Unit 1: Lymphatic System & Immunity

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Essential Questions:

- How do nonspecific and specific body defenses keep the human body healthy?
- How does the lymphatic system function in maintaining homeostasis?
- What is the difference between vaccines and antibiotics?

Unit Objectives:

- Describe the anatomy of the lymphatic system
- Describe the structure and function of lymph nodes, thymus and spleen
- Explain the basic functions of the human immune system
- Compare and contrast specific and nonspecific immune responses
- Compare and contrast innate and adaptive immunity
- Describe the role of vaccines in acquired immunity

Unit Vocabulary:

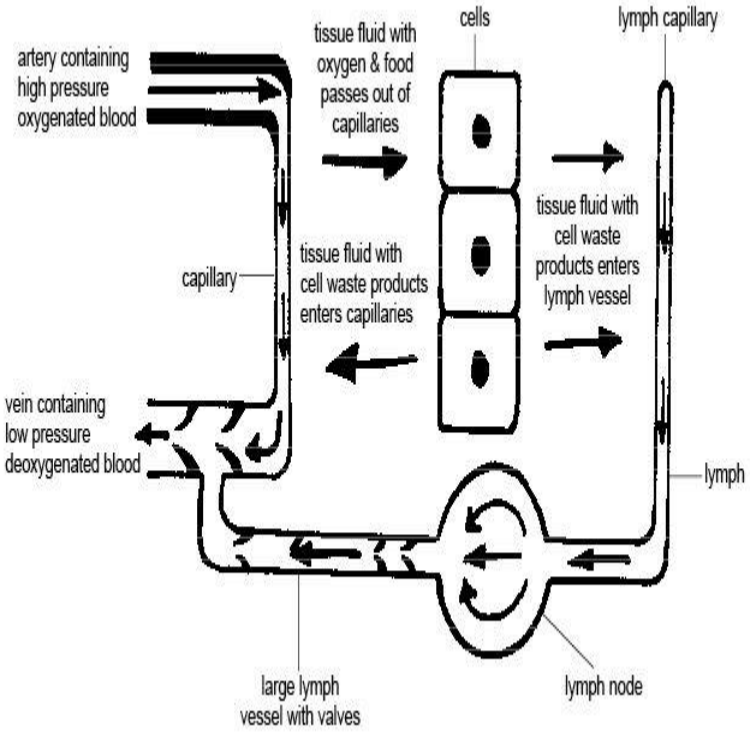
Edema
Lymph
Immunity
Inflammatory response
Pyrogens
Antigen
Antibody
T cell
B cell
Humoral
Adaptive
Innate
Vaccine
Lymph nodes
Thymus
Spleen
Interferon
Natural killer cells
Phagocytosis
Plasma cells

Lesson 1: Lymphatic pathways

Objective:

- Identify the locations of major lymphatic pathways
- Explain how lymphatic circulation is maintained
- Describe the structure and function of lymph nodes, thymus and spleen

The **lymphatic system** consists of **lymphatic vessels**, **lymph**, **lymphoid tissues and organs**. **Lymph** originates in the peripheral tissues and is delivered to the venous system. Lymph consists of **interstitial fluid**, **lymphocytes** and **macrophages**. It has a number of roles. The lymphatic system produces, maintains, and distributes lymphocytes. Primary lymphoid structures contain stem cells that differentiate into B, T, and NK cells and include **bone marrow** and **thymus**. Secondary lymphoid structures are organs or tissue where activated lymphocytes divide to produce additional lymphocytes of the same type. **Lymph nodes** and **tonsils** are examples of secondary lymphoid structures. The lymphatic system also helps to maintain normal blood volume and eliminate variation in chemical composition of interstitial fluid. Fluid continually leaks from the systemic capillary beds. The net movement of fluid out of the systemic circulation is approximately 72% of blood volume per day. The lymphatic system returns this fluid to the circulation and in the process helps to even out local variation in the composition of interstitial fluid. Lastly the lymphatic system provides an alternative route for the transport of hormones, nutrients and waste. Lipids absorbed by the small intestines is absorbed and carried to the circulation by lymphatic vessels called **lacteals.**

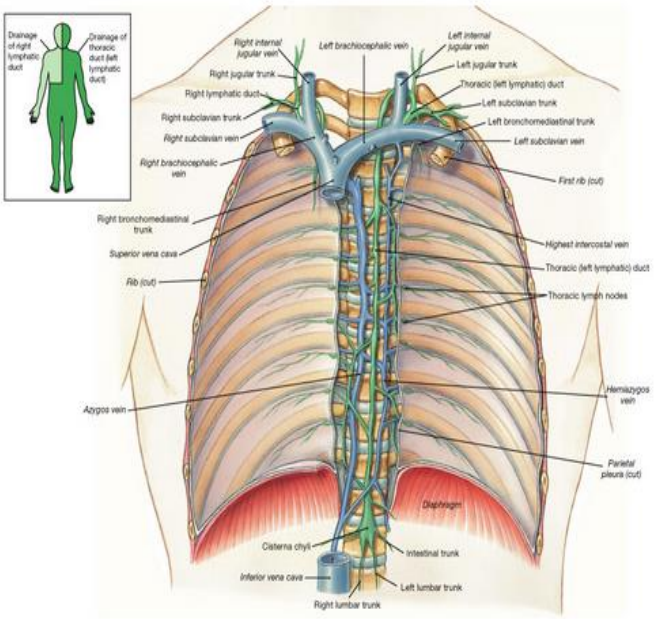


Structure of Lymphatic Vessels

The lymphatic system is an active pumping system driven by segments that have a function similar to peristalsis. They lack a central pump (like the heart in the cardio vascular system), so smooth muscle tissue contracts to move lymph along through the vessels. Skeletal muscle contractions also move lymph through the vessels. The lymphatic vessels make their way to the lymph nodes, and from there the vessels form into trunks. In general, the lymph vessels bring lymph fluid toward the heart and above it to the subclavian veins, which enable lymph fluid to re-enter the circulatory system through the vena cava.

