22. Immune System and the Body’s Defense

I. Overview of Diseases Caused by Infectious Agents

Disease can be caused by a variety of factors, some have causes within our bodies (e.g., genetic disorders and cancer) and some have external causes (e.g., injury or infection). Infectious agents that cause harm to the body are often called pathogens. Your textbook describes five categories of infections agents (Table 22.1): bacteria, viruses, fungi, protozoans, and multicellular parasites.

II. Overview of the Immune System

Mechanisms your body employs to defend against pathogens, cancers, etc. make up your body’s immune system. This system differs from other systems studied in the class in that it is a system composed primarily of individual cells spread throughout the body, rather than a discrete system of organs. However, the cells of the immune system do work in a cooperative manner to provide a clear function for the body.

Immune cells and their locations
The primary cells of the immune system are the leukocytes:
- The granulocytes—neutrophils, eosinophils, and basophils.
- Monocytes—which become macrophages when they leave the blood and enter other tissues.
- Lymphocytes—which include T-cells, B-cells, and natural killer (NK) cells.

Although leukocytes circulate in the blood, most of the leukocytes in the body are found in other locations:
- Lymphatic tissue—macrophages and lymphocytes are housed in secondary lymphatic structures.
- Select organs—macrophages can be found in most organs of the body, including the lungs, brain, etc.
- Epithelial layers of the skin and mucous membranes—dendritic cells are phagocytes (related to monocytes) that patrol the skin and mucous membranes looking to devour pathogens.
- Connective tissues—mast cells (which are similar to basophils) are located throughout the body’s connective tissues, especially in the dermis of the skin and those tissues that line the respiratory, digestive, and urogenital tracts. You should recall their functions from A&P I.

Comparison of innate immunity and adaptive immunity
Defense is provided by the immune system in two general ways: (1) The innate (or nonspecific) system attempts to protect the body from all invaders. The first line of defense in the innate system is provided by the skin and mucosae, which act as physical barriers to invasion. The second line of defense includes phagocytic cells and antimicrobial proteins, which attempt to contain the spread of any invaders that get past the first line of defense. The innate system provides a generic but immediate defense against toxins and pathogens. (2) The adaptive (or specific) system can mount specific attacks against specific invaders. This system can provide a more effective defense against a specific invader, but it takes more time for the adaptive system to do this.
to coordinate an attack. The two systems generally act together in fighting an infection.

**III. Innate Immunity**

Preventing entry
The thick, keratinized stratum corneum provides a nearly impenetrable barrier to pathogens that might try to enter the body through intact skin. Mucous membranes also provide an effective barrier against most potential invaders. Various secretions also help prevent entry into the body:

1. Fluids secreted onto the skin (*e.g.*, sweat and sebum) contain chemicals that inhibit growth of microorganisms.
2. The stomach secretes hydrochloric acid and proteases that kill microorganisms in the food we eat.
3. Saliva and tears contain lysozyme to kill bacteria residing in the mouth or on the surfaces of the eye.
4. Mucous membranes produce mucus to trap microorganisms. Cilia lining internal passages sweep mucus out of the body or into the digestive tract. Mucus also contains lysozyme.

Various harmless (an often beneficial) microorganisms live on your skin and within exposed tracts of the body. Many of these microorganisms inhibit the growth of potentially harmful microorganisms.

Cellular defenses
Phagocytic cells patrol the body’s tissues in search of invaders that have breached the surface barriers. The chief phagocytes are macrophages and neutrophils. They engulf pathogens (as well as damaged cells or cellular debris) and chemically digest them inside of structures called phagolysosomes (Fig. 22.3a).

In response to an infection, basophils and mast cells release chemicals that cause inflammation and serve as attractants for other cells of the immune system (Fig. 22.3b). You should already be familiar with the chemicals histamine and heparin.

**Natural killer (NK) cells** are lymphocytes that specialize in detecting and killing cancer cells and cells infected by viruses. Whereas other lymphocytes act against specific targets, NK cells are less particular and can kill a broad range of targets. NK cells destroy cells by attacking the target cell’s membrane. They produce chemicals called perforins, which create channels in the target cell membrane and lead to destruction of the target cell (Fig. 22.3c).

**Eosinophils** are most important in defending against invaders too large for phagocytosis, such as parasitic worms (Fig. 22.3d). They can also phagocytize antigen-antibody complexes.

