

# 9 THE IMMUNE SYSTEM

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## Overview

The immune system is a complex system that is responsible for protecting us against infections and foreign substances. There are three lines of defense: the first is to keep invaders out (through skin, mucus membranes, etc), the second line of defense consists of non-specific ways to defend against pathogens that have broken through the first line of defense (such as with inflammatory response and fever). The third line of defense is mounted against specific pathogens that are causing disease (B cells produce antibodies against bacteria or viruses in the extracellular fluid, while T cells kill cells that have become infected). The immune system is closely tied to the lymphatic system, with B and T lymphocytes being found primarily within lymph nodes. Tonsils and the thymus gland are also considered lymph organs and are involved in immunity. We often don't realize how effective the immune system is until it fails or malfunctions, such as when the lymphocytes are attacked by HIV in an AIDS patient.

## The Immune System as a Castle

The immune system is a silent wonder. While we are very aware of our heart beating and the breaths we take, we are much less aware of our immune system that protects us from thousands of potentially deadly attacks every day.

In this chapter we will discuss the immune system we each possess that is working around the clock, protecting us from disease and death.

A good way to start understanding the immune system is to liken it to a castle. A castle, like our bodies, is a fortress. A castle has three lines of defense:

- *First*, A moat and drawbridge. The first line of defense in our bodies are physical and chemical barriers - our skin, stomach acids, mucous, tears, vaginal opening, of which the last three mostly produce lysozyme to destroy harmful incoming pathogens.
- *Second*, Sentries and archers who stand on the castle wall. In our bodies the second line of defense is non-specific immune responses - macrophages, neutrophils, interferons, and complement proteins. This line of defense also includes fever and inflammatory response as nonspecific defenses.
- *Third*, Soldiers within the castle. Our third line of defense is specific immune responses - T Cells and B Cells. There are many types of each which work like a close knit team to destroy pathogens.

If pathogens (invaders) try and succeed in penetrating the first line of defense, then the second line of defense is ready to act. If both the first and second line of defense fail, then the third line of defense will act. It is when all three lines of defense are breached that we get sick and are subject to disease.

So what we are trying to say is that the immune system is a set of mechanisms of defense,

protecting an organism from infection by identifying and attacking pathogens. This is a difficult task, since pathogens range from viruses to parasitic worms and must be detected with absolute specificity as they are "hidden" amongst normal cells and tissues. Pathogens are also constantly changing themselves to avoid detection and successfully infect and destroy their hosts.

## Lymphatic System

The lymphatic system and the immune system are terms that are used interchangeably to refer to the body's ability to defend against pathogens. The lymphatic system is comprised of three interrelated functions: (1) Removal of excess fluids, lymph, from body tissues, (2) Absorption of fatty acids and subsequent transport of fat, chyle, to the circulatory system and (3) Formation of white blood cells (WBCs), and initiation of immunity through the formation of antibodies, lending specific resistance to pathogens.

### Lymphatic Pathways

The lymphatic system acts as a secondary circulatory system, except it collaborates with white blood cells in lymph nodes to protect the body from being infected by cancer cells, fungi, viruses or bacteria. Unlike the circulatory system, the lymphatic system is not closed and has no central pump; the lymph moves slowly and under low pressure due to peristalsis, the operation of semilunar valves in the lymph veins, and the milking action of skeletal muscles. Like veins, lymph vessels have one-way, semilunar valves and depend mainly on the movement of skeletal muscles to squeeze fluid through them. Rhythmic contraction of the vessel walls may also help draw fluid into the lymphatic capillaries. This fluid is then transported to progressively larger lymphatic vessels culminating in the right lymphatic duct (for lymph from the right upper body) and the thoracic duct (for the rest of the body); these ducts drain into the circulatory system at the right and left subclavian veins.

### Lymph

Lymph originates as blood plasma that leaks from the capillaries of the circulatory system, becoming interstitial fluid, filling the space between individual cells of tissue. Plasma is forced out of the capillaries by hydrostatic pressure, and as it mixes with the interstitial fluid, the volume of fluid accumulates slowly. Most of the fluid is returned to the capillaries by osmosis. The proportion of interstitial fluid that is returned to the circulatory system by osmosis is about 90% of the former plasma, with about 10% accumulating as overflow. The excess interstitial fluid is collected by the lymphatic system by diffusion into lymph capillaries, and is processed by lymph nodes prior to being returned to the circulatory system. Once within the lymphatic system the fluid is called lymph, and has almost the same composition as the original interstitial fluid.

### Edema

Edema is the swelling that forms when too much tissue fluid forms or not enough taken away. It can be caused by a variety of conditions such as allergic responses (too much vasodilation), starvation (lack of albumin in blood lowers osmotic pressure and decreases amount of fluid returning to capillaries), and lymphatic disorders (e.g. blockage due to parasite in elephantiasis, or removal of

lymph nodes due to a radical mastectomy). Edema is common in the lower extremities when people spend a lot of time sitting, because the fluid return is based largely on the massaging action of skeletal muscles.

## Lymphatic Vessels and Ducts

The lymphatic vessels are similar in structure to the cardiovascular veins, meaning they also have valves. They are dependent upon the contraction of skeletal muscle, respiratory movements and valves that do not allow backward flow. The vessels merge before entering one of two ducts.

- **Thoracic Duct:** This duct is much larger than the lymphatic duct. It serves the abdomen, lower extremities and the left side of the upper body (head, neck, and arm)
- **Right Lymphatic Duct:** This duct serves all of the right side of the upper body and thoracic area (head, neck).

## Organs, Tissues and Cells 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. The function of memory cells is to recognize specific antigens in the future.

**Primary Lymphatic Organs** The primary lymphatic organs are the red bone marrow and the thymus. They are the site of production and maturation of lymphocytes, the type of white blood cell that carries out the most important work of the immune system.

- **Red 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. Only 5% of T lymphocytes ever leave the thymus. They only leave if they are able to pass the test: if they react with “self” cells, they die. If they have the potential to attack a foreign cell, they leave the thymus.