Lymphatic vessels, also called **lymphatics,** range in size from lymphatic capillaries to large diameter lymphatic ducts. **Lymphatic capillaries,** also known as **terminal lymphatics,** consists of a complex of blind-ended, small diameter vessels that collect the lymph in the peripheral tissues. Fluid and larger particulate matter, including viruses and bacteria, enter these capillaries between overlapping endothelial cells that act as one-way valves. Interstitial fluid in this way is constantly monitored. From the lymphatic capillaries lymph flows into larger and large vessels as they go toward the **lymphatic trunks** that deliver the blood to the venous system. Pressure within these larger vessels is small and the larger vessels have one-way valves that insure that fluid flows in the right direction. Fluid movement in these vessels is aided by skeletal muscle contraction, respiratory movements that produce pressure gradients and contraction of smooth muscle in the walls of the larger vessels.

If the flow of lymph in these lymphatic vessels slows or is blocked, the interstitial fluid is not drained from the tissue and the tissue becomes distended and swollen. This condition is called **lymphedema.**



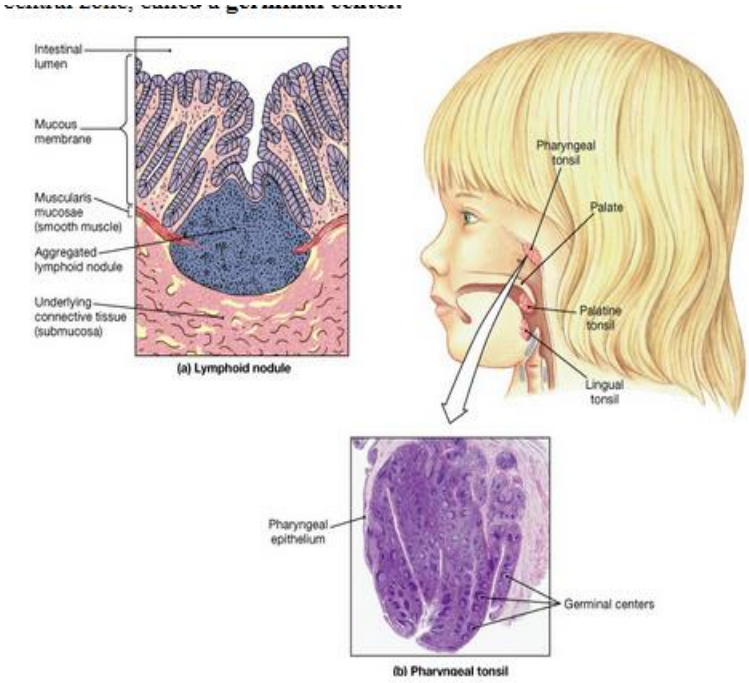
Lymphatic vessels are most densely distributed near **lymph nodes**: bundles of lymphoid tissue that filter the lymph fluid of pathogens and abnormal molecules. Adaptive immune responses usually develop within lymphatic vessels. Large lymphatic vessels can be broadly characterized into two categories based on lymph node distribution.

- **Afferent lymphatic vessels** flow into a lymph node and carry unfiltered lymph fluid.
- **Efferent lymphatic vessels** flow out of a lymph node and carry filtered lymph fluid. Lymph vessels that leave the thymus or spleen (which lack afferent vessels) also fall into this category.

Lymph nodes are most densely distributed around the pharynx and neck, chest, armpits, groin, and around the intestines. Afferent and efferent lymph vessels are also most concentrated in these areas, so they can filter lymph fluid close to the end of the lymphatic system, where fluid is returned into the cardiovascular system. Conversely, lymph nodes are not found in the areas of the upper **central nervous system**, where tissue drains into **cerebrospinal fluid** instead of lymph, though there are some lymph vessels in the meninges. There are few lymph nodes at the ends of the limbs. The efferent lymph vessels in the left and lower side of the body drain into the left subclavian vein through the **thoracic duct,** while the efferent lymph vessels of the right side of the body drain into the right subclavian vein through the **right lymphatic duct**.

Lymphoid Tissue

Lymphoid tissues are connective tissues dominated by **lymphocytes**. Lymphoid tissues include:



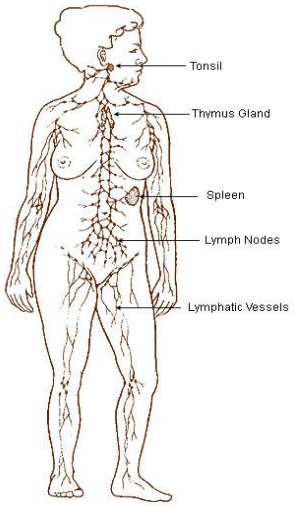
- **Lymphoid nodules**

Lymphoid nodules are dense concentrations of lymphocytes in the **areolar connective tissue** of the mucous membranes. Nodules are not surrounded by fibrous capsules and often have a pale, central zone, called a **germinal center.**

- **Tonsils**

Tonsils are large concentration of lymphoid nodules in the wall of the pharynx. These tonsils include the **pharyngeal tonsil** on the posterior superior wall of the pharynx, **palatine tonsils** on the posterior margin of the oral cavity and the **lingual tonsils** at the base of the tongue.

