The Immune System and Primary Immunodeficiency Diseases

Chapter 1

The immune system is composed of a variety of different cell types and proteins. Each element performs a specific task aimed at recognizing and/or reacting against foreign material.

Organization and Development of the Immune System

The immune system is a wonderful collaboration between cells and proteins that work together to provide defense against infection. These cells and proteins do not form a single organ like the heart or liver. Instead, the immune system is dispersed throughout the body to provide rapid responses to infection *(Figure 1)*. Cells travel through the bloodstream or in specialized vessels called lymphatics. Lymph nodes and the spleen provide structures that facilitate cell-to-cell communication.

The bone marrow and thymus represent training grounds for two cells of the immune system (B-cells and T-cells, respectively). The development of all cells of the immune system begins in the bone marrow with a hematopoietic (blood-forming) stem cell *(Figure 2)*. This cell is called a "stem" cell because all the other specialized cells arise from it. Because of its ability to generate an entire immune system, this is the cell that is most important in a bone marrow or hematopoietic stem cell transplant. It is related to embryonic stem cells, but is a distinct cell type. In most cases, development of one cell type is independent of the other cell types.

Primary immunodeficiencies can affect only a single component of the immune system or multiple cells and proteins. To better understand the immune deficiencies discussed later, this section will describe the organization and maturation of the immune system.

Although all components of the immune system interact with each other, it is typical to consider two broad categories of immune responses: the innate immune system and the adaptive immune system.

Innate immune responses are those that rely on cells that require no additional "training" to do their jobs. These cells include neutrophils, monocytes, natural killer (NK) cells and a set of proteins termed the complement proteins. Innate responses to infection occur rapidly and reliably. Even infants have excellent innate immune responses.

Adaptive immune responses comprise the second category. These responses involve T-cells and B-cells, two cell types that require "training" or education to learn not to attack our own cells. The advantages of the adaptive responses are their long-lived memory and the ability to adapt to new germs.

Central to both categories of immune responses is the ability to distinguish foreign invaders (things that need to be attacked) from our own tissues, which need to be protected. Because of their ability to respond rapidly, the innate responses are usually the first to respond to an "invasion." This initial response serves to alert and trigger the adaptive response, which can take several days to fully activate.

Early in life, the innate responses are most prominent. Newborn infants do have antibodies from their mother but do not make their own antibodies for several weeks.

The adaptive immune system is functional at birth, but it has not gained the experience necessary for optimal memory responses. Although this formation of memory occurs throughout life, the most rapid gain in immunologic experience is between birth and three years of age. Each infectious exposure leads to training of the cells so that a response to a second exposure to the same infection is more rapid and greater in magnitude.

Over the first few years of life, most children catch a wide variety of infections and produce antibodies directed at those specific infections. The cells producing the antibody "remember" the infection and provide long-lasting