**Secondary Lymphatic Organs**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. The secondary organs include the spleen, lymph nodes, tonsils, Peyer’s patches, and the appendix.

- **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.

- **Tonsils** are often the first organs to encounter pathogens and antigens that come into the body by mouth or nose. There are 3 pairs of tonsils in a ring about the pharynx.

- **Peyer’s patches**, located in the wall of the intestine and the appendix, attached to the cecum of the large intestine, intercept pathogens that come into the body through the intestinal tract.

## Leukocytes

The primary cells of the immune system are the *leukocytes* or white blood cells(WBC). Most leukocytes are much larger than red blood cells, but they are not nearly as numerous. A microliter of whole blood contains about 5 million red blood cells but only about 7000 leukocytes.

Although most leukocytes circulate through the blood, they usually leave the capillaries and function extravascularly (outside the vessels). Some types of leukocytes can live out in the tissue for several months, but others may live for only hours or days. Leukocytes can be distinguished from one another in stained tissue samples by the shape and size of the nucleus, the staining characteristics of the cytoplasm and the cytoplasmic inclusions, and the regularity of the cell border.

Leukocytes are divided into six basic types: eosinophils, basophils, neutrophils, monocytes, lymphocytes, and dendritic cells.

One functional group of leukocytes is the **phagocytes**, WBC that engulf and ingest their targets by phagocytosis. This group includes the neutrophils, macrophages, monocytes (which are macrophage precursors), and eosinophils. A second functional group is the **cytotoxic cells**, so named because they kill the cells they attack. This group includes eosinophils and some types of lymphocytes.

Lets take a closer look at the six basic types of leukocytes.

### **Eosinophils**

Eosinophils fight parasites and contribute to allergic reactions. They are easily recognized by the bright pink staining granules in their cytoplasm. Normally, there are only a few eosinophils found in the peripheral circulatory. They account for only 1-3% of all leukocytes. The life span of a typical eosinophil in the blood is about 6-12 hours. Eosinophils are known to attach to large parasites and release substances from their granules that damage or kill the parasite. Because eosinophils kill pathogens, they are classified as cytotoxic cells. Eosinophils also participate in allergic reactions, by contributing to inflammation and tissue damage by releasing toxic enzymes.

### **Basophils**

Basophils release histamine and other chemicals. Basophils are rare in circulation but are easily recognized in a stained blood smear by the large, dark blue granules in their cytoplasm. They also release mediators that contribute to inflammation. The granules contain histamine, heparin (an anticoagulant), cytokines, and other chemicals involved in allergic and immune responses.

### **Neutrophils**

Neutrophils "eat" bacteria and release cytokines. Neutrophils are the most abundant WBC, 50-70% of the total. They are easily identified by a segmented nucleus. Neutrophils, like other leukocytes are formed in the bone marrow. They are phagocytic cells that typically ingest and kill bacteria. Most neutrophils remain in the blood but can leave the circulation if attracted to an extravascular site of damage or infection. In addition to ingesting bacteria and foreign particles, neutrophils release a variety of cytokines.

### **Monocytes**

Monocytes are the precursor cells of tissue macrophages. Monocytes are not that common in the blood 1-6% of WBC. Once out of the blood, monocytes enlarge and differentiate into macrophages. Some tissue macrophages patrol the tissues, creeping along by amoeboid motion. Others find a location and remain fixed in place. Macrophages are the primary scavengers within tissues. Macrophages also remove larger particles, such as old RBC and dead neutrophils. Macrophages play an important role in the development of acquired immunity. After they ingest and digest molecular or cellular antigens, fragments of processed antigen are inserted into the macrophage membrane as part of surface protein complexes.

**Lymphocytes** Lymphocytes are the key cells that mediate the acquired immune response of the body. Only about 5% of lymphocytes are found in circulation. They constitute 20-30% of all WBC. Most

lymphocytes are found in lymphoid tissues, where they are more likely to encounter invaders. By one estimate, the adult body contains a trillion lymphocytes at any one time.

### **Dendritic Cells**

Dendritic cells activate lymphocytes. They are antigen-presenting cells characterized by long, thin processes that resemble neuronal dendrites. Dendritic cells are found in the skin called Langerhans cells and also in various organs. When dendritic cells recognize and capture antigens, they migrate to secondary lymphoid tissues, where they present the antigens to lymphocytes.

## **Defenses Against Infection**

### **Innate Defense – first line of defense**

Physical and chemical barriers are the body's first line of defense.

#### **Physical or Mechanical barriers**

- **Skin**

One of the body's first line of defenses against bacteria and other harmful organisms is the skin. Our skin is a barrier which stops infection from entering the body. Millions of microorganisms live harmlessly on the skin and in the air around us. Sebaceous glands in the skin produce sweat and sebum, which, combined help to protect the skin. Both substances contain antiseptic properties, of *lysozyme* is the main property. Although our skin is a good defense, it isn't perfect. The skin itself can also become infected by bacteria, viruses, fungi or tiny parasites. Some examples of these are: boils, impetigo; ringworm, athlete's foot; cold sore, wart, verruca; and scabies.

- **Mucus membranes**

Another very important first line of defense is our mucus membranes. The mucous membranes (or mucosae; singular: mucosa) line various body cavities that are exposed to the external environment and internal organs. It is at several places continuous with skin: at the nostrils, the lips, the ears, the genital area, and the anus. The nose and mouth serve as passageways for air going to and from the lungs. As we inhale and exhale, the mucus membranes that line these passageways warm and humidify the air. It has been said that there is more bacteria contained in a human mouth than the sum of all the people that have ever lived on the earth. Mucus membranes serve different functions, however, their more important job is to secrete mucus that traps bacteria and other foreign debris that irritates the lining of the respiratory tract. This mucus is produced and stored in the sinuses by other mucus membranes. We get congested when there is excessive fluid in the sinus cavities. This is a result of an increase in mucus secretions, as well as an increase in the amount of fluids that passes across the blood vessels of the mucus membranes that line the nose and sinus. There are also many chemicals, such as pesticides and anthrax that are absorbed through the skin. All mucous membranes are ciliated. *Cilia* are thin, tail-like projections extending approximately 5–10 micrometers outwards from the cell body. Their main function is to move things across their surface.