- **Aggregated lymphoid nodules**

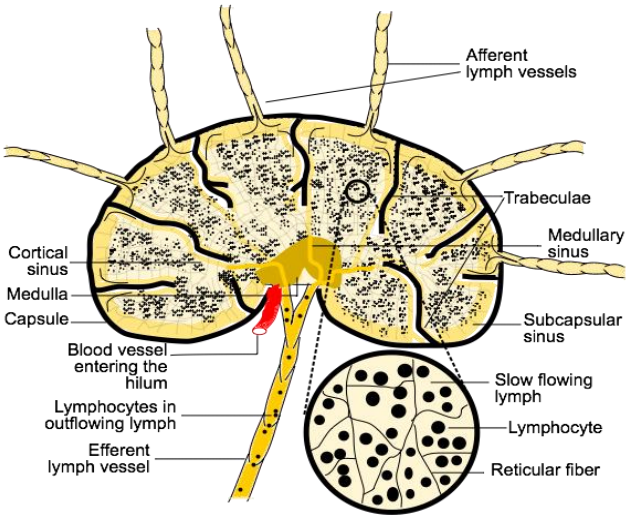


Aggregated lymphoid nodules are found in the small intestines and are called **Peyer's patches**. These are also found in the appendix.

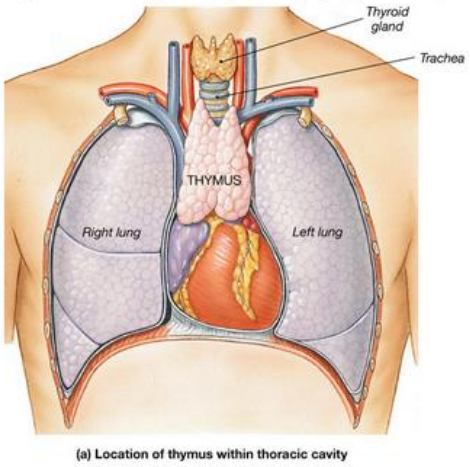
Lymphoid Organs

Lymphoid organs on the other hand are separated from surrounding tissue by a fibrous capsule. Lymphoid organs include:

- **Lymph nodes**



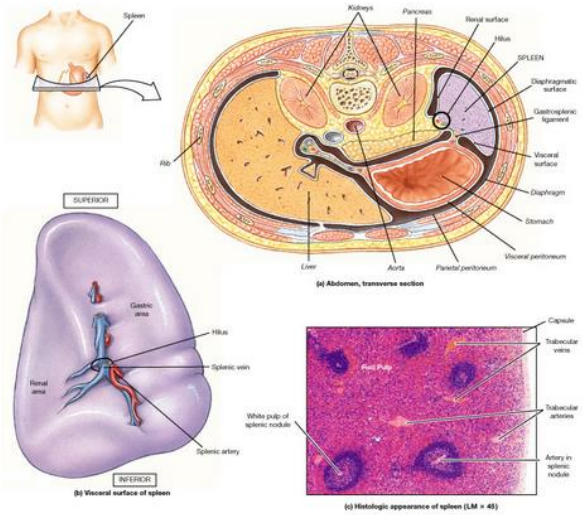
Lymph nodes vary in size from 1 to 25 mm and are designed to filter and purify lymph before it reaches the venous system. Lymph nodes are shaped like lima beans with an indentation called a **hilus**. The hilus is where blood vessels and nerves enter the node. Fibrous extensions from the capsule of the node, called **trabeculae,** extend into the node. The capsule and trabeculae provide support for sinuses that allow lymph to flow through the node. Lymph is delivered to the lymph node by afferent lymphatics and is carried away from the lymph node by efferent lymphatics. The node can be divided into two regions. The outer region of the node, near the fibrous capsule, is called the **cortex.** It contains lymphoid nodules with germinal centers. The **medulla** is deeper inside the node where elongate masses of cells called **medullary cords** are found. The lymph nodes contain a large number of **B and T lymphocytes,** which are transported throughout the node during many components of the **adaptive immune response.** When a lymphocyte is presented with an **antigen** (such as by an activated helper T cell), B cells become activated and migrate to the germinal centers of the node, where they proliferate and **differentiate** to be specific to that antigen. When **antibody-producing B cells** are formed, they migrate to the medullary (central) cords of the node. Stimulation of the lymphocytes by antigens can accelerate the migration process to about ten times normal, resulting in the characteristic swelling of the lymph nodes that is a common symptom of many infections. The lymphocytes are transported through lymph fluid and leave the node through the efferent vessels to travel to other parts of the body to perform adaptive immune response functions.



(a) Location of thymus within thoracic cavity

- **Thymus**

The **thymus** is located posterior to the sternum. The thymus reaches is greatest absolute size at puberty and then gradually decreases in size as the functional cells die and are replaced by fibrous connective tissue. It is an important primary lymphoid organ where lymphocytes mature into **T lymphocytes.**



- **Spleen**

The **spleen** is the largest lymphoid organ in the body. The functions of the spleen include the removal of abnormal red blood cells and other cells by **phagocytosis,** storage of iron from recycled from broken down red blood cells and the initiation of the immune response.

Lesson 2: Innate Immunity

Objective:

- List and describe the nonspecific body defense mechanisms

Every day we are alive, humans encounter potentially harmful disease-causing organisms, or **pathogens**, like bacteria or viruses. Yet most of us are still able to function properly and live life without constantly being sick. That's because the human body requires a multilayered immune system to keep it running smoothly.

Self vs. Non-self: How does the body know?

In order to be effective, the immune system needs to be able to identify which particles are foreign, and which are a part of your body.

- ***Self*** refers to particles, such as proteins and other molecules, that are a part of, or made by, your body. They can be found circulating in your blood or attached to different tissues. Something that is self should not be targeted and destroyed by the immune system. The non-reactivity of the immune system to self-particles is called tolerance.

- ***Non-self*** refers to particles that are not made by your body and are recognized as potentially harmful. These are sometimes called *foreign bodies*. Non-self-particles or bodies can be bacteria, viruses, parasites, pollen, dust, and toxic chemicals. The non-self-particles and foreign bodies that are infectious or pathogenic, like bacteria, viruses, and parasites, make proteins called antigens that allow the human body to know that they intend to cause damage.

- ***Antigens*** are anything that causes an immune response. Antigens can be entire pathogens, like bacteria, viruses, fungi, and parasites, or smaller proteins that pathogens express. Antigens are like a name tag for each pathogen that announce the pathogens' presence to your immune system. Some pathogens are general, whereas others are very specific. A general antigen would announce "I'm dangerous", whereas a specific antigen would announce "I'm a bacterium that will cause an infection in your gastrointestinal tract" or "I'm the influenza virus".

The body possesses many mechanisms that impart **innate (nonspecific) defenses**. The function of these mechanisms are to prevent microorganisms from gaining a foothold in the body and to destroy them if they penetrate to the deeper tissues. **Innate immunity** provides the first line of defense against invading bacteria. The skin and mucous membranes provide physical and chemical barriers to infection. The normal bacterial flora antagonize colonization of body surfaces by nonindigenous bacteria. The internal tissues invariably contain bactericidal substances. The most noteworthy antibacterial substance is the enzyme **lysozyme,** which is present in mucus and all bodily tissues and secretions. If these barriers are penetrated, the body contains cells that respond rapidly to the presence of the invader. These cells include **macrophages** and **neutrophils** that engulf foreign organisms and kill them. Bacterial invasion is also challenged by the activation of **complement** in blood and tissues and the incitement of an **inflammatory process** which has the tendency to focus both the innate and adaptive immune defenses on the site of invasion.

Species resistance

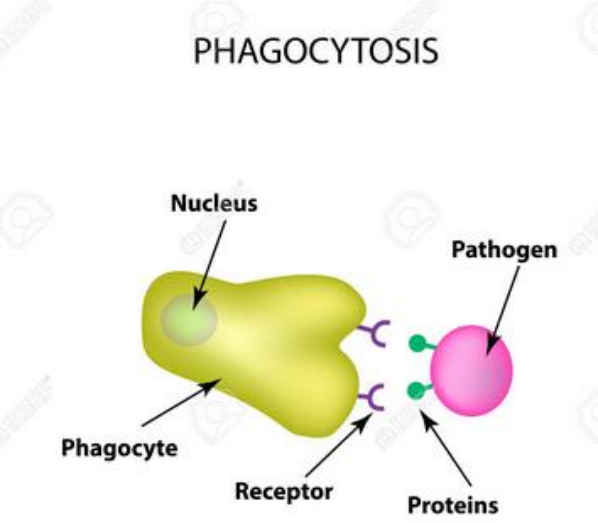
Certain animals are naturally resistant or non-susceptible to certain **pathogens.** Certain pathogens infect only humans, not lower animals, e.g. syphilis, gonorrhea, measles, poliomyelitis. On the other hand, certain pathogens (e.g. canine distemper virus) do not infect humans. *Shigella* infects humans and baboons but not chimpanzees.

Mechanical barriers

Mechanical barriers at the portal of entry represent the first line of defense for the body. These defenses are normally part of the body's anatomy and physiology. The **skin** is a representative example. The outermost layers of skin consist of compacted, cemented cells impregnated with the insoluble protein keratin. The thick top layer is impervious to infection and water. In the unbroken state, it usually is not penetrated by pathogens. The **mucous membranes** of the urinary, respiratory, and digestive tracts are another example. They are moist and permeable, but their fluids, such as tears, mucus, and saliva, rid the membrane of irritants. **Nasal hairs** trap particles in the respiratory tract, and the fluids exert a flushing action. **Cilia** on the cells sweep and trap particles in the respiratory tract, and coughing ejects irritants.

Chemical defenses

Among the nonspecific chemical defenses of the body are the secretions of lubricating glands. The tears and saliva contain the enzyme **lysozyme**, which breaks down the peptidoglycan of the cell wall of Gram-positive bacteria. The **lactic acid** of the vagina imparts defense, and the extremely caustic **hydrochloric acid** of the stomach is a barrier to the intestine. Semen contains the antimicrobial substance**s spermine** that inhibits bacteria in the male urogenital tract. **Lymphocytes** and **fibroblasts** produce hormone like peptides called **interferons** in response to viruses and tumor cells. Once released from the virus-infected cell, interferon binds receptors on uninfected cells, stimulating them to synthesize proteins to block replication of a variety of viruses. They also stimulate phagocytosis and infection resistance in other cells. **Complement** is a group of proteins found in plasma and other body fluids that stimulate inflammation, attracts phagocytes, and enhances phagocytosis.

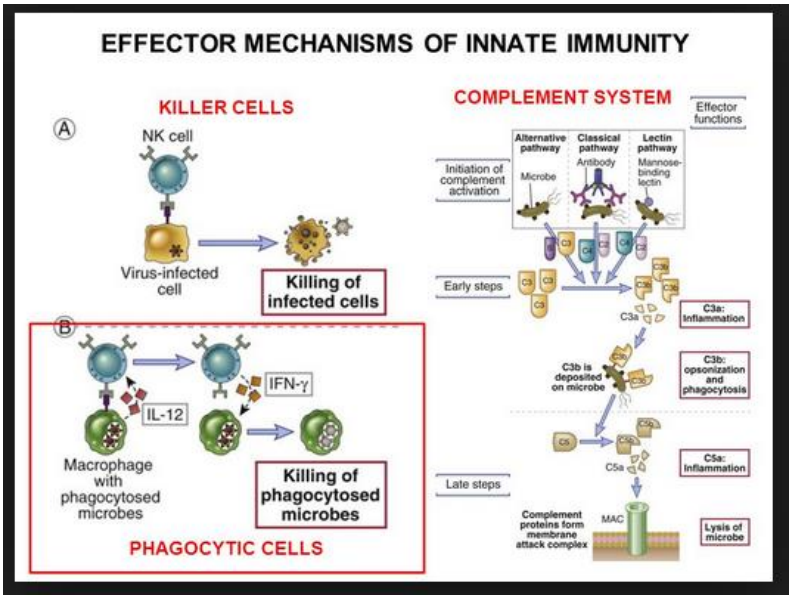


Genetic barriers

The hereditary characteristics of an individual are a deterrent to disease as well. For example, humans suffer HIV infection because their T-lymphocytes have the receptor sites for the human immunodeficiency virus. Dogs, cats, and other animals are immune to this disease because they do not possess the genes for producing the receptor sites. Conversely, humans do not suffer canine distemper because humans lack the appropriate receptor sites for the virus that causes the disease.

Natural Killer NK cells

Natural Killer cells are small population of lymphocytes. They are different from the other lymphocytes that provide specific defense mechanisms. They can defend against various viruses and cancer cells by secreting cytolytic substances called **perforins** that lyse the cell membrane, destroying the infected cells. NK cells also secrete chemicals that enhance inflammation.

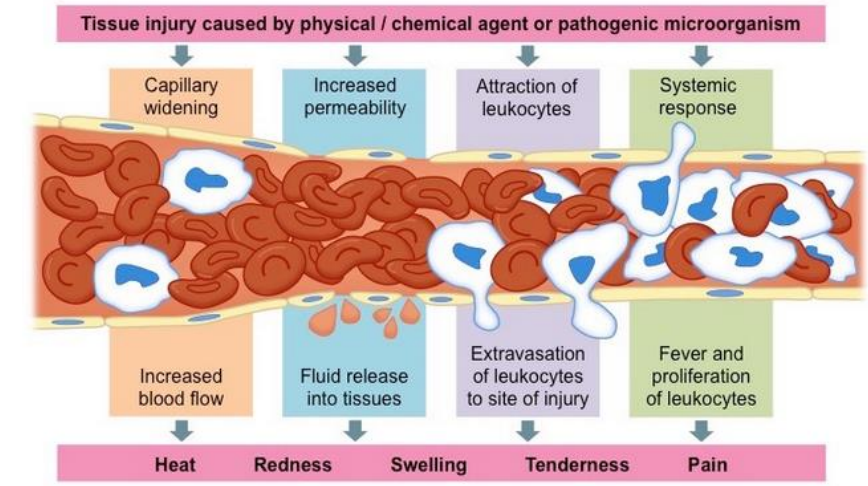


Inflammation

Inflammation is a nonspecific response to any trauma occurring to tissues. It is accompanied by signs and symptoms that include heat, swelling, redness, and pain. Inflammation mobilizes components of the immune system, sets into motion repair mechanisms, and encourages phagocytes to come to the area and destroy any microorganisms present. Inflammation can be controlled by nervous stimulation and chemical substances called **cytokines.** These chemical products of tissue cells and blood cells are responsible for many of the actions of inflammation. The loss of fluid leads to a local swelling called **edema.** In some types of inflammation, phagocytes accumulate in the whitish mass of cells, bacteria, and debris called **pus.**

Fever

Fever is considered a nonspecific defense mechanism because it develops in response to numerous traumas. Fever is initiated by circulating substances called **pyrogens**, which affect the brain's **hypothalamus** and cause the latter to raise the temperature. Although excessive fever can be dangerous, fever is believed to have a beneficial role because it retards the growth of temperature-sensitive microorganisms (for example, leprosy bacilli), and it increases the metabolism of body cells while stimulating the immune reaction and the process of phagocytosis.



Lesson 3: Adaptive Immunity

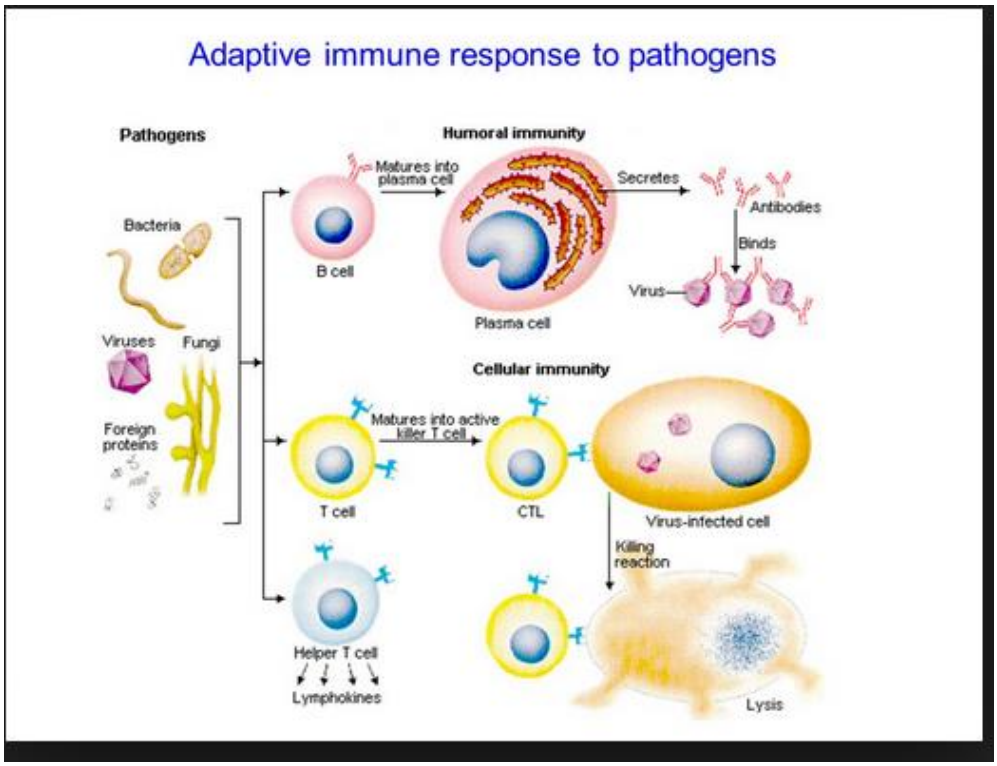
Objective:

- List and describe the specific body defense mechanisms

Have you ever wondered how your recovery time for the common cold, the flu, or small infections seems to get shorter after you've been exposed and successfully recovered the first time? The adaptive immune system, also called ***acquired immunity,*** uses specific antigens to strategically mount an immune response. Unlike the innate immune system, which attacks only based on the identification of general threats, the adaptive immunity is activated by exposure to pathogens, and uses an immunological memory to learn about the threat and enhance the immune response accordingly. The **adaptive immune** response is much slower to respond to threats and infections than the innate immune response, which is primed and ready to fight at all times.

Cells of the adaptive immune system

Unlike the innate immune system, the adaptive immune system relies on fewer types of cells to carry out its tasks: **B cells** and **T cells.** Both B cells and T cells are lymphocytes that are derived from specific types of stem cells, called **multipotent hematopoietic stem cells**, in the bone marrow. After they are made in the bone marrow, they need to mature and become activated. Each type of cell follows different paths to their final, mature forms.



B cells

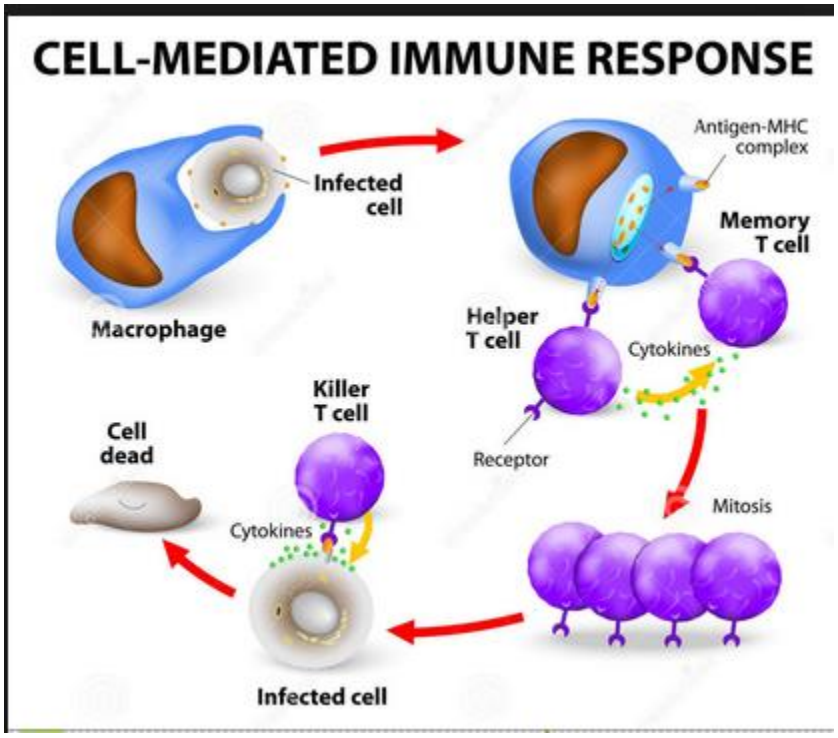
After formation and maturation in the bone marrow (hence the name "B cell"), the naive **B cells** move into the lymphatic system to circulate throughout the body. In the lymphatic system, naive B cells encounter an antigen, which starts the maturation process for the B cell. B cells each have one of millions of distinctive surface antigen-specific receptors that are inherent to the organism's DNA. For example, naive B cells express antibodies on their cell surface, which can also be called **membrane-bound antibodies.**

When a naive B cell encounters an antigen that fits or matches its membrane-bound antibody, it quickly divides in order to become either a **memory B cell** or an **effector B cell,** which is also called a **plasma cell.** Antibodies can bind to antigens directly. The antigen must effectively bind with a naive B cell's membrane-bound antibody in order to set off **differentiation**, or the process of becoming one of the new forms of a B cell. Memory B cells express the same membrane-bound antibody as the original naive B cell, or the "**parent B cell**". Plasma B cells produce the same antibody as the parent B cell, but they aren't membrane bound. Instead, plasma B cells can secrete antibodies. Secreted antibodies work to identify

free pathogens that are circulating throughout the body. When the naive B cell divides and differentiates, both plasma cells and memory B cells are made.

B cells also express a specialized receptor, called the **B cell receptor** *(BCR)*. B cell receptors assist with antigen binding, as well as internalization and processing of the antigen. B cell receptors also play an important role in signaling pathways. After the antigen is internalized and processed, the B cell can initiate signaling pathways, such as cytokine release, 7 to communicate with other cells of the immune system

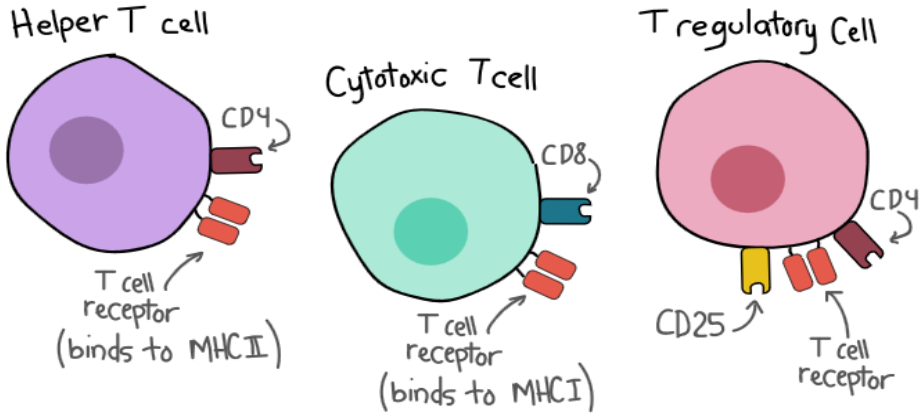
T cells



Once formed in the bone marrow, **T progenitor cells** migrate to the thymus (hence the name "T cell") to mature and become T cells. While in the thymus, the developing T cells start to express **T cell receptors** *(TCRs)* and other receptors called *CD4* and *CD8* receptors. All T cells express T cell receptors, and either CD4 or CD8, not both. So, some T cells will express CD4, and others will express CD8. Unlike antibodies, which can bind to antigens directly, T cell receptors can only recognize antigens that are bound to certain receptor molecules, called **Major Histocompatibility Complex class 1 (MHCI) and class 2 (MHCII)**. These MHC molecules are membrane-bound surface receptors on **antigen-presenting cells,** like dendritic cells and **macrophages**. CD4 and CD8 play a role in T cell recognition and activation by binding to either MHCI or MHCII. T cell receptors have to undergo a process called **rearrangement**, causing the nearly limitless recombination of a gene that expresses T cell receptors. The process of rearrangement allows for a lot of binding diversity. This diversity could potentially lead to accidental attacks against self-cells and molecules because some rearrangement configurations can accidentally mimic a person's self-molecules and proteins. Mature T cells should recognize only foreign antigens combined with self-MHC molecules in order to mount an appropriate immune response.
In order to make sure T cells will perform properly once they have matured and have been released from the thymus, they undergo two selection processes:

1. **Positive** selection ensures MHC restriction by testing the ability of MHCI and MHCII to distinguish between self and nonself proteins. In order to pass the positive selection process, cells must be capable of binding only self-MHC molecules. If these cells bind nonself molecules instead of self-MHC molecules, they fail the positive selection process and are eliminated by apoptosis.
2. **Negative** selection tests for self-tolerance. Negative selection tests the binding capabilities of CD4 and CD8 specifically. The ideal example of self-tolerance is when a T cell will only bind to self-MHC molecules presenting a foreign antigen. If a T cell binds, via CD4 or CD8, a self-MHC molecule that isn't presenting an antigen, or a self-MHC molecule that presenting a self-antigen, it will fail negative selection and be eliminated by **apoptosis.**

These two selection processes are put into place to protect your own cells and tissues against your own immune response. Without these selection processes, autoimmune diseases would be much more common. After positive and negative selection, we are left with three types of mature T cells:

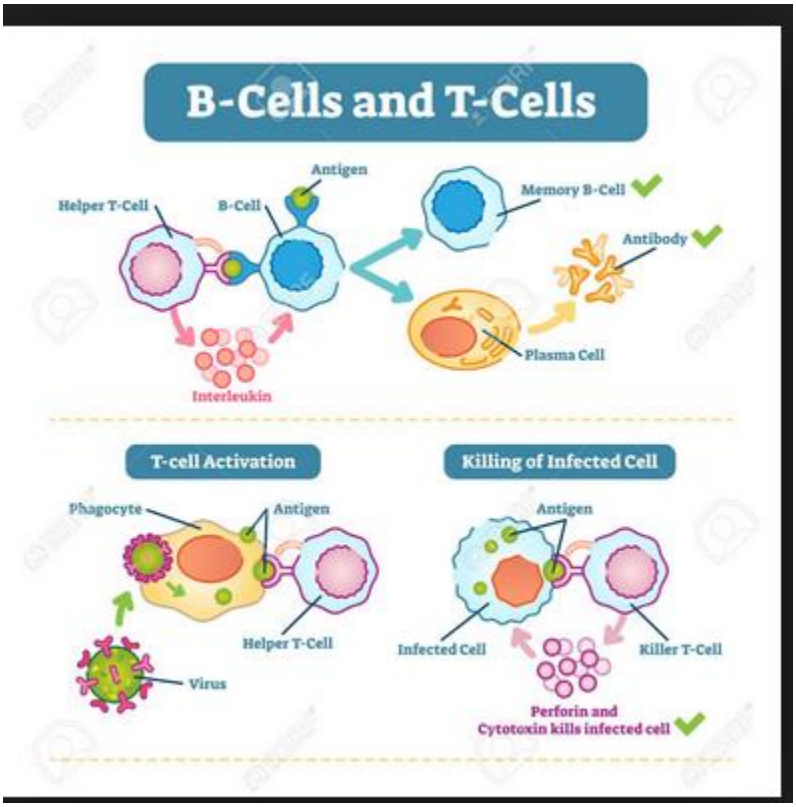


- **Helper T** cells express CD4, and help with the activation of B cells, and other immune cells.
- **Cytotoxic T** cells express CD8 and are responsible for removing pathogens and infected host cells.
- **T regulatory** cells express CD4 and another receptor, called CD25. T regulatory cells help distinguish between self and nonself molecules, and by doing so, reduce the risk of autoimmune diseases.
-

Humoral vs. Cell Mediated Immunity

Immunity refers to the ability of your immune system to defend against infection and disease. There are two types of immunity that the adaptive immune system provides, and they are dependent on the functions of B and T cells, as described above.

Humoral immunity is immunity from serum antibodies produced by plasma cells. More specifically, someone who has never been exposed to a specific disease can gain humoral immunity through administration of antibodies from someone who has been exposed and survived the same disease. "Humoral" refers to the bodily fluids where these free-floating serum antibodies bind to antigens and assist with elimination.



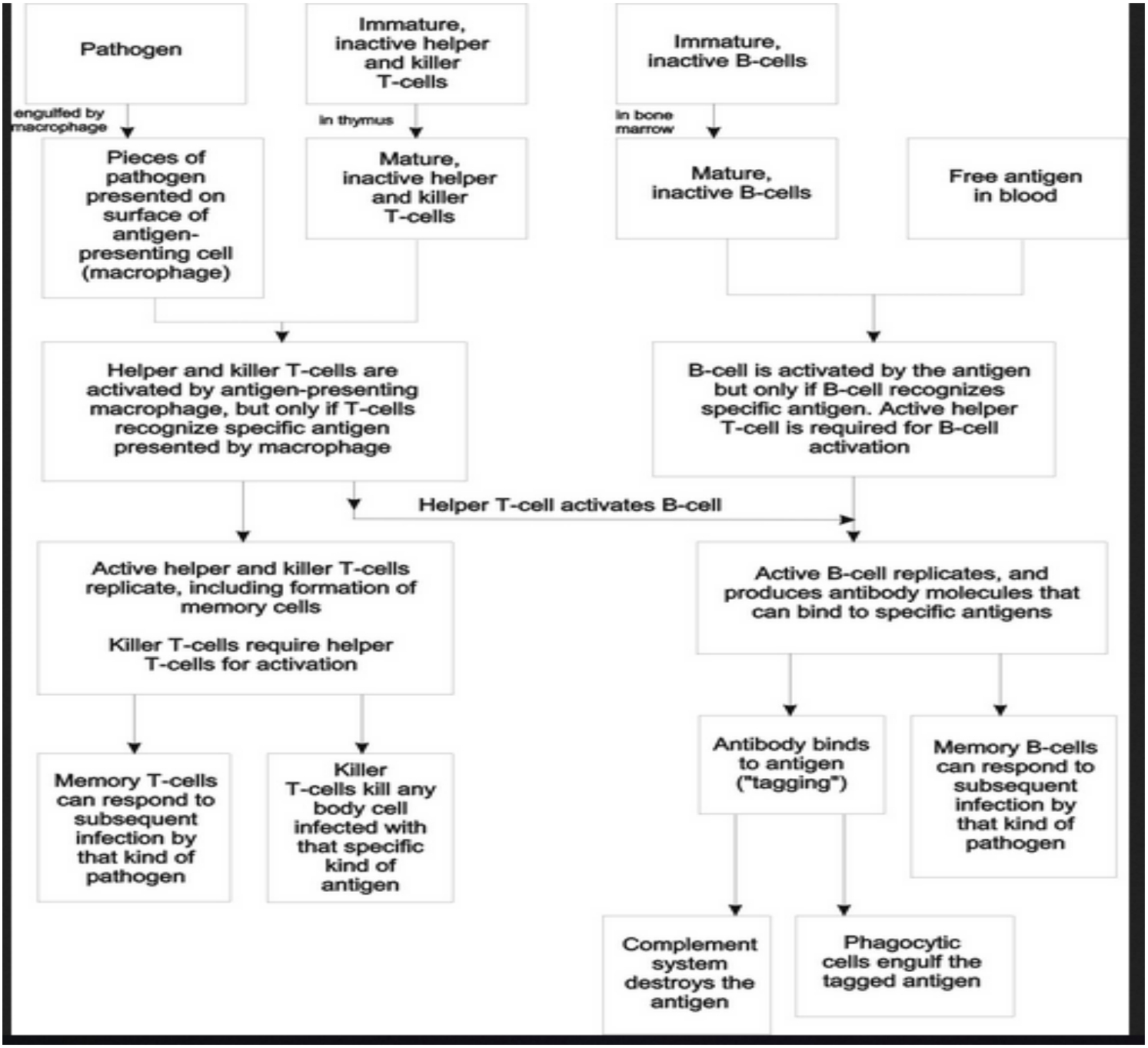
Cell-mediated immunity can be acquired through T cells from someone who is immune to the target disease or infection. "Cell-mediated" refers to the fact that the response is carried out by **cytotoxic cells**. Much like humoral immunity, someone who has not been exposed to a specific disease can gain cell-mediated immunity through the administration of cells from someone that has been exposed and survived the same disease. The cells act to activate other immune cells, while the cells assist with the elimination of pathogens and infected host cells.

Immunological memory

Because the adaptive immune system can learn and remember specific pathogens, it can provide long-lasting defense and protection against recurrent infections. When the adaptive immune system is exposed to a new threat, the specifics of the antigen are memorized so we are prevented from getting the disease again. The concept of

immune memory is due to the body's ability to make antibodies against different pathogens. A good example of immunological memory is shown in **vaccinations**. A vaccination against a virus can be made using either active, but weakened or attenuated virus, or using specific parts of the virus that are not active. Both attenuated whole virus and virus particles cannot actually cause an active infection. Instead, they mimic the presence of an active virus in order to cause an immune response, even though there are no real threats present. By getting a vaccination, you are exposing your body to the antigen required to produce antibodies specific to that virus, and acquire a memory of the virus, without experiencing illness.

Some breakdowns in the immunological memory system can lead to **autoimmune diseases**. Molecular mimicry of a self-antigen by an infectious pathogen, such as bacteria and viruses, may trigger autoimmune disease due to a cross-reactive immune response against the infection. One example of an organism that uses molecular mimicry to hide from immunological defenses is *Streptococcus* infection.



Innate Immunity vs. Adaptive Immunity: A summary

The following chart compares and summarizes all of the important parts of each immune system:

Attribute	Innate Immunity	Adaptive Immunity
Response Time	Fast: minutes or hours	Slow: days
Specificity	Only specific for molecules and molecular patterns associated with general pathogens or foreign particles	Highly specific! Can discriminate between pathogen vs. non-pathogen structures, and miniscule differences in molecular structures
Major Cell Types	Macrophages, Neutrophils, Natural Killer Cells, Dendritic Cells, Basophils, Eosinophils	T cells, B cells, and other antigen presenting cells
Key Components	Antimicrobial peptides and proteins, such as toxic granules	Antibodies
Self vs. Nonself Discrimination	Innate immunity is based on self vs. nonself discrimination, so it has to be perfect	Not as good as the innate immune system, but still pretty good at determining which is which. Problems in self vs. nonself discrimination result in autoimmune diseases
Immunological Memory	None	Memory used can lead to faster response to recurrent or subsequent infections
Diversity and Customization	Limited: Receptors used are standard and only recognize antigen patterns. No new receptors are made to adapt the immune response	Highly diverse: can be customized by genetic recombination to recognize epitopes and antigenic determinants.