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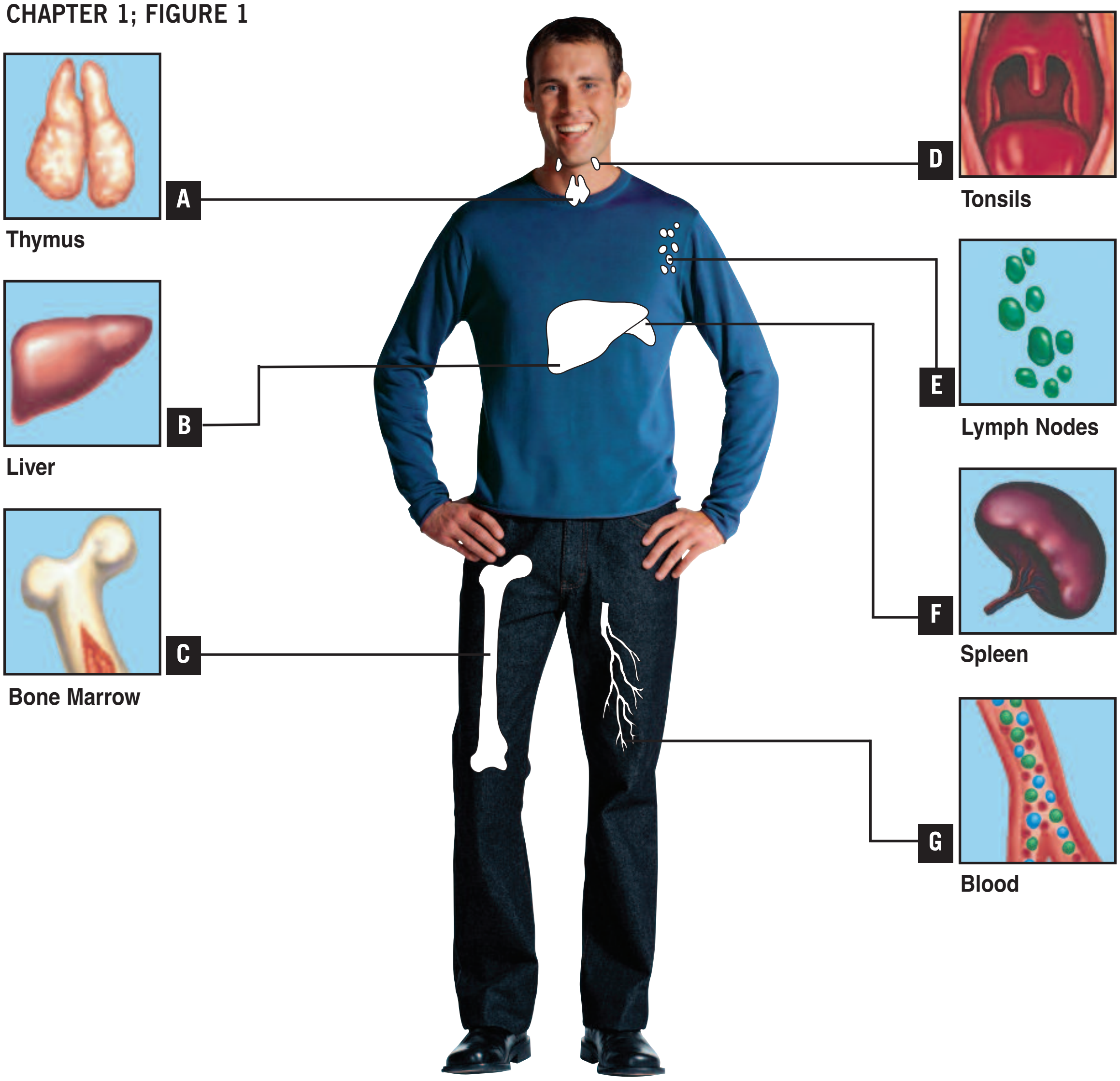
Major Organs of the Immune System

CHAPTER 1; FIGURE 1



A. Thymus: The thymus is an organ located in the upper chest. Immature lymphocytes leave the bone marrow and find their way to the thymus where they are "educated" to become mature T-lymphocytes.

B. Liver: The liver is the major organ responsible for synthesizing proteins of the complement system. In addition, it contains large numbers of phagocytic cells which ingest bacteria in the blood as it passes through the liver.

C. Bone Marrow: The bone marrow is the location where all cells of the immune system begin their development from primitive stem cells.

