Second line of defense

When microbes penetrate the first line of defense, they encounter a second line of defense that includes defensive cells, such as

1-Phagocytic cells

2-Inflammation

3- Fever

4- Antimicrobial substances.

Before we look at the phagocytic cells, it will be helpful to first have an understanding of the cellular components of blood.

Leukocytes are divided into two main categories based on their appearance under a light microscope: **granulocytes** and **agranulocytes**.

1- Granulocytes: They are differentiated into three types of cells on the basis of how the granules stain: **neutrophils, basophils, and eosinophils**.

-**Neutrophils** are also commonly called polymorphonuclear leukocytes (PMNs), or polymorph.
Neutrophils, which are highly phagocytic and motile, are active in the initial stages of an infection. They have the ability to leave the blood, enter an infected tissue, and destroy microbes and foreign particles.

- **Basophils**: release substances, such as histamine, that are important in inflammation and allergic responses.

-**Eosinophils** are somewhat phagocytic and also have the ability to leave the blood. Their major function is to produce toxic proteins against certain parasites, such as helminths. Although eosinophils are physically too small to ingest and destroy helminths, they can attach to the outer surface of the parasites

and discharge peroxide ions that destroy them. Their number increases significantly during certain parasitic worm infections and hypersensitivity (allergy) reactions.

2- **Agranulocytes**: There are three different types of agranulocytes: **monocytes**, **dendritic cells**, and **lymphocytes**.

-**Monocytes** are not actively phagocytic until they leave circulating blood, enter body tissues, and mature into macrophages.

-**Dendritic cells** are especially abundant in the epidermis of the skin, mucous membranes, the thymus, and lymph nodes. The function of dendritic cells is to destroy microbes by phagocytosis and to initiate adaptive immunity responses.

-**Lymphocytes** include **natural killer cells**, **T cells**, and **B cells**. Natural killer (NK) cells are found in blood and in the spleen, lymph nodes, and red bone marrow. NK cells have the ability to kill a wide variety of infected body cells and certain tumor cells. NK cells attack any body cells that display abnormal or unusual plasma membrane proteins. The binding of NK cells to a target cell, such as an infected human cell, causes the release of vesicles containing toxic substances from NK cells. Some granules contain a protein called **perforin**, which inserts into the plasma membrane of the target cell and creates channels in the membrane. As a result, extracellular fluid flows into the target cell and the cell bursts, a process called **cytolysis**. Other granules of NK cells release granzymes, which are protein-digesting enzymes that induce the target cell to undergo apoptosis, or self-destruction.

T cells and B cells are not usually phagocytic but play a key role in adaptive immunity. They occur in lymphoid tissues of the lymphatic system and also circulate in blood.

The Lymphatic System

Lymphoid tissue contains large numbers of lymphocytes, including T cells, B cells, and phagocytic cells that participate in immune responses.
Lymph nodes are the sites of activation of T cells and B cells, which destroy microbes by immune responses.

Question…..

- Compare the structures and function of monocytes and neutrophils.
- Describe the six different types of white blood cells, and name a function for each type.

Phagocytes

Phagocytosis is the ingestion of a microorganism or other substances (such as debris) by a cell. The cells that perform this function are collectively called **phagocytes**, all of which are types of white blood cells or derivatives of white blood cells.

Actions of Phagocytic Cells

When an infection occurs, both **granulocytes** (especially **neutrophils**, but also **eosinophils** and **dendritic cells**) and **monocytes** migrate to the infected area. During this migration, monocytes leave the blood and migrate into tissues where they enlarge and develop into **macrophages**.

Some macrophages, called **fixed macrophages**, are resident in certain tissues and organs of the body.

Fixed macrophages are found in the liver (Kupffer's cells), lungs (alveolar macrophages), nervous system (microglial cells).

Other macrophages are motile and are called **free macrophages,** which roam the tissues and gather at sites of infection or inflammation.

