(Immunology)---- Lec # 1

Part (1): Basic Immunology
Part (2): Clinical Immunology

Basic : Introduction to Immunology

- **Immunology** is the study of physiological mechanisms that humans and other animals use to defend their bodies from invading organisms.

- **Immunity:** Is the body's ability to fight off harmful micro-organisms- PATHOGENS- that invade it. The immune system produces antibodies or cells that can deactivate pathogens.

- **The immune system** is a network of **cells, tissues,** and **organs** that work together to defend the body against attacks by "foreign" invaders.

. These foreign invaders are primarily microbes- tiny organisms such as bacteria, parasites, and fungi that can cause infections. Viruses also cause infections, but are too primitive to be classified as living organisms.

. The human body provides an ideal environment for many microbes. It is the immune system's job to keep them out or, failing that, to seek out and destroy them.

To understanding the **immunology**, in this and the next lectures, you need to understand the basic features of **normal immune responses** and **immune-mediated diseases**. I will discuss how the immune system fights microbes and how its abnormalities cause a variety of diseases. So, you need to know the following:

I- The Normal Immune Response
II- How The Immune System Causes Disease?

Cells of the immune system:

Neutrophils, Lymphocytes, Monocytes/Macrophage, Dendritic Cells, Mast Cells, Eosinophils, Basophils and Other Blood Cells: Megakaryocytes and Erythrocytes.

Organs of the Immune System: The immune system consists of a network of lymphatic organs, tissues, and cells. These structures are supported by the reticuloendothelial system: loose connective tissue with a network of reticular fibers. Phagocytic cells, including monocytes and macrophages, are located in the reticular connective tissue. When micro-organisms invade the body, or the body encounters antigens (**such as pollen**), antigens are transported to the lymph. Lymph is carried through the lymph vessels to regional lymph nodes. In the lymph nodes, the macrophages and dendritic cells phagocytose the antigens, process them, and present the antigens to lymphocytes, which can then start producing antibodies or serve as memory cells.

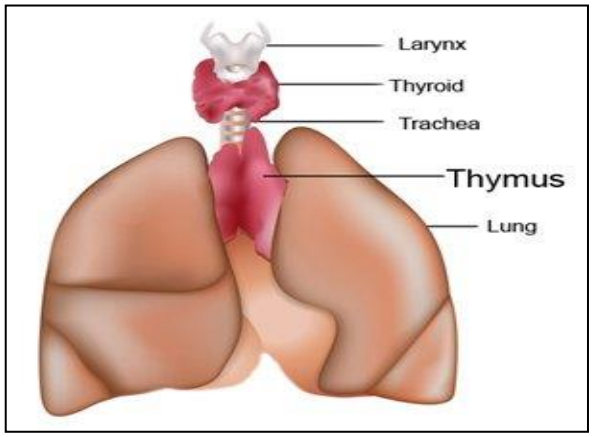
There are two groups of immune system organs.

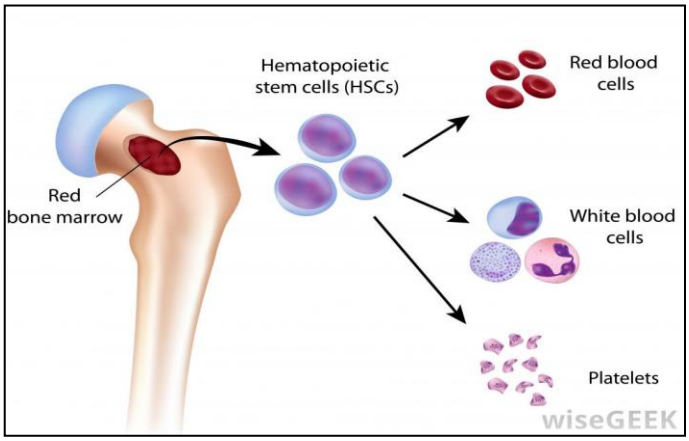
- **Primary Lymphatic Organs** (Central)-- organs where ***immature*** **lymphocytes** develop
  - Thymus
  - Bone marrow

Red bone marrow, the soft, spongy, nutrient rich tissue in the cavities of certain long bones, is the organ that is the site of blood cell production. Some of the white blood cells produced in the marrow are: neutrophils, basophils, eosinophils, monocytes, and lymphocytes. Lymphocytes differentiate into B lymphocytes and T lymphocytes. Red bone marrow is also the site of maturation of **B lymphocytes**. T lymphocytes mature in the **thymus**.