D. Tonsils: Tonsils are collections of lymphocytes in the throat.

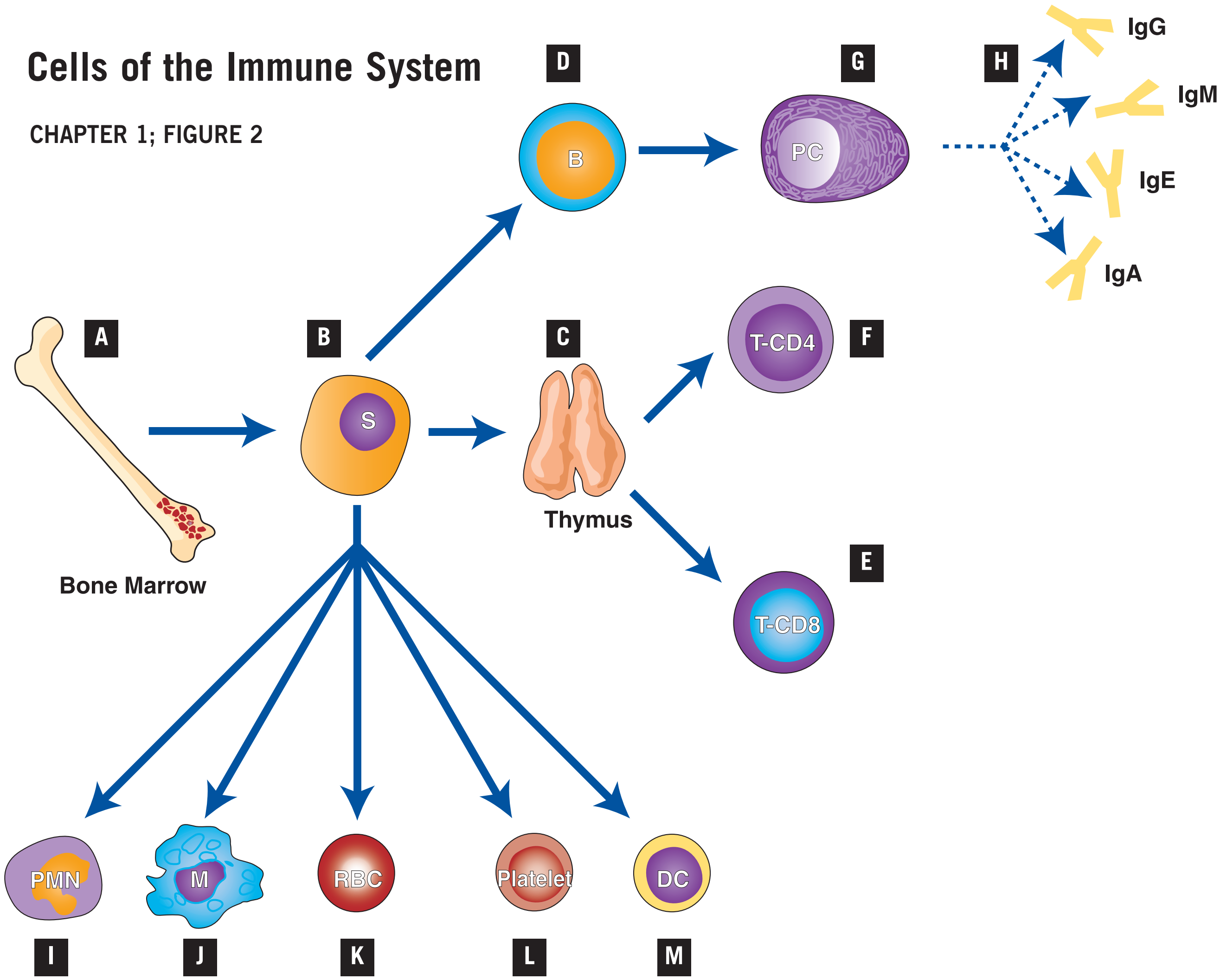
E. Lymph Nodes: Lymph nodes are collections of B-lymphocytes and T-lymphocytes throughout the body. Cells congregate in lymph nodes to communicate with each other.

F. Spleen: The spleen is a collection of T-lymphocytes, B-lymphocytes and monocytes. It serves to filter the blood and provides a site for organisms and cells of the immune system to interact.

G. Blood: Blood is the circulatory system that carries cells and proteins of the immune system from one part of the body to another.

Cells of the Immune System

CHAPTER 1; FIGURE 2



A. Bone marrow: The site in the body where most of the cells of the immune system are produced as immature or stem cells.