The Mechanism of Phagocytosis

phagocytosis will divide into four main phases:

1- chemotaxis
2- adherence
3- ingestion
4- digestion

1- Chemotaxis

Chemotaxis is the chemical attraction of phagocytes to microorganisms. Among the chemotactic chemicals that attract phagocytes are microbial products, components of white blood cells and damaged tissue cells, cytokines_ released by other white blood cells, and peptides derived from complement.

2- Adherence

Adherence is the attachment of the phagocyte's plasma membrane to the surface of the microorganism or other foreign material. Adherence is facilitated by the attachment of pathogen-associated molecular patterns (PAMPs) of microbes to receptors, such as Toll –like receptors (TLRs), on the surface of phagocytes. The binding of PAMPs to TLRs not only initiates phagocytosis, but also induces the phagocyte to release specific cytokines that recruit additional phagocytes.

Microorganisms can be more readily phagocytized if they are first coated with certain serum proteins that promote attachment of the microorganisms to the phagocyte. This coating process is called **opsonization**. The proteins that act as **opsonins** include some components of the complement system and antibody molecules.

3-Ingestion

During this process, the plasma membrane of the phagocyte extends projections called pseudopods that engulf the microorganism. Once the microorganism is surrounded, the pseudopods meet and fuse, surrounding the microorganism with a sac called a **phagosome**, or phagocytic vesicle.

The membrane of a phagosome has enzymes that pump protons (H+) into the phagosome, reducing the pH to about 4. At this pH, hydrolytic enzymes arc activated.

4- Digestion

In this phase of phagocytosis, the phagosome pinches off from the plasma membrane and enters the cytoplasm. Within the cytoplasm, it contacts Lysosomes that contain digestive enzymes and bactericidal substance on contact, the phagosome and lysosome membranes fuse to form a single larger structure called a **phagolysosome**.

Intracellular killing:

Intracellular killing is done by two mechanisms:

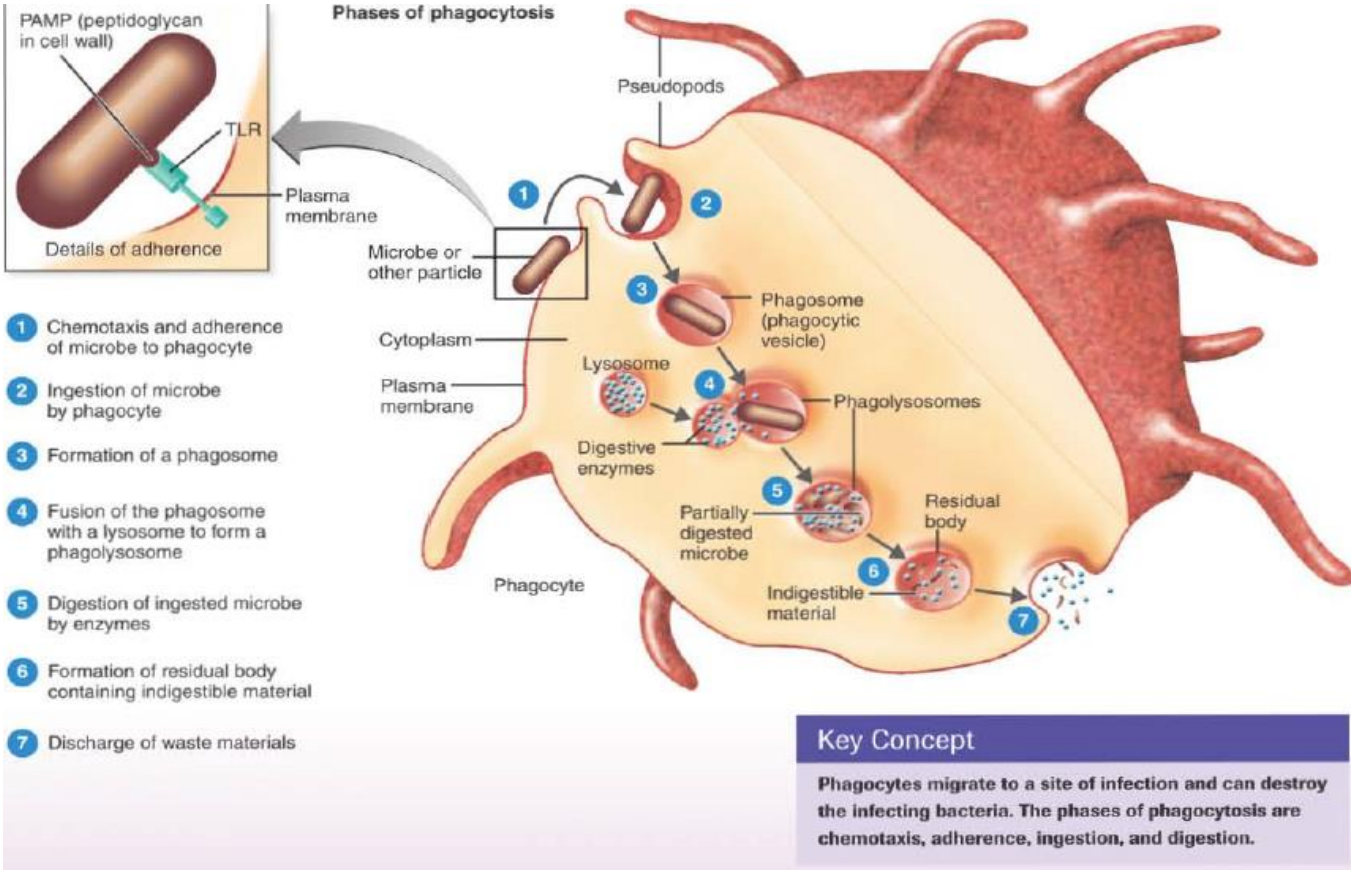
-Oxygen dependent mechanisms

Oxygen is converted to the following products which kill the microbe:

Lysosomes also contain enzymes that can produce toxic oxygen products such as superoxide radical (O^{2-}) , hydrogen peroxide (H_2O_2), nitric oxide (NO), singlet oxygen, and hydroxyl radical ($OH\cdot$)

-Non oxygen dependent mechanisms

The microbe is killed by many hydrolytic and proteolytic enzymes such as lysozyme which hydrolyzed peptidoglycan in bacterial cell walls. A variety of other enzymes, such as lipases, proteases, ribonuclease, and deoxy ribonuclease, hydrolyze other macromolecular components of microorganisms.



Microbial Evasion of Phagocytosis

The ability of a pathogen to cause disease is related to its ability to evade phagocytosis. Some bacteria have structures that inhibit adherence, such as the M protein and capsules.

- M protein of *Streptococcus pyogenes* inhibits the attachment of phagocytes to their surfaces and makes adherence more difficult.

-Organisms with large **capsules** include *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. Heavily encapsulated microorganisms like these can be phagocytized only if the phagocyte traps the microorganism against a rough surface, such as a blood vessel, blood dot, or connective tissue fiber, from which the microbe cannot slide away.

Other microbes may be ingested but not killed. For example, *Staphylococcus* produces leucocidins that may kill phagocytes by causing the release of the phagocyte's own lysosomal enzymes into its cytoplasm. Streptolysin released by streptococci has a similar mechanism.
A number of intracellular pathogens secrete pore-forming toxins that lyse phagocyte cell membranes once inside the phagocyte. For example, *Trypanosoma cruzi* (the causative agent of American trypanosomiasis), and *Listeria monocytogenes* (the causative agent of listeriosis), produce membrane attack complexes that lyse phagolysosome membranes and release the microbes into the cytoplasm of the phagocyte, where they propagate.
Still other microbes have the ability to survive inside phagocytes. *Coxiella burnetii,* the causative agent of Q fever, actually requires the low pH inside a phagolysosome to replicate.

Listeria monocytogenes, Shigella (the causative agent of shigellosis), and *Rickettsia* (the causative agent of Rocky Mountain spotted fever and typhus) have the ability to escape from a phagosome before it fuses with a lysosome.

- Biofilms also play a role in evading phagocytes. Bacteria that are part of biofilms are much more resistant to phagocytosis because the phagocytes can not detach bacteria from the biofilm prior to phagocytosis.