Thymus Gland: The thymus gland is located in the upper thoracic cavity posterior to the sternum and anterior to the ascending aorta. The thymus is an organ that is more active in children, and shrinks as we get older. Connective tissue separates

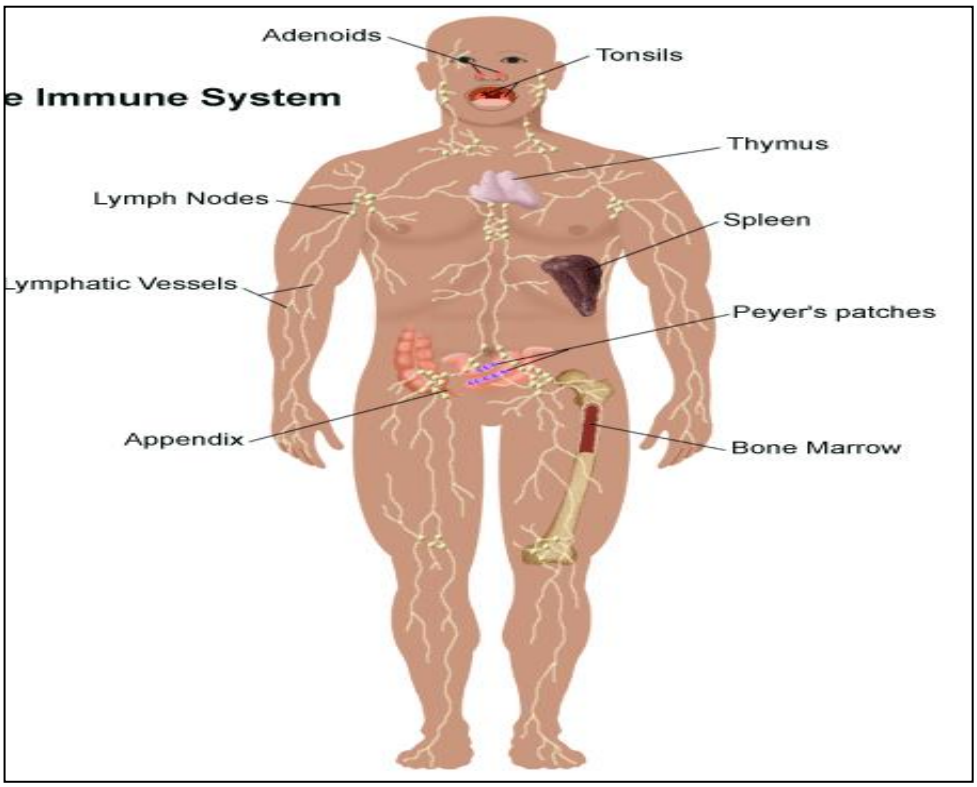
the thymus into lobules, which contain lymphocytes. **Thymic** hormones such as **thymosin** are produced in the thymus gland. Thymosin is thought to aid in the maturation of T lymphocytes. **The Thymus** is critical to the immune system. Without a thymus, a person has no ability to reject foreign substances, blood lymphocyte level is very poor, and the body's response to most antigens is either absent or very weak Immature T lymphocytes travel from the bone marrow through the bloodstream to reach the thymus. Here they mature and for the most part, stay in the thymus.





Secondary Lymphatic Organs (**Peripheral**)-- tissues where antigen is localized so that it can be effectively exposed to ***mature*** **lymphocytes**. The secondary lymphatic organs also play an important role in the immune system as they are places where lymphocytes find and bind with antigens This is followed by the proliferation and activation of lymphocytes.

- Lymph nodes
- Appendix
- Peyer's Patches (of GI tract)
- Tonsils
- Adenoids
- Spleen
- MALT (**M**ucosal-**A**ssociated **L**ymphoid **T**issue)



The spleen, The spleen is a ductless, vertebrate gland that is closely associated with the circulatory system, where it functions in the destruction of old red blood cells in holding a reservoir of blood. located in the upper left region of the abdominal cavity, is divided into partial compartments. Each compartment contains tissue known as **white pulp** and **red pulp**. The white pulp contains **lymphocytes** and the red pulp acts in blood filtration. When blood enters the spleen and flows through the sinuses for filtration, lymphocytes react to pathogens, macrophages engulf debris, and also remove old, worn out red blood cells. A person **without** a spleen is more susceptible to infections and may need supplementary antibiotic therapy for the rest of their life.

