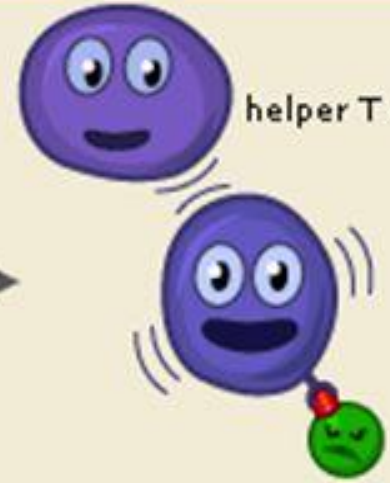


B cell activation

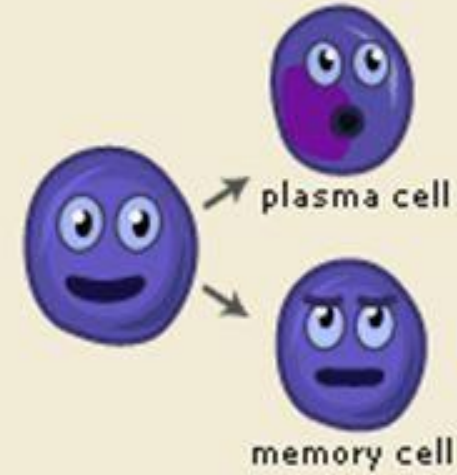
Kill virally infected cells



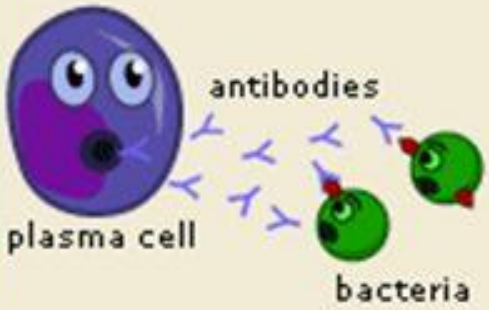
1.
The B cell finds an antigen which matches its receptors.



2.
It waits until it is activated by a helper T cell.

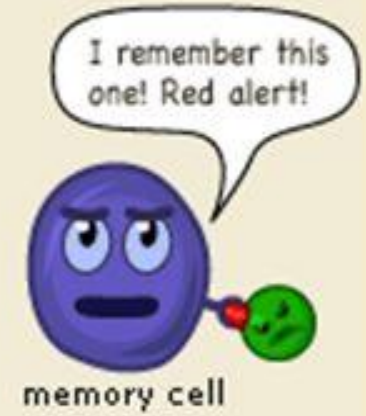


3.
Then the B cell divides to produce plasma and memory cells.



4.
Plasma cells produce antibodies that attach to the current type of invader.

5.
"Eater cells," prefer intruders marked with antibodies, and "eat" loads of them.



6.
If the same intruder invades again, memory cells help the immune system to activate much faster.

Physiological Leukocytosis

- Increase in number of leucocytes above 11.000/mm^3.

- It occurs in the following conditions:
  - Muscular exercise
  - Emotions
  - Cold bath
  - Cold or hot weather
  - Pregnancy
  - Labor
  - Pain
  - Anesthesia
  - After meals.

Physiological Variations in WBCs Count

- **Age:**
  - **Infants: about 20,000 /mm^3**
  - **Children:10,000 to 15,000/mm^3**
  - **Adults: 4,000 and 11,000/mm^3**

- **Sex: males have more WBCs than females.**
- **Diurnal variation: Minimum in early morning and maximum in the afternoon.**
- **Exercise: Increases slightly.**
- **Sleep: Decreases.**
- **Emotional conditions like anxiety: Increases.**
- **Pregnancy: Increases.**
- **Menstruation: Increases.**
- **Parturition: Increases.**

Pathological Leukocytosis

Condition	Definition	Causes
Neutrophilia	An increase in the number of neutrophils	❑ Infections: of all types as acute or chronic, bacterial, viral or fungal. ❑ Inflammation as rheumatic fever ❑ Tissue damage as trauma, burn ❑ Malignant tumors ❑ Smoking.
Eosinophilia	an increase in the number of eosinophils	❑ Allergic conditions as asthma, hay fever, skin allergy ❑ Parasitic infection ❑ Leukemia
Basophilia	an increase in the number of basophils	❑ Allergic conditions as asthma, hay fever, skin allergy ❑ Leukemia
Monocytosis	an increase in the number of momocytes	❑ Chronic infection as in tuberculosis ❑ Leukemia
Lymphocytosis	an increase in the number of lymphocytes	❑ Chronic bacterial and viral infections ❑ Leukemia

Leukemia

- It is a malignant disease of bone marrow causing marked increase in WBCs may reach 500.000/mm^3.

- Leukemia is associated with anemia and bleeding tendency (due to decrease in bone marrow area responsible for RBCs and platelet synthesis respectively).

Leukopenia

- Leukopenia (leucopenia) means a decrease in the total leucocyte count below 4.000/mm^3.
- In this condition the body is not protected against infections and death may occur.
- It is caused by:
  - Bone marrow depression by radiation, drugs, and cancer chemotherapy.
  - Some bacterial infections as typhoid fever, brucellosis.
  - Some viral infections as AIDS, influenza, hepatitis.

Objectives;

Intended learning outcomes (ILOs)

After reviewing the PowerPoint presentation and the associated learning resources, the student should be able to:

- Outline components of the immune system.
- List the types of white blood cells(WBCs).
- Describe the structure of the different types of WBCs.
- Outline differential WBCs count.
- Summarize the stages of formation of the different WBCs.
- State the functions the different types of WBCs.
- Describe the role of the WBCs in immune responses and defending against infection.
- Explain the process of phagocytosis.
- Recognize leukocytosis, leukopenia and leukemia.

Thank You