**Antimicrobial proteins**
A variety of antimicrobial proteins assist in defense by attacking pathogens directly or hindering their ability to reproduce. **Interferons (IFNs)** are released by some cells that have been infected by viruses. IFNs are able to hinder reproduction of viruses, and they activate macrophages and NK cells to seek out and destroy other virus-infected cells (Fig. 22.4).
Complement is a system of at least thirty proteins that circulate in the blood in an inactive state. Activated complement amplifies the inflammatory response and it directly kills cells. Activation of the complement system results in several effects that assist in defense of the body (Fig. 22.5):

- **Opsonization**–binding of complement proteins or antibodies to a pathogen makes it an easier target for phagocytosis.
- Inflammation–complement enhances the inflammatory response by activating mast cells and basophils.
- **Cytolysis**–several complement proteins work together to form a membrane attack complex (MAC), which puts holes in the target cell plasma membrane, causing lysis of the target cell.

Inflammation

Infection, chemicals, heat, and physical trauma produce the inflammatory response in tissue. Inflammation involves redness, heat, swelling, and pain in the injured or infected area. The inflammatory response begins with the release of chemicals from injured tissue, phagocytes, lymphocytes, mast cells, basophils, and the blood. These chemicals include histamine, leukotrienes, prostaglandins, and others (Table 22.4).

One effect of these chemicals is dilation of small blood vessels and increased permeability of capillaries in the vicinity of the injury or infection. This causes both hyperemia, increased blood flow, and edema, swelling, at the site of infection or injury.

Also, endothelial cells of the capillaries produce cell-adhesion molecules (CAMs) that enable leukocytes to stick to capillary walls. Leukocytes traveling through the blood can stick to the CAMs, exit the blood vessel, and migrate to where they are needed.

Inflammation has the result of a net movement of fluid from the blood to the infected/injured tissue. This fluid brings with it chemicals, nutrients, and cells that are able to fight infection and heal damaged tissue. Edema causes an increase of pressure in the interstitial fluid, which drives more fluid into the lymphatic system. This fluid is likely to contain pathogens that have entered the body, and they can be detected by cells in the lymphatic system.

Fever

Fever, which is defined as an abnormally high body temperature, is a systemic response to infection. After exposure to foreign invaders, leukocytes may release chemicals called pyrogens, which cause the body temperature to rise. Fever appears to cause the spleen to sequester zinc and iron, which are required by bacteria to multiply. Increased temperature also elevates the body’s metabolic rate, which speeds up the process of tissue repair.

IV. Adaptive Immunity: An Introduction

Introduction of a foreign substance into the body may initiate an adaptive immune response. The result is multiplication (cloning) of lymphocytes to create an army of cells that are able to recognize and fight the specific invader. Whereas the innate defenses are able to act immediately (or at least very quickly), the adaptive system takes several days to develop a full response. T-lymphocytes are responsible for carrying out what is called the cell-mediated response of adaptive immunity, and B-lymphocytes carry out the humoral response.
Antigens

An antigen is a substance that can provoke an adaptive immune response. Most antigens are proteins; some are polysaccharides. It makes sense that most antigens are proteins, as proteins are the organic molecules with the most diversity among organisms. Consider that sugars like glucose, fructose, and sucrose, and lipids such as cholesterol and fatty acids are used by many (maybe most?) organisms. Thus, you would not want these molecules to trigger the immune system.

An antigen that is foreign to the body is, simply enough, called a foreign antigen. For example, if a streptococcus bacterium enters my body, various proteins on the surface of the bacterium would be recognized by my cells of my adaptive immune system. These molecules would be considered foreign antigens.

The term self-antigen is used to describe various proteins found on the surfaces of cells that are recognized as self by that person’s immune system, but would be seen as foreign if placed in another individual.

It is typical that the immune system recognizes only part of an antigen molecule as being antigenic. The part of the antigen that the immune system recognizes is called the antigenic determinant (or epitope). Many antigens are large enough molecules that they have more than one epitope. Also be aware that a particular pathogen may contain numerous different molecules that are antigenic. So, a bacterium may have multiple antigens, some with more than one epitope, all capable of triggering a host’s immune system.

General structure of lymphocytes

Each T-cell and B-cell produces a rather unique receptor for a particular antigen (Fig. 22.9). Each receptor is composed of several proteins that form a “receptor complex,” and each lymphocyte may have about 100,000 copies of the receptor complex on its outer surface. The receptor complex is referred to as a TCR on a T-cell or a BCR on a B-cell.