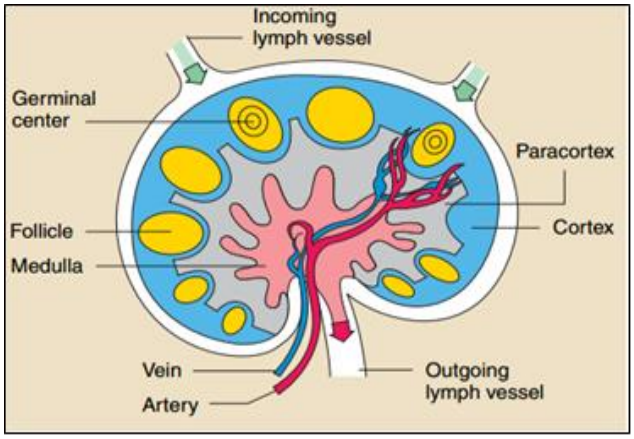
Lymph Nodes: are small oval shaped structures located along the lymphatic vessels. They are about 1-25 mm in diameter. Lymph nodes act as filters, with an internal honeycomb of connective tissue filled with lymphocytes that collect and destroy bacteria and viruses. They are divided into compartments, each packed with B lymphocytes and a sinus. As lymph flows through the sinuses, it is filtered by macrophages whose function is to engulf pathogens and debris. Also present in the sinuses are T lymphocytes, whose functions are to fight infections and attack cancer cells. Lymph nodes are in each cavity of the body except the dorsal cavity.

Physicians can often detect the body's reaction to infection by feeling for swollen, tender lymph nodes under the arm pits and in the neck, because when the body is fighting an infection, these lymphocytes multiply rapidly and produce a characteristic swelling of the lymph nodes.

The **lymph node** contains numerous specialized structures.

T cells concentrate in the paracortex.

B cells in and around the germinal centers, and **plasma cells** in the medulla.



Types of Immunity

There are two types of immune response: innate and adaptive body defenses

I. A variety of cells and structures work together to protect the human body from bacterial, fungal, parasite and viral infection. This resistance to disease (also known as immunity) allows the body to maintain its health.

A. There are two primary defense systems in the body that work both independently and cooperatively to provide resistance to disease.

Those two systems are:

1. **The Innate (Non-specific) System**
2. **The Adaptive (Specific) System**

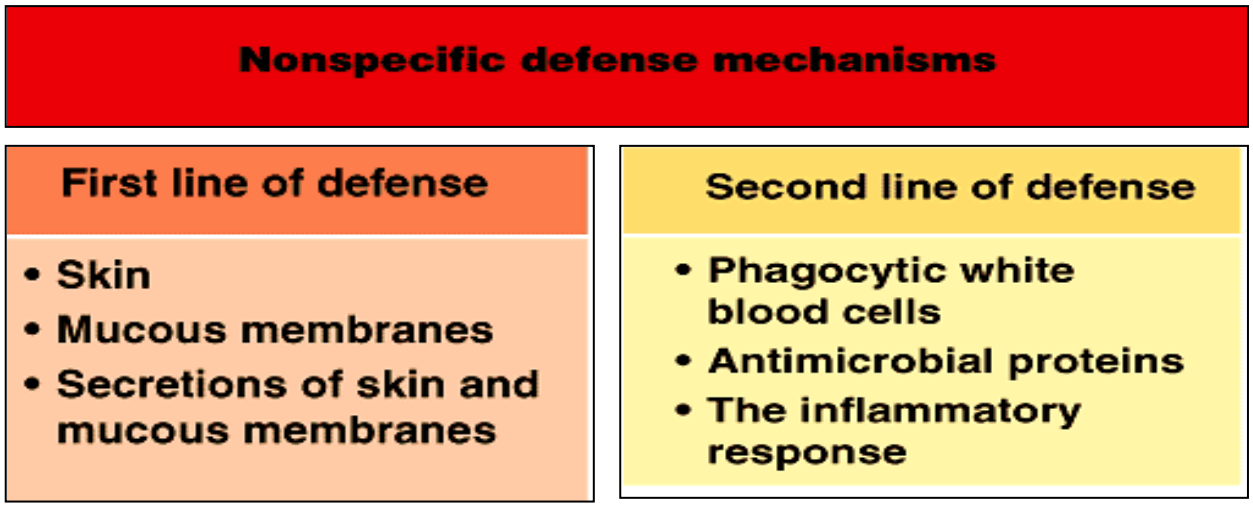
B. The immune system is considered to be a ***functional system*** instead of an organ system. It is composed of chemicals and trillions of immune cells that inhabit lymphoid tissue and circulate in body fluids. When functioning properly, this system protects the body from infectious microorganisms and cancer cells.