- **Mucociliary escalator**

The mucociliary clearance of the respiratory tract is an important defense mechanism against foreign debris and inhaled pathogens. The cilia that line the upper and lower airways are lined with a thin layer of mucus. These beat rapidly to propel particles that are trapped in the mucus layer to the pharynx. Defective mucociliary clearance predisposes our respiratory tracts to recurrent infections. These ciliary defects may be either congenital or acquired by infection, toxins or drugs.

### **Chemical Defenses**

- **Tears, saliva**

Tears and saliva contain *lysozyme*, an antiseptic enzyme that attacks cell walls of bacteria and breaks them down.

- **Stomach acids**

Glands in the stomach lining produce hydrochloric acid. This acid kills most invading organisms that are swallowed and take up residence there.

## **Non-specific responses to infection - 2nd line of defense**

We are born with built in nonspecific defenses that all respond in the same way to invading pathogens. The outermost defense our body has is our skin. The sebaceous glands produce sweat and sebum, which contain ANTISEPTIC properties which protect. This bacteria-killing substance called LYZOSOME is also found in tears and saliva. Acidic urine in the urinary tract and friendly bacteria in the genital tract prevent the multiplying of harmful organisms in these areas. Most invading organisms in the stomach are killed by gland production of hydrochloric acid. These are a few examples of how the outer defenses protect us. All outer defenses work together as the body's first line of defense.

### **Inflammatory response**

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*.

#### *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 involved (functio laesa). When an injury occurs, a capillary and several tissue cells are apt to rupture, releasing histamine and kinins. 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.

### *Phagocytosis by neutrophils and macrophages*

In the event of a break in the skin, neutrophils, monocytes (and macrophages) arrive and attempt to engulf and destroy the invaders. Phagocytosis is receptor-mediated event, which ensures that only unwanted particles are ingested. Stimulated macrophages can bring about an explosive increase in the number of leukocytes by producing Colony Stimulating Factors (CSFs). The CSFs pass by way of the blood to the bone marrow, where they stimulate the production and the release of white blood cells (WBCs), primarily neutrophils. Lymphocytes in nearby lymph nodes produce specific antibodies to attack the microbes. During the conflict, some neutrophils die and become mixed with dead tissue, bacteria, living white cells, etc. This thick yellow-white fluid is called *pus*. When a person has an illness, an examination of the numbers and types of WBC's in their blood can be very useful.

### **Complement System**

The 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 small plasma proteins that work together to form the primary end result of cytolysis by disrupting the target cell's plasma membrane.

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

### **Interferon in response to viral infection**

Interferon (IFNs) are 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.

### **Adaptive Defense (Specific Defense--third line of defense)**

This part of the immune system directly targets invading microbes. Our specific immune defenses respond to *antigens*. An antigen is a protein (or polysaccharide) molecule, typically on the cell membrane, that the body recognizes as *nonsel*f. They are found on microbes, foreign cells, or on cancer cells. Normally our immune system does not respond to our own antigens (if it does, then this is an

autoimmune disease). Sometimes we develop an immune response to a harmless antigen, such as pollen or cat dander (this is an allergic response).

## Lymphocytes

Specific immunity is dependent upon two types of lymphocytes, the B cells and the T cells. Their names are based on where in the body they mature. B cells mature in the bone marrow, and T cells mature in the thymus gland. In comparison, both B and T cells can recognize and target antigen-bearing cells, although they go about this in different ways. B and T cell lymphocytes are capable of recognizing an antigen because they have specific receptor molecules on their surface which exactly fit individual antigens (like a lock and a key). Any B or T cell can only respond to one type of antigen. The body does not know ahead of time which antigens it will encounter, but rather makes receptor sites for a huge number of possible antigens. It is estimated that for the million or so antigens we encounter in our lifetime we have an equal number of specific lymphocytes for each possible antigen.

### B Cells Produce Antibodies

*B cell* lymphocytes are responsible for antibody-mediated immunity (humoral immunity). They produce antibodies, which are proteins that bind with and neutralize specific antigens. Antibodies do not directly kill bacteria, but mark them for destruction. When antibodies bind to viruses they can prevent the viruses from infecting cells. When antibodies bind to toxins they can neutralize the toxin (why we get immunized against the tetanus toxin). Humoral immunity works best fighting against target viruses, bacteria, and foreign molecules that are soluble in blood and lymph *before* the bacteria or viruses have entered into cells (extracellular bacteria and extracellular viruses).

B cells produce two different types of cells:

- plasma cells
- memory cells

#### Plasma cells

As B cells mature during embryonic development, they develop surface receptors that allow them to recognize specific antigens. Then they travel in the bloodstream, distributing throughout the lymph nodes, spleen, and tonsils. Once B cells reach their destination, they remain inactive until they encounter a foreign cell with an antigen that matches their particular receptor site (most B cells remain inactive for your entire life). The foreign antigen can be presented to the B cell directly, but usually macrophages and T cell lymphocytes (helper T cells) interact with B cells as Antigen Presenting Cells to bring about antibody production. Upon such an encounter, the B cell's receptors will bind to the antigen. The appropriate B cell is *turned on* or stimulated. It then grows bigger, and rapidly multiplies into a large homogenous group (clone). Most of these cells are *plasma cells*, which actively secrete antibody that will bind with the original stimulating antigen. While most of the B cells remain in the lymphatic system, the antibodies are secreted into the lymph fluid which then enters into the blood plasma to circulate throughout the body. Although the clone cells only live a few days, their antibodies remain and circulate in the blood and lymph, gradually decreasing in number.

#### Antibody Structure and Function

There are different classes of antibodies, or immunoglobulins (Ig), such as IgA, IgG, IgE, and IgM. They can attach to the surface of a microbe and make it more easily phagocytized by neutrophils, monocytes and macrophages. Anything that simplifies phagocytosis is called an *opsonin*. The process of antibodies attaching to invaders can be termed 'opsonization.' Some antibodies can bind and inactivate certain poisons or toxins and are called *antitoxins* (tetanus immunizations stimulate your body to produce antibodies against the tetanus toxin rather than against the bacteria that produces the toxin). Still other antibodies can bind to the surface of microbes and prevent their attachment to the body's cells (thus preventing viruses from entering host cells). Also, some of them can stimulate nine proteins found in plasma, called *complement*.

### Memory B cells

At the time of activation some of the clones become memory B cells. These cells are long lived and have recorded the information about the foreign antigen so antibodies can be made more quickly, and in greater amount, in case a second exposure should occur. Since the second response is much stronger than the first and puts more antibodies into circulation, we often receive "booster shots" for immunizations.

### T Cells Attack Infected Cells

Defending the body against intracellular pathogens is the role of T lymphocytes, which carry out *cell-mediated immunity*(CMI). Macrophages phagocytize invading microbes and present parts of the microbe (antigens) to the T cell lymphocytes. The appropriate T cell is *turned on* or stimulated. The activated T cell rapidly multiplies into a large homogenous group (clone) of *cytotoxic T cells* (Tc cells).

- (a) Attack organisms directly, Also kill infected cells

These cytotoxic T cells migrate to the site of infection (or disease) and produce chemicals which directly kill the invader. Cytotoxic T cells release "perforin" that causes pores to form in the plasma membrane of the target cell, resulting in lysis.

- (b) T cells develop in the thymus gland from immature precursor cells that migrate there from the bone marrow.
- (c) Killer and helper T cells
- (d) Memory T Cells

A portion of these activated T cells become *memory T cells* (Tm). These cells record the information about the foreign antigen so T cells can respond more quickly, and more strongly, if a second exposure occurs. A portion of the T cells become *T helper cells* (TH) or *T suppressor cells* (Ts). TH cells stimulate other T cells and B cells by releasing *cytokines* and other stimulatory chemicals. Ts cells suppress the immune response. Experience has shown that cell mediated immunity is most useful to the body by: Protecting against microbes which exist inside of our body's cells (intracellular bacteria and intracellular viruses). Protecting against fungal infections. Protecting against protozoan parasites. Protecting against cancer cells.

## IMMUNE RESPONSE PATHWAYS

The innate response starts first, and it is reinforced by the more specific acquired response. The two pathways are interconnected, so cooperation and communication is essential.

### INFLAMMATION

What happens when bacteria invade? If the first line of defense fails, bacteria can reach the extracellular fluid. There they usually cause an inflammatory response. This response coats antigens on the bacterial surface, with antibodies. Then in return the antibodies will ingest the antigens with phagocytic cells. This is characterized by a red, swollen warm area that is tender or painful. In addition to the nonspecific inflammatory response, lymphocytes attracted to the area produce antibodies keyed to the specific type of bacteria. If the infection continues it will produce a fever.

- What causes a fever?

During an infection macrophages may release *cytokines* (see glossary), such as interleukin-1, that travel to the hypothalamus and induce a change in the *thermostat* setting. When the thermostat is raised to a new normal temperature, the previous body temperature now registers as too cold. To increase the temperature to the new level, our body shunts blood away from the skin (leaving it feeling cold and clammy), the heart rate increases, and we shiver to generate heat until we reach the new set point. The hypothalamus may subsequently lower the thermostat, in which case we suddenly feel hot and start to sweat as our body attempts to cool off. A person may cycle between chills and sweats during the course of an infection. While a fever can be dangerous if it gets too high, or if a patient is weak or has heart trouble, there is some evidence suggesting that the body may overcome an infection faster if a fever is allowed to run its course.

### INTRACELLULAR DEFENSE

What happens when virus's invade the body?

First they encounter an extracellular phase just like the bacteria did. In the early stages of a viral infection, innate immune responses and antibodies can help control the invasion of the virus. Once the virus enters the body's host cells cytotoxic T lymphocytes are the main defense against intracellular viruses. These cells look for infected host cells, then destroy them.

### ACQUIRED IMMUNITY: ANTIGEN-SPECIFIC RESPONSES

Acquired immunity responses are antigen-specific responses in which the body recognizes a foreign substance and selectively reacts to it. This is mediated primarily by lymphocytes. Acquired immunity overlaps with the process of innate immunity. Acquired immunity can be subdivided into active immunity and passive immunity.

**Active Immunity** occurs when the body is exposed to a pathogen and produces its own antibodies. Active immunity is active because it is the "activation" of your immune system. Active immunity can occur naturally, when a pathogen invades the body, or artificially, like when we are given vaccinations

containing disabled or killed pathogens. The body does require prior exposure to an antigen to develop an active immunity. Some parents expose their children to some antigens so they will have immunity to these diseases later in life.

**Passive Immunity** occurs when we acquire antibodies made by another human or animal. Passive immunity is passive because it requires no response from the person's immune system. In passive immunity you are not presenting the body with foreign antigens. Therefore your immune system will not need to use B cells, and we know that if the B cells are never introduced your body isn't making antibodies and it isn't making memory B cells. The transfer of antibodies from mother to fetus across the placenta is one example. Injections containing antibodies are another. Sometimes travelers going abroad may be injected with gamma globulin, but this passive immunity last only about three months. Passive immunizations are used to protect people who have been exposed to infections or toxins, like snake venom or tetanus.

## ALLERGIC RESPONSES/INFLAMMATORY RESPONSES

An allergy is an inflammatory immune response to a nonpathogenic antigen. Left alone, the antigen is not harmful to the body, but if someone is sensitive to the antigen, the body produces an inflammatory response designed to get rid of it. Allergic inflammatory responses can range from mild tissue damage to fatal reactions. The immune response in allergies is called *sensitivity* or *hypersensitivity* to the antigen. **Immediate hypersensitivity reactions** are mediated (immune destruction) by antibodies and occur within minutes of exposure to antigens, which are called allergens. **Delayed hypersensitivity reactions** are mediated by helper T cells and macrophages and may take several days to develop.

What happens during a immediate hypersensitivity reaction?

- 1-Foreign protein or antigen is introduced
- 2-Macrophage cell ingests (phagocytosis)
- 3- Activation of Th lymphocyte
- 4-Th (helper) lymphocyte
- 5-Foreign protein bound by membrane antibodies
- 6-B lymphocyte
- 7-Antigen processing (MHC II type)
- 8-Antigen-MHC II complex (antigen presentation)
- 9-Production of antigen-specific antibodies
- 10-Activation of B lymphocyte with active Th

2. Upon reexposure, the body reacts more strongly and rapidly. The allergen binds to IgE already present on mast cells, triggering the immediate release of histamine, cytokines, and other mediators that cause allergic symptoms. The severity of the reaction varies, ranging from localized reactions near the site of where the allergen entered, such as a rash. To the most severe allergic reaction called *anaphylaxis*. In an anaphylactic reaction, massive release of histamine and other cytokines cause widespread vasodilation, circulatory collapse, and severe bronchoconstriction. Unless treated promptly, anaphylaxis can result in death.

Skin tests for allergies of certain allergens can be injected into the skin. This is a good way to find out what one might be allergic to so they can eliminate further exposure. Allergens that can cause

immediate hypersensitivity include bee stings, pollen and certain foods. Allergies that cause chronic allergic rhinitis and asthma are highly due to dust mites (dermatophgoides). It is not their bodies that cause the reaction, but rather it's feces. Allergic attacks usually stop when the histamine has been depleted. This can be stopped faster with an antihistamine drug or nasal spray.

What happens in a delayed hypersensitivity? It could take hours or days for symptoms to occur in a delayed hypersensitivity. Delayed hypersensitivity is cell mediated with a T lymphocyte response. Secretion of lymphokines, instead of histamine, happens in a delayed hypersensitivity. So, the treatment would be a corticosteroid instead of an antihistamine. Examples of a delayed hypersensitivity would be, poison sumac, poison oak and poison ivy. Skin tests for certain diseases are also considered examples like TB test and the Mantoux test.

## Infectious Organisms and Immunization

### Beneficial Organisms

#### Intestinal bacteria

- Bacteria are prokaryotic (before nucleus) cells that we see usually as bacilli (rods) or cocci (spheres). While they are the major cause of many diseases both fatal and mild, bacteria are also our friends and can be of great service to us. Many bacteria in our bodies help prevent pathogens from becoming established. "Good bacteria" helps protect us from "bad bacteria". The large intestine is packed with *normal microflora* that digest substances otherwise indigestible. This process provides our bodies with additional vitamins, fatty acids and nutrients. Another example is the microflora that is in the vagina that helps maintain an acidic pH, which discourages the growth of infectious organisms. These are examples of our immune system's first line of defense.

### Harmful Organisms

#### Viruses

- Viruses are non-living particles consisting of protein and nucleic acid that infect cells in biological organisms. They can reproduce only by invading and taking over other cells as they lack the cellular machinery for self reproduction. A virus is about ten times smaller than a bacteria. Some viruses you will recognize are: *influenza, herpes, measles, and the common cold*. Some viruses are particularly dangerous because they can undergo a period of latency, during which they are hidden in the cell and do not reproduce. *Influenza* and *HIV* are examples of viruses that frequently mutate, thus making it nearly impossible to achieve a long-lasting immunity.

#### Bacteria

- Bacteria can be deadly. They are the major cause of preventable infections and death. Some well known illnesses are caused by bacteria: *staph infections, strep infections, tuberculosis, food poisoning, tetanus, leprosy, and pneumonia*. Because bacterial cells are different from

human cells, compounds can be found that can kill specific bacterial targets while leaving the human patient unharmed. Antibacterial agents can be successful in wiping out a bacterial infection. The problem with antibiotics is that many strains of bacteria are growing resistant to them. Plus, our bodies are not getting the chance to develop immunity to certain bacteria. It may be better to use probiotics (new supplements that promote the growth of healthy and helpful bacteria) rather than depend on antibiotics so much.

### Protozoans

- The protozoans are mostly eukaryotic unicellular organisms with organelles and a nucleus.
- *Malaria* is the most dangerous disease caused by protozoans and is endemic in about 50% of the populations on Earth. Two to four million people die each year from malaria, a million of these are under the age of five. malaria is caused by one of the *Plasmodium* species of mosquitoes.

### Fungi

- Fungi are more like animals and humans than they are like bacteria because of their eukaryotic cells. Though they produce large, visible colonies on old bread, molds and yeasts are in the category of microscopic fungi. Yeasts are one-celled and reproduce by budding. Molds exist as cell chains, called hyphae.
- *Mycoses* are diseases caused by fungi. Because of the similarity between human cells and fungal cells, it has been difficult for scientists to design antibiotics that are effective against fungi and do not harm humans. Some of the diseases caused by fungi are: *tineas*, *vaginal infection* (candidiasis), and *histoplasmosis*.

**Diagnosis** Infectious diseases are diagnosed by laboratory techniques such as microscopy and culture. Since many bacteria have no color, scientists have developed special staining procedures to more accurately diagnose.

- Culture

Bacteria and fungi can be identified by growing them on plates until colonies are visible. Viruses are cultured on eggs or live cells.

- Antibiotic sensitivity

After colonies of bacteria are grown on plates, discs are placed on the plates that contain different antibiotics. Bacteria will not grow around the most effective antibiotic.

- Tests for viruses

Since viruses are too small to be seen with a light microscope, viral infections can be diagnosed indirectly by their effects on cells. Some viruses cause changes to the surface of cultured cells, causing them to stick together.

## Immunization

While some infectious diseases are common and can occur many times in the same person, others can only occur once in a lifetime thanks to the immune system and its ability to remember the organism and prevent following infections. To avoid an epidemic of a grave disease such as polio, before the disease can be acquired, an immunization can create a man-made "memory".