As noted above, a given lymphocyte makes receptors that will bind to a particular antigen. This is not the result of any specific intent for the cell to recognize a particular antigen. In other words, your body does not intentionally make cells with receptors to match an antigen on the streptococcus bacterium. Rather, your body makes billions of lymphocytes, each with receptors that will recognize something. Because there are so many lymphocytes, if streptococcus (or any other pathogen) gets into your body, chances are pretty much 100% that some lymphocytes in the body will be able to recognize it.

A B-cell is able to bind directly to an antigen and begin its response. A T-cell requires that antigen be presented to the T-cell and its receptors by another cell. Each T-cell has coreceptors (Fig. 22.9a) that allow it to recognize this other cell:

- Cells known as helper T-cells have coreceptors called CD4 receptors. Each TCR on a helper T-cell is associated with a CD4 receptor.
- Cells known as cytotoxic T-cells have coreceptors called CD8 receptors. Each TCR on a cytotoxic T-cell is associated with a CD8 receptor.
Antigen presentation and MHC molecules
As mentioned in the previous section, in order for a T-cell to recognize an antigen, the antigen must be presented. There are certain cells of the immune system that have the specific function of presenting antigen to helper and cytotoxic T-cells. These cells are called antigen-presenting cells (APCs), and they include dendritic cells, macrophages, and B-lymphocytes. However, you will soon learn that most cells of your body have the ability to present antigens to the immune system.

The presentation of antigen to T-cells requires that the antigen be attached to a special group of glycoproteins, called MHC, found on the surfaces of cells. These proteins are coded by a group of genes called the major histocompatibility complex (hence the abbreviation MHC).

Millions of different combinations of MHC genes can be found in the human population, so generally only identical twins have the same MHC molecules. The combination of MHC molecules on cells in a person’s body is the combination that is recognized as self. If cells with another combination of MHC enter the body (as may occur during an organ transplant), then they will be recognized as foreign.

There are two general classes of MHC molecules found within a person:

**Class I MHC** molecules are displayed by nearly all cells of the body. Class I MHC molecules are made in the rough ER, and they bind fragments of protein (peptides) that come from within the cell (Fig. 22.10). These MHC molecules and associated peptides are then displayed on the cell’s outer surface. Most of the time, these peptides are parts of normal cellular proteins, and they are recognized by the immune system as self. However, if a cell has been infected or become cancerous, it will typically produce abnormal proteins. Fragments of these abnormal proteins are displayed on the cell’s surface with the class I MHC molecules, where cytotoxic T-cells can recognize the abnormal particles as foreign antigens. The T-cell’s CD8 receptors bind to the class I MHC molecules and its TCR binds to the antigen (Fig. 22.12).

This is essentially a way for an infected or cancerous cell to advertise its condition to the immune system and set itself up for destruction by cytotoxic T-cells.

**Class II MHC** molecules are displayed on the surfaces of APCs (APCs also display class I MHC). Class II MHC molecules are made in the rough ER, and they bind peptide fragments from foreign molecules that have been engulfed by the APC (Fig. 22.11). Because these antigens have been brought into the APC from the outside, they are called exogenous antigens. After the exogenous antigen is bound to the MHC molecule, the MHC molecule migrates to the cell’s surface to display the exogenous antigen (which is foreign). Class II MHC molecules are recognized by helper T-cells, with CD4 receptors binding to the class II MHC molecules and TCR binding to the antigen (Fig. 22.12).

This alerts helper T-cells to the presence of an infection or other danger to the body that requires action by the immune system.
V. Activation and Clonal Selection of Lymphocytes

Recall from Chapter 18 the basics of lymphocyte formation from hemocytoblasts. Immature lymphocytes are basically identical, but at some point they become immunocompetent—able to recognize specific antigens. T-cells become immunocompetent in the thymus; B-cells become immunocompetent in the bone marrow. Once a lymphocyte becomes immunocompetent, it displays its receptors (TCRs or BCRs) on its surface. These receptors are unique to the specific lymphocyte and will bind only to a specific antigen.