Defense Mechanisms:

1. External defense
2. Internal Defense
3. Immune Defense

II. <u>INNATE (NON-SPECIFIC) DEFENSES</u>-this system responds quickly to protect the body from pathogens and infection.

A. There are <u>two major lines: first and second line of defense that make up the Innate Defensive System</u>:



1. <u>Surface barriers or external body membranes</u> which prevent the penetration of pathogens into the body. These barriers can produce a number of chemicals that provide protection for the body (acids, enzymes, mucin, defensins).

2. <u>Inflammation</u>-which includes a variety of proteins, cells and phagocytes which work together to prevent the spread of pathogens throughout the body. Any break in the skin will allow bacteria to enter the body. These foreign microbes will cause swelling and reddening at the site of injury. This reaction by the body is called an inflammatory reaction or inflammatory response.

B. <u>Surface Barriers: Skin and Mucosae</u>:

1. This system works well as long as the thick keratinized epithelial tissue of the skin is not broken.
a. The thick protein **<u>keratin</u>** is also resistant to the acids and bases secreted by most bacteria. Recall that this protein is abundant in the skin.

2. **Mucous Membranes** line body cavities that open directly to the outside of the body.

Specific functions of mucous membranes in innate body defense include:

(Mechanical & Chemical defenses):

a. Saliva, mucus, nose hair, ciliary escalator: Serving as sticky surfaces to trap microorganisms before they enter body systems (such as the digestive and respiratory systems).
b. Some membranes secrete chemicals that are toxic to some bacteria. For example the skin secretes **sebum** which kills some bacteria.
c. Mucosa in the stomach secrete **hydrochloric acid** and **protein-digesting** enzymes, both of which act to kill microorganisms.
d. Saliva cleanses the oral cavity and teeth.
e. **Lysozyme** is secreted onto the surface of the eye. This enzyme functions by destroying bacteria. **Lacrimal apparatus:** Continual washing and blinking prevents microbes from settling on the eye surface.
f. Vaginal secretions: Remove microbes from genital tract.
g. Transferrin: Iron-binding proteins in blood which inhibit bacterial growth by reducing available iron.

3. On occasion, the various membranes of the body are nicked, scratched and cut. When this occurs, microbes can invade deeper into the human body. At this point, the internal innate defenses take over to fight off the invaders.

C. There are a number of **internal innate defenses** that help to fight off invading microorganisms. These include phagocytic cells, natural killer cells, antimicrobial proteins, fever and inflammation.

D. Cells and Chemicals Involved In **Internal** Innate Defense

1. **Phagocytes**-cells that feed on and destroy invading microorganisms.

a. Types of Phagocytic Cells

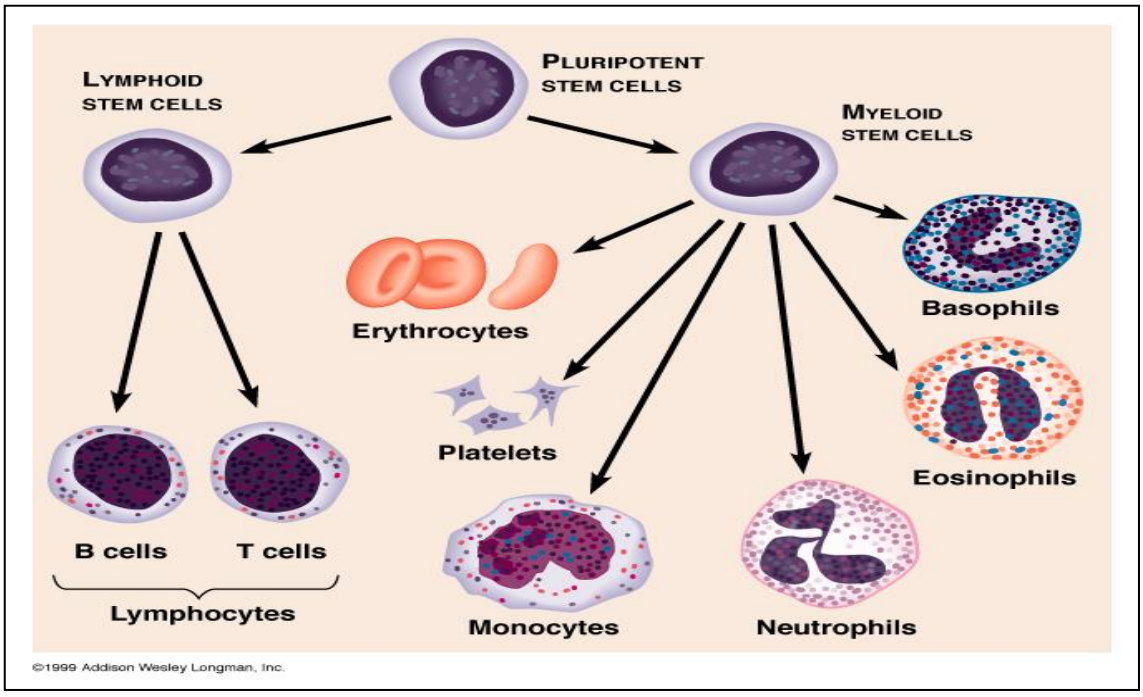
1) **Macrophages**-primary phagocytes in the body. These are derived from leukocytes known as monocytes which leave the bloodstream, enter tissues and develop into macrophages.