- Active immunization

A person receives an injection (vaccine) that contains dead or harmless living forms of an organism. The vaccine stimulates the immune system to produce antibodies and memorize the organism. If there is a later exposure to this organism and subsequent infection, the antibodies will stop the infection.

- Passive immunization

Blood containing antibodies is taken from animals or humans who have recently had an infection. Blood serum is made that contains the antibodies, and then injected into the person. The antibodies either attack an infection that is present or provide short-term protection.

- Genetically engineered viruses

Genetic engineering is a technique that alters or changes the DNA of a plant or animal by inserting new genetic information from another organism. After these organisms replicate, vaccines and hormones are made that can help fight disease.

- Hepatitis B vaccine

The gene of the surface antigen of Hepatitis B virus is implanted into the DNA of a single bacterium. The bacteria produces viral antigens which are then implanted to stimulate the immune system.

## IMMUNE SYSTEM DISORDERS

The immune system is a very complex and highly developed system, yet it has a very simple mission, seek and destroy invaders. When the immune system does not function properly it leaves the body open for attacks from an array of diseases. We classify these into three broad categories; autoimmunity, immunodeficiencies, and hypersensitivities.

Anything that can trigger the immune response is called an antigen. An antigen can be a microbe such as a virus, or even a part of a microbe. Tissues of cells from another person also carry nonself markers and act as antigens. This explains why tissue transplants can be rejected. In abnormal situations, the immune system can mistake self for nonself and launch an attack against the body's own cells or tissues. The result is called an autoimmune disease. Some forms of arthritis and diabetes are autoimmune diseases. In other cases, the immune system responds to a seemingly harmless foreign substance such as a dust mite. The result is allergy, and this kind of antigen is called an allergen.

## The Allergic response

Type 1 hypersensitivity is an allergic reaction provoked by reexposure to a specific antigen. Exposure may be by ingestion, inhalation, injection, or direct contact. The reaction is mediated by IgE antibodies and produced by the immediate release of histamine, tryptase, arachidonate and derivatives by basophils and mast cells. This causes an inflammatory response leading to an immediate (within seconds to minutes) reaction.

The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock. Treatment usually involves epinephrine, antihistamines, and corticosteroids.

### Hay Fever

Hay fever involves an allergic reaction to pollen and results in allergic rhinitis (inflammation of the nasal mucosa). It is most common in the haying season, which is why the ailment was named hay fever. A virtually identical reaction occurs with allergy to mold, animal dander, dust, and similar inhaled allergens. Particulate matter in polluted air and chemicals such as chlorine and detergents, which can normally be tolerated, can greatly aggravate the condition. The pollens that cause hay fever vary from person to person and from region to region; generally speaking, the tiny, hardly visible pollens of wind-pollinated plants are the predominant culprits.

## Autoimmune Disorders

For reasons we do not fully understand, sometimes the immune system attacks the body the way it normally would attack a germ or foreign substance. The genes some people inherit can contribute to their susceptibility to develop an autoimmune disease. Most autoimmune diseases effect woman more than men.

- In **Juvenile-onset diabetes** the immune system starts attacking and eliminating the cells in the pancreas that make insulin.
- **Multiple Sclerosis** is a chronic degenerative disorder of the central nervous system where the immune system starts attacking and destroying vital myelin in the brain and spinal cord. This causes multiple sclerosis (scars) on the myelin sheath resulting in loss of nerve function.
- Another fairly known disorder is **Rheumatoid Arthritis** this is when the immune system starts attacking the tissue inside your joints.
- There is another disorder, **Organ and Tissue Transplants**, that is classified under immuno-deficiencies but in reality is not a failure of the immune system. In transplants, foreign tissue is placed inside the body. These tissues do not perfectly match the surrounding cells. The body sees this as something that should not be there and sends messages to attack and kill it. This can make transplanting nearly impossible. This problem can not be completely prevented but it can be diminished by making sure the donor tissue is a close match to the recipient tissue. In addition, the recipient is placed on immuno-suppressing drugs to try and prevent the immune system from attacking and rejecting the new organ or tissue.

- **Vitiligo** is an autoimmune disorder in which the immune system destroys pigment-making cells called melanocytes. This results in irregularly shaped milky-white patches of skin on different parts of the body. This is the condition which Michael Jackson claims to have.

## Immunodeficiency Diseases

When the immune system is presented with foreign antigens in association with dendritic cells, a vigorous immune response ensues. (Antigens are the molecules on the surface of invader cells that announce them as different from the body's cells.). Alternatively, dendritic cells can be exploited during the development of many immune based diseases.

### AIDS and HIV

Acquired immunodeficiency disease (AIDS) is a well-known immune system disease. Acquired Immune Deficiency Syndrome or acquired immunodeficiency syndrome (AIDS or Aids) is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the human immunodeficiency virus (HIV). The late stage of the condition leaves individuals prone to opportunistic infections and tumors. Although treatments for AIDS and HIV exist to slow the virus's progression, there is no known cure. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid, and breast milk. This transmission can come in the form of anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, or breastfeeding, or other exposure to one of the above bodily fluids. AIDS is the most severe manifestation of infection with HIV. HIV is a retrovirus that primarily infects vital components of the human immune system such as CD4+ T cells (a subset of T cells), macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells. CD4+ T cells are required for the proper functioning of the immune system. When HIV kills CD4+ T cells so that there are fewer than 200 CD4+ T cells per microliter ( $\mu\text{L}$ ) of blood, cellular immunity is lost, leading to the condition known as AIDS. Acute HIV infection progresses over time to clinical latent HIV infection and then to early symptomatic HIV infection and later to AIDS, which is identified on the basis of the amount of CD4+ T cells in the blood and the presence of certain infections.

In the absence of antiretroviral therapy, the median time of progression from HIV infection to AIDS is nine to ten years, and the median survival time after developing AIDS is only 9.2 months. However, the rate of clinical disease progression varies widely between individuals, from two weeks up to 20 years. Many factors affect the rate of progression. These include factors that influence the body's ability to defend against HIV such as the infected person's general immune function. Older people have weaker immune systems, and therefore have a greater risk of rapid disease progression than younger people. Poor access to health care and the existence of coexisting infections such as tuberculosis also may predispose people to faster disease progression. The infected person's genetic inheritance plays an important role and some people are resistant to certain strains of HIV.

## Different Types of T Lymphocyte Cells

Several different subsets of T cells have been described, each with a distinct function.

**Cytotoxic T cells** (Tc cells) destroy virally infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as CD8<sup>+</sup> T cells, since they express the CD8 glycoprotein at their surface.

**Helper T cells**, (Th cells) are the "middlemen" of the adaptive immune system. Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or "help" the immune response. These cells (also called CD4<sup>+</sup> T cells) are a target of HIV infection; the virus infects the cell by using the CD4 protein to gain entry. The loss of Th cells as a result of HIV infection leads to the symptoms of AIDS.

**Memory T cells** are a subset of antigen-specific T cells that persist long-term after an infection has resolved. They quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune system with "memory" against past infections. Memory cells may be either CD4<sup>+</sup> or CD8<sup>+</sup>.

**Regulatory T cells** (Treg cells), formerly known as suppressor T cells, are crucial for the maintenance of immunological tolerance. Their major role is to shut down T cell mediated immunity towards the end of an immune reaction and to suppress auto-reactive T cells that escaped the process of negative selection in the thymus. Two major classes of regulatory T cells have been described, including the naturally occurring Treg cells and the adaptive Treg cells.

**Treg cells** (also known as CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> Treg cells) arise in the thymus, whereas the adaptive Treg cells (also known as Tr1 cells or Th3 cells) may originate during a normal immune response. Naturally occurring Treg cells can be distinguished from other T cells by the presence of an intracellular molecule called FoxP3. Mutations of the FOXP3 gene can prevent regulatory T cell development, causing the fatal autoimmune disease IPEX.

**'Natural Killer T cells'** (*NKT cells*) are a special kind of lymphocyte that bridges the adaptive immune system with the innate immune system. Unlike conventional T cells that recognize peptide antigen presented by major histocompatibility complex (MHC) molecules, NKT cells recognize glycolipid antigen presented by a molecule called CD1d. Once activated, these cells can perform functions ascribed to both Th and Tc cells (i.e. cytokine production and release of cytolytic/cell killing molecules).

**THE FUNCTIONS OF T LYMPHOCYTES** T lymphocytes cells help with all components of the immune system, including cell elimination by killer T cells and maintaining roles by helper and suppressor T cells. Although the specific mechanisms of activation vary slightly between different types of T cells, the "two-signal model" in CD4<sup>+</sup> T cells holds true for most.

## The Immune System Pioneers

### Ilya Mechnikov and the Phagocyte Cells

In 1882, a Russian scientist named Ilya Mechnikov was experimenting with the larvae of the sea star. He stuck a thorn in the larvae and then he noticed that something really weird happened. Strange cells started gathering near the point of insertion. The cells that were surrounding the thorn were eating any foreign substance that was entering through the ruptured skin. Mechnikov decided to name these

new cells "phagocytes", in Greek meaning "devouring cells."

This discovery was very important since it helped scientists how the body defends itself against disease. If the phagocyte encountered anything foreign, they absorb and destroy it. Phagocytes also play an important part in activating the immune response in the rest of the body.

## Paul Ehrlich and the Side-chain Theory

Ehrlich supposed that living cells have side-chains. These side chains can link with a particular toxin, just as Emil Fisher said enzymes must bind to their receptors "like a key in a lock."

He theorized that a cell under threat grew additional side-chains to bind the toxin, and that these additional side chains broke off to become the antibodies that circulate through the body. It was these antibodies that Ehrlich first described as "magic bullets" in search of toxins.

Ehrlich figured that if a compound could be made that selectively targeted a disease causing organism, then a toxin for that organism could be delivered along with the agent of selectivity. Hence, a "magic bullet" would be created that killed only the organism targeted.

Ehrlich predicted autoimmunity calling it "horror autotoxicus".

In 1908, Ehrlich and Mechnikov received the Nobel Prize.

## Review Questions

1-When neutrophils and macrophages squeeze out of capillaries to fight off infection it is called:

- A) phagocytosis
- B) hemolysis
- C) interleukin
- D) diapedesis
- E) folliculitis

2-During a great battle between your WBC's and an aggressive microbe, an inflammatory response has been initiated. Redness and edema has kicked in what else does the body do to protect itself?

- A) Histamine cause vasodilation
- B) Hypothalamus raises the thermostat
- C) Neutrophils engulf and destroy the microbe
- D) Living and dead WBC and bacteria accumulate
- E) All of the above

3-Specificity and memory are associated with which body defense mechanism?

- A) inflammatory response
- B) phagocytosis by macrophages and neutrophils
- C) interferon

- D) T cell and B cell responses
- E) anatomical barriers in the body

4-An additional chemical defense found in tears and saliva?

- A) T lymphocytes
- B) saline
- C) lysozyme
- D) EFC

5-Which of the following does complement protein perform

- A) They cause antibody release
- B) T cell development
- C) The release of histamine
- D) Promotes tissue repair
- E) Mast cell degranulation

6-Which substance induces fever?

- A) Pyrogen
- B) Pus
- C) Monocytes
- D) Edema
- E) Interferon

7-Major function(s) of the lymphatic system is/are?

- A) provide route for return of extracellular fluid
- B) act as drain off for inflammatory response
- C) render surveillance, recognition, and protection against foreign materials via lymphocytes, phagocytes, and antibodies.
- D) a and c
- E) all of the above

8-An antigen is:

- A) a chemical messenger that is released by virus infected cells
- B) a lymphocyte responsible for cell-mediated immunity
- C) something that coats the inside of lungs, causing infection
- D) a protein or other molecule that is recognized as non-self
- E) a thick yellow-white fluid

9-A foreign substance, usually a protein, that stimulates the immune system to react, such as by producing antibodies is a \_\_\_\_\_.

- A) allergen
- B) antigen
- C) histamine

- D) mast cell
- E) interferon

10-When a macrophage ingests an invading bacteria and takes the antigen to a lymph node, what happens next?

- A) the macrophage will present it to the first B-cell it encounters, and the B-cell will in turn change its surface receptors to match the antigen
- B) a B-cell will only become activated if it already has a match for the antigen
- C) a matching B-cell will become activated into a cytotoxic T-cell
- D) the cells of the lymph node will release histamine
- E) the lymph node will increase production of neutrophils

11-What is the most common portal of entry for diseases, into the body?

- A) Respiratory system
- B) Endocrine system
- C) Hematacrit system
- D) Any opening into the body.

12-This gland shrinks in size during adulthood, and has hormones that function in maturation of T-lymphocytes:

- A) lymph nodes
- B) thymus
- C) spleen
- D) GALT
- E) tonsils

13-Which of the following is not a mechanical factor to protect the skin and mucous membranes from infection?

- A) Layers of cells
- B) Tears
- C) Saliva
- D) Lysozyme
- E) None of the above

14-Where is the site of maturation for a B cell?

- A) thymus
- B) bone marrow
- C) pancreas
- D) cortex

15-Nonspecific resistance is

- A) The body's ability to ward off diseases.
- B) The body's defenses against any kind of pathogen.

- C) The body's defense against a particular pathogen.
- D) The lack of resistance.
- E) None of the above.

## GLOSSARY

**Antibody:** Antibody or (immunoglobulin) is a protein generated by the immune system (B cells) in response to a foreign substance (antigen).

**Antibody titer:** A test done to check the immunity of vaccination, when identification of a low immunity to a vaccine a booster shot can be given to increase the immunity.

**Antigen:** Protein (or polysaccharide) molecule that the body recognizes as nonself. Substance body recognizes as foreign such as, fungi, viruses, protozoans, parasitic worms, pollen, poison ivy plant resin, insect venom, and transplanted organs.

**Antiseptic:** Antimicrobial substance applied to living tissue or skin to prevent infection.

**Apoptosis:** Programmed cell death

**B Cell:** Lymphocytes that are responsible for antibody-mediated immunity

**Basophils:** WBC that release histamine and other chemicals

**Chemotaxis:** Movement of cells, phagocytes especially, they move in a specific direction in a tumbling fashion like rolling this is all due to a chemical stimulant.

**Complement System:** Biochemical cascade of the immune system that helps clear pathogens from an organism, and promote healing

**Cytokines:** Regulatory peptides that control cell development, differentiation, and the immune response

**Dendritic:** cells that activate lymphocytes

**Diapedesis:** The movement of WBC's for the blood to the surrounding tissue. A mechanism of the kind phagocyte that will walk or crawl out of the blood stream to site of infection.

**Edema:** Swelling that forms when too much tissue fluid forms or not enough taken away

**Eosinophils:** WBC that fight parasites and contribute to allergic reactions

**Histamine:** Histamine is a chemical involved in inflammation, this chemical makes capillaries leaky, in this it will move more fluid out into the tissue spaces.

**IgA:** Found in breast milk, mucus, saliva, and tears. This immunoglobulin functions to stop the pathogens before entry to the internal environment.

**IgD:** This immunoglobulin is found on B-cells and function is not known.

**IgE:** This immunoglobulin is combined with mast cells that in turn release histamine, this kind of globulin is released in the presence of an allergic response or parasitic infection.

**IgG:** This immunoglobulin is the majority of the specific immunity against bacteria and viruses in the extracellular fluid.

**IgM:** This immunoglobulin is associated to antibodies that react to incompatibility of ABO and Rh factor grouping.

**Immunoglobulins:** Proteins that are antibodies receptors on the surface of B-cells, there are five classes.

**Kinins:** Kinins is a chemical involved in inflammation, it is inactive in blood plasma but become activated by tissue damage and in turn stimulate pain receptors in skin.

**Leukocytes:** primary cells of the immune system; also called white blood cells

**Lymph:** fluid of the lymph system; originates as blood plasma that leaks from the capillaries of the circulatory system, becoming interstitial fluid, filling the space between individual cells of tissue

**Lymphocytes:** The key cells that mediate the acquired immune response of the body

**Lymph Nodes:** Small oval shaped structures located along the lymphatic vessels

**Lysosome:** Organelle containing digestive enzymes (acid hydrolases) that digest viruses, bacteria, food particles and worn out organelles

**Lysozyme:** Enzyme that attacks cell walls of bacteria and breaks them down; found and used as an antiseptic property in the body's first line of defense (ie. saliva, tears, sweat, etc)

**Macrophages:** WBC that are the primary scavengers within tissues

**Membrane Attack Complex (MAC):** Work in the same way as the perforins of the NK cells that is it punches holes in the membrane that causes lysis.

**Neutrophils:** WBC that "eat" bacteria and release cytokines

**Opsonin:** Any substance that promotes a phagocytosis by binding a microbe to a phagocyte.

**Perforin:** Protein secreted by cytotoxic T cells, causes pores to form in the plasma membrane of the target cell resulting in lysis.

**Peyer's Patches:** located in the wall of the intestine and the appendix, attached to the cecum of the large intestine, intercept pathogens that come into the body through the intestinal tract

**Phagocytes:** WBC that engulf and ingest their targets by phagocytosis

**Pyrogens:** Foreign substances and or microorganisms that causes hypothalamic thermoregulatory center to increase and causes fever (pyrexia), are called pyrogens.

**Right Lymphatic Duct:** Lymphatic duct that serves all of the right side of the upper body and thorasic area(head,neck)

**Spleen:** 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

**T Cell:** cells that carry out cell-mediated immunity

**Thoracic Duct:** Lymphatic duct that serves the abdomen, lower extremities and the left side of the upper body(head,neck, and arm)

**Thymus Gland:** Gland that contains lymphocytes; produces thymosin that is thought to aid in the maturation of T lymphocytes

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