Until a lymphocyte encounters an antigen it can recognize it is said to be naïve. Immunocompetent but naïve lymphocytes spread to the lymph nodes, spleen, and other lymphoid organs where they await encounters with antigens. A blood-borne antigen may meet up with a lymphocyte in the spleen; an antigen that entered a break in the skin may be taken by a dendritic cell to a nearby lymph node; an antigen that enters the body through a mucous membrane may meet up with a lymphocyte in the tonsils or MALT. Once a lymphocyte encounters its antigen it differentiates into an activated lymphocyte. The initial contact between a lymphocyte and antigen is referred to as an antigen challenge.

Be sure to understand the meanings of the words immunocompetent, naïve, and activated in relation to T and B-cell development.

Activation of T-lymphocytes

T-cell activation requires a two-stop process (Fig. 22.15):

Step 1—first stimulation. As described previously, helper T-cells bind to antigens attached to class II MHC displayed by APCs. Cytotoxic T-cells bind to antigens attached to class I MHC.

Step 2—second stimulation. A helper T-cell that has bound its antigen will release interleukin 2 (IL-2), which stimulates the helper T-cell to divide and form a clone of helper T-cells that can recognize the particular antigen (they will all have the same TCR). A cytotoxic T-cell that has bound its antigen also requires stimulation by IL-2 released from helper T-cells. This stimulates the cytotoxic T-cell to divide and form a clone.

If helper T-cells are not proliferating during an infection, what is the effect on cytotoxic T-cells?

What is the purpose of forming a clone of lymphocytes?

When a T-cell multiplies to form a clone, the majority of cells in the clone are activated T-cells. These cells fight the antigen then die off. A clone of T-cells also contains memory T-cells, which remain in the body for an extended period of time (months or years). The memory T-cells enable the body to rapidly mount an immune response if the body is exposed to the antigen again.
Activation of B-lymphocytes
B-cell activation is also a two-step process (Fig. 22.15):

**Step 1—first stimulation.** Whereas T-cells require the presentation of antigen by APCs, B-cells can bind directly to their antigens.

**Step 2—first stimulation.** Interleukin 4 (IL-4) released from activated helper T-cells stimulates the B-cell to divide and form a clone.

When a B-cell multiplies to form a clone, the majority of cells in the clone are plasma cells. Plasma cells produce antibody molecules against the antigen then die off. A clone of B-cells also contains memory B-cells.

Lymphocyte recirculation
It is estimated that only 1 in 100,000 to 1,000,000 lymphocytes can bind to a particular antigen upon the first exposure. Therefore, a considerable period of time may pass from when an antigen enters the body to when it is detected by a lymphocyte that can recognize it. Immunocompetent lymphocytes regularly circulate throughout the body, traveling through the blood and lymph. This reduces the average time it takes for a lymphocyte to detect its antigen, compared to what it would be if each lymphocyte stayed in one location.

VI. Effector Response at Infection Site

Effector response of T-lymphocytes
Several days after exposure to an antigen, an activated helper T-cell leaves its secondary lymphatic structure and migrates to where it is needed to defend the body. Helper T-cells stimulate the proliferation of other T-cells and B-cells that have already bound to antigen. In fact, without signals from helper T-cells, there is generally little or no specific immune response (think of the disease AIDS). Cytokines released by helper T-cells also enhance the functions of non-lymphocyte WBCs to assist in defense.

Cytotoxic T-cells are the only T-cells that can kill other cells. Hence, they are sometimes called “killer T cells.” Activated cytotoxic T-cells leave the secondary lymphatic structures and roam the body looking for cells displaying the proper MHC-antigen combination. Once a cytotoxic T-cell finds such a target, it attaches to the target cell membrane and releases perforin molecules to lyse it. The T-cell is then able to move on and attack another target (Fig. 22-16). Although cytotoxic T-cells have the same killing method as NK cells, and similar sounding names, they are different! NK cells are non-specific, and cytotoxic T-cells are specific.

The roles of T-cells in the immune system are often referred to generally as cell-mediated immunity.

Effector response of B-lymphocytes
The primary role of a plasma cell is to produce antibody molecules. A plasma cell typically remains in its secondary lymphatic structure and releases antibodies that circulate through the body via lymph and blood. A single plasma cell can produce hundreds of millions of antibody...
molecules over its life span of about five days. The structure and effects of antibody molecules are discussed next.

Because antibody molecules circulate in the body fluids (humors), the role of B-cells in the immune system is often referred to as humoral immunity.