B. Stem cells: These cells have the potential to differentiate and mature into the different cells of the immune system.

C. Thymus: An organ located in the chest which instructs immature lymphocytes to become mature T-lymphocytes.

D. B-Cells: These lymphocytes arise in the bone marrow and differentiate into plasma cells which in turn produce immunoglobulins (antibodies).

E. Cytotoxic T-cells: These lymphocytes mature in the thymus and are responsible for killing infected cells.

F. Helper T-cells: These specialized lymphocytes "help" other T-cells and B-cells to perform their functions.

G. Plasma Cells: These cells develop from B-cells and are the cells that make immunoglobulin for the serum and the secretions.

H. Immunoglobulins: These highly specialized protein molecules, also known as antibodies, fit foreign antigens, such as polio, like a lock and key. Their variety is so extensive that they can be produced to match all possible microorganisms in our environment.

I. Neutrophils (Polymorphonuclear PMN Cell): A type of cell found in the blood stream that rapidly ingests microorganisms and kills them.

J. Monocytes: A type of phagocytic cell found in the blood stream which develops into a macrophage when it migrates to tissues.

K. Red Blood Cells: The cells in the blood stream which carry oxygen from the lungs to the tissues.

L. Platelets: Small cells in the blood stream which are important in blood clotting.

M. Dendritic Cells: Important cells in presenting antigen to immune system cells.

(Organization and Development of the Immune System continued)

immunity to it. Similarly, T-cells can remember viruses that the body has encountered and can make a more vigorous response when they encounter the same virus again. This rapid maturation of the adaptive immune system in early childhood makes testing young children a challenge since the expectations for what is normal change with age. In contrast to the adaptive immune system, the innate immune system is largely intact at birth.

Components of the Immune System

Each major component of the immune system will be discussed separately below. Immune deficiencies can affect a single component or multiple components. The manifestations of immune deficiencies can be a single type of infection or a more global susceptibility to infection. Because of the many interactions between the cells and proteins of the immune system, some immune deficiencies can be associated with a very limited range of infections. For these immune deficiencies, there are other elements that "take up the slack" and can compensate at least partly for the missing piece. In other cases, the ability to defend against infection is very weak over all and the person may have significant problems with infections.

The cells of the immune system can be categorized as lymphocytes (T-cells, B-cells and NK cells), neutrophils, and monocytes/macrophages. These are all types of white blood cells. The major proteins of the immune system are predominantly signaling proteins (often called cytokines), antibodies, and complement proteins.

Lymphocytes of the Immune System

B-Cells

B-cells (sometimes called B-lymphocytes and often named on lab reports as CD19 or CD20 cells) are specialized cells of the immune system whose major function is to produce antibodies (also called immunoglobulins or gamma-globulins). B-cells develop in the bone marrow from hematopoietic stem cells. As part of their maturation in the bone marrow, B-cells are trained or educated so that they do not produce antibodies to healthy tissues. When mature, B-cells can be found in the bone marrow, lymph nodes, spleen, some areas of the intestine, and the bloodstream.

When B-cells encounter foreign material (antigens), they respond by maturing into another cell type called plasma cells. B-cells can also mature into memory cells, which allows a rapid response if the same infection is encountered again. Plasma cells are the mature cells that actually produce the antibodies. Antibodies, the major product of plasma cells, find their way into the bloodstream, tissues, respiratory secretions, intestinal secretions, and even tears. Antibodies are highly specialized serum protein molecules.

For every foreign antigen, there are antibody molecules specifically designed to fit that antigen, like a lock and key. For example, there are antibody molecules that physically fit the poliovirus, others that fit diphtheria, and still others that fit the measles virus. The variety of different antibody molecules is extensive so that B-cells have the ability to produce them against virtually all

(Lymphocytes of the Immune System continued)

microbes in our environment. However, each plasma cell produces only one kind of antibody.

When antibody molecules recognize a microorganism as foreign, they physically attach to it and set off a complex chain of events involving other components of the immune system that work to eventually destroy the germ. Antibodies vary with respect to their specialized functions in the body. These variations are determined by the antibody's chemical structure, which in turn determines the class of