2) Neutrophils- most abundant type of leukocyte in the body, these become phagocytic upon encountering infectious materials in the body.

3) Eosinophils- another type of leukocyte in the body, these can be phagocytic but they are best known for fighting parasitic worms.

4) Free Macrophages- can move throughout the body searching for and destroying foreign invaders. Alveolar macrophages in the lungs are examples of free macrophages.

5) Fixed Macrophages- are permanent residents of specific organs in the body. Kupffer Cells in the liver and microglia in the brain are examples of fixed macrophages.



b. Events That Occur In Phagocytosis

1) **Adherence**- the phagocyte adheres to the pathogen. This is accomplished when the phagocyte recognizes either the protein or carbohydrate signature of the pathogen.

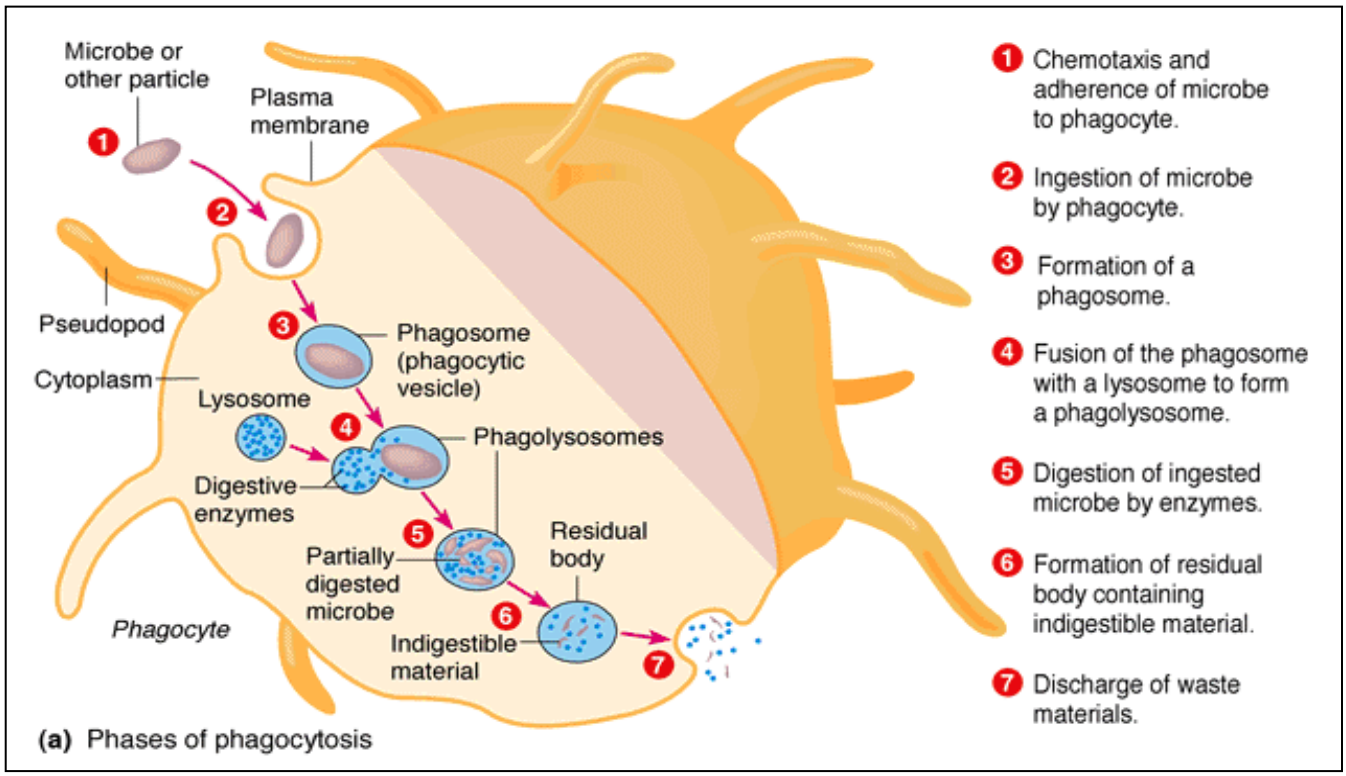
a) **Opsonization**- process in which proteins and antibodies coat the outer covering around a pathogen. This provides "handles" for the phagocyte to attach to; thus increasing the efficiency of phagocytosis.

2) Phagocytosis of the pathogen: **Stages of Phagocytosis**

1- Ingestion: Plasma membrane of phagocytes extends projections (pseudopods) which engulf the microbe. Microbe is enclosed in a sac called phagosome.

2- Digestion: Inside the cell, phagosome fuses with lysosome to form a phagolysosome.
Lysosomal enzymes kill most bacteria within 30 minutes and include:
Lysozyme: Destroys cell wall peptidoglycan
Lipases and Proteases
RNAses and DNAses
After digestion, residual body with undigestable material is discharged.

Process of Phagocytosis



2. Natural Killer Cells- cells in the blood and lymph that can lyse and kill cancer cells and virus-infected cells before the adaptive immune response is initiated.

a. These are not specific and they develop from granular leukocytes.
b. Again, proteins on the specific cell identify those cells for the natural killer cells.

c. These destroy cells by releasing chemicals known as **perforins** which destroy the nucleus of cells (Killer Cells are not phagocytic). Natural killer cells are not phagocytic.

D. Inflammation

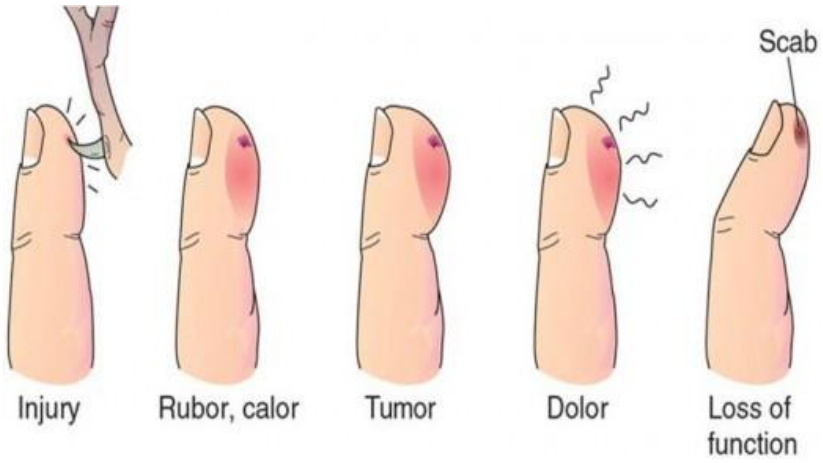
The inflammatory response is initiated when body tissues are injured. The primary goal of inflammation is to clear the injured area of pathogens, dead cells and any other debris so that tissue repair can begin.

2. Benefits of Inflammation:

a. Prevents the spread of damaging agents into the body.
b. Removes cell debris and pathogens
c. Sets the stage for repair.
d. Turns on the adaptive immune system

3. Events in Inflammation: Swelling, redness, heat, and pain:

Inflammation is characterized by the following quintet: swelling (tumor), redness (rubor), heat (calor), pain (dolor) and dysfunction of the organs. When an injury occurs, a capillary and several tissue cells are apt to rupture, releasing **histamine** and **kinins** and **prostaglandins**. These cause the capillaries to dilate, become more permeable, and leak fluid into these tissues. Dilation and fluid leaking into the tissues causes swelling, redness, and heat. The swelling and kinins stimulate nerve endings, causing pain. If there has been a break in the skin due to the injury, invading microbes may enter. A common cause of inflammation after surgery is serous fluid. This is a mixture of plasma, lymph and interstitial fluids .seeping from the damaged cells and vessels. If enough serous fluid accumulates a mass called a seroma may form. Treatment of a seroma may involve the removal of the fluid with a needle into a syringe, a process called aspiration.



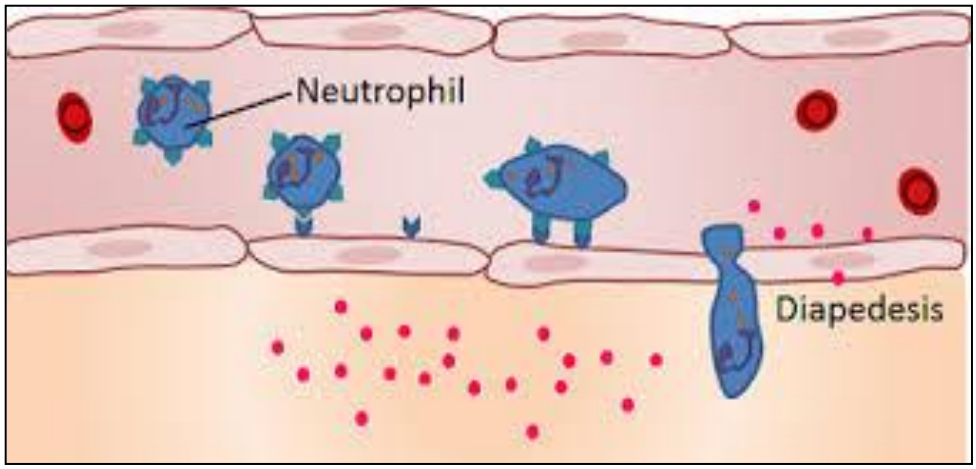
Beta defensing: are often released in the injury site during inflammation. These antibiotic type agents function by fighting bacterial growth. A number of phagocytic cells move into the injured area during inflammation.

What Mobilizes Phagocytic Cells During Inflammation?

a. Leukocytosis- the release of phagocytic cells (especially neutrophils) into blood vessels. Within hours, these cells are transported to the site of injury. This is triggered by leukocytosis-inducing factors.

b. Diapedesis- the movement of neutrophils through the walls of capillaries into the site of inflammation.

c. In severely damaged areas, **pus** (mixture of dead neutrophils, broken down tissue cells, dead pathogens) may accumulate. If this material is not removed, it may be walled off by collagen fibers; thus forming an **abscess** that has to be surgically removed.



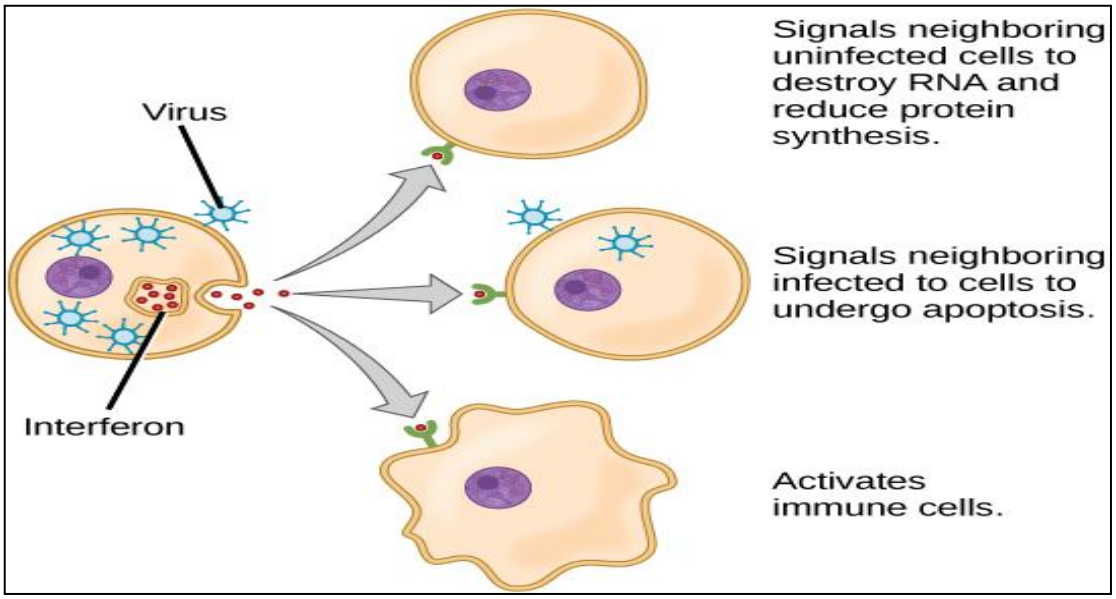
E. Antimicrobial Proteins- attack microbes directly or they limit the ability of microbes to reproduce.

Types of antimicrobial proteins include:

1. Interferons- proteins secreted by some cells that are infected by viruses. These proteins stimulate healthy cells to produce a protein known as PKR which functions by preventing viruses from undergoing protein synthesis.

Interferon in response to viral infection:

Interferon (IFNs) is naturally occurring **glycoproteins** involved in non-specific immune responses. Interferons do just as their name states they "interfere" with viral growth. **Interferons** are initiated from a cell that has been infected by a virus. When a cell has been infected by a virus the virus will then cause the cell to make viral nucleic acid. This nucleic acid acts as a signal and it causes the cell to realize that it has been infected with a virus. So the cell will start making and sending out interferons. The IFN's that the cell sends out go to nearby healthy cells and warns them of a virus. The healthy cells then start intracellular changes that help the cells to be more resistant to the virus.



2. Complement System- this refers to a group of plasma proteins that circulate through the blood in an inactive state. These proteins are activated by the immune response itself.

a. These proteins destroy cells via **cell lysis.**
b. Complement is activated via 3 primary pathways:

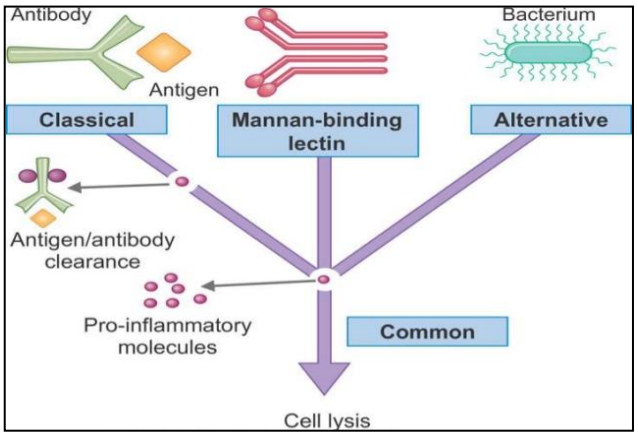
1) The Classical Pathway-involves the formation of antibodies to destroy invading microbes.
2) The Alternative Pathway-occurs when certain complement proteins are triggered by polysaccharides on the membranes of invading microorganisms.

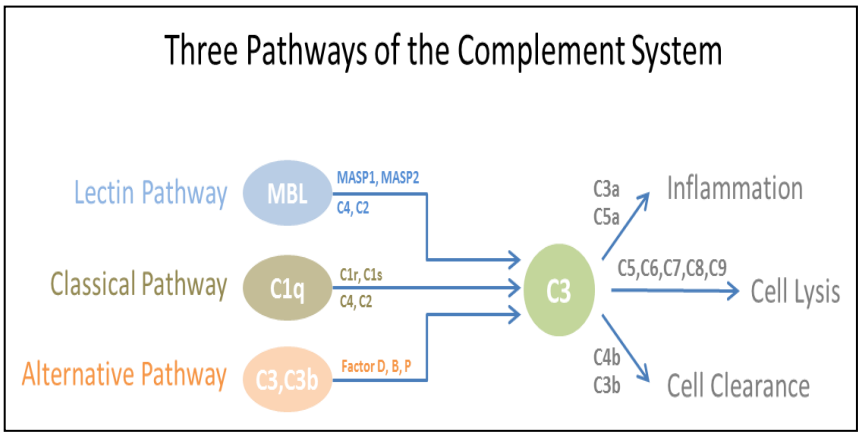
3) <u>The Lectin Pathway</u>-involves the release of proteins known as **lectins** that attach to foreign invaders, thus triggering complement Proteins.

Complement System: Is a biochemical cascade of the immune system that helps clear pathogens from an organism, and promote healing. It is derived from many **<u>small plasma proteins</u>** that work together to form the primary end result of <u>cytolysis by disrupting the target cell's plasma membrane</u>.

Complement is activated by <u>antigen-antibody complexes</u> and causes holes to form in the plasma membrane of foreign microbes or cells (**lysis**). The complement system <u>is considered a nonspecific defense</u>, but it can be activated against specific microbes that have been <u>marked with antibodies</u>.

Hemolytic transfusion reactions are caused by complement activation after a person expresses antibodies against the antigens found on the inappropriately donated blood. **Hemolytic Disease of the Newborn** (HDN) is due to maternal antibodies against the Rh factor crossing the placenta, binding to the baby's red blood cells, and stimulating the baby's own complement system to lyse its red blood cells.





G. <u>Fever</u> - abnormally high body temperature. This is another defense against infection.

<u>1.</u> Recall that the hypothalamus regulates body temperature. In response to microbial invasion, leukocytes and macrophages secrete chemicals known as **<u>pyrogens</u>** which initiate the hypothalamus to raise body temperature.

<u>2.</u> Mild fever appears to have a positive effect on the body since it:

a. Reduces release of certain nutrients by the liver and spleen (Microbes require these nutrients to grow and multiply).
b. Increases metabolism; thus increasing repair processes.

3. Extreme fever can be dangerous since it denatures enzymes.

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