### VII. Immunoglobulins

The word “antibody” is a term for a type of protein also known as an **immunoglobulin**. An antibody molecule does not destroy its target directly, but it “tags” the target for destruction by other components of the immune system.

**Structure of immunoglobulins**

The body can produce a nearly limitless variety of immunoglobulin molecules against a nearly limitless variety of antigens. Despite the tremendous variety in antibody molecules, they all share a common basic structure (Fig. 22.17). Each antibody is made of four polypeptide chains (two “heavy chains” and two “light chains”). The four chains are bonded together to form a Y-shaped molecule called an **antibody monomer**.

The **variable regions** of the antibody form the tips of the Y. These are the parts that are different among all the antibodies, and these variable regions form the two parts of the antibody that can bind to antigen (the **antigen-binding sites**). Because each antibody has two binding sites, a single antibody can simultaneously bind two antigens, cross-linking them together in a process called **agglutination**. The **constant regions** of the antibody form the stem of the Y. The structure of the constant region determines to which one of five categories the antibody belongs.

**Actions of antibodies**

As noted above, antibodies cannot by themselves destroy antigens. However, they are able to neutralize and assist in their destruction in the following ways:

- **Neutralization**—binding of antibodies to harmful chemicals or various sites on bacteria or viruses often renders the chemical or pathogen ineffective.
- **Agglutination**—agglutination of cellular targets inactivates them and makes them easy prey for phagocytes.
- **Complement fixation**—the constant region of some antibodies binds to complement and helps complement attack the target.
- **Opsonization**—when antibodies are attached to an antigen they make it easier for phagocytic cells to recognize and destroy the antigen.
- **Activation of NK cells**—certain antibodies trigger the activity of NK cells.

**Classes of immunoglobulins**

The five major classes of immunoglobulins (Ig) are as follows (Table 22.6). The acronym G-MADE might help you to remember.

**IgG** is the most abundant antibody and it can be found in the blood, lymph, and other body fluids during an immune response. These antibodies can perform all of the functions described in the
previous section. IgG can cross the placental boundary to confer immunity to a fetus.

**IgM** exists primarily as a pentamer (five molecules joined together). The monomeric form is found on the B-cell surface where it acts as a receptor for antigen. IgM is generally the first type of antibody released by a plasma cell during a primary immune response (see below), and it circulates in the blood plasma. The pentameric form has ten antigen binding sites and is therefore particularly good at agglutination. It also fixes and activates complement.

**IgA** exists primarily as a dimer and is found in secretions including saliva, sweat, intestinal juice, and milk. It helps prevent attachment of pathogens to epithelial cell surfaces.

**IgD** is attached to the surface of B-cells (along with the monomeric form of IgM) where it acts as the receptor for antigen.

**IgE** is produced by plasma cells in the skin, mucosae of the digestive and respiratory tracts, and tonsils. Basophils and mast cells can bind to the stem portion of IgE, and binding causes the release of histamine and other chemicals that are important to inflammation and allergic responses.

### VIII. Immunologic Memory and Immunity

**Immunologic memory**

The first time the body is challenged with antigen the body produces a **primary immune response** (Fig. 22.20). Because it takes time for the activated B-cells to respond to the challenge and proliferate, the peak of antibody production occurs about two weeks after the initial challenge. If the body is exposed to the same antigen at a later time, memory cells initiate a **secondary immune response** that is both more rapid (peaking in less than a week) and more intense (with much higher levels of antibody) than the primary immune response.

**Active and passive immunity**

Immunity is generally acquired **naturally**; a person encounters an antigen as a normal part of life, and the body reacts. Immunity can also be acquired **artificially** in the form of a **vaccine**. The enhanced speed and intensity of the secondary immune response is the basis for the success of vaccination.

Whether it is acquired naturally or artificially, humoral immunity is said to be **active** if the person’s own B-cells produce the antibodies. A person can also acquire antibodies from other sources, in which case the immunity is acquired **passively**. For example, a developing fetus gets antibody molecules from its mother’s blood. These antibodies remain in the baby for several months after birth. A baby also obtains antibodies from the mother by drinking the mother’s milk. Passive immunity may also be acquired by an injection of antibodies. For example, gamma globulin may be given to a person with hepatitis, and antivenoms for snake bites are antibody molecules against the particular venom. Injection of antibodies can provide rapid protection when the danger is too great to wait for the body to produce its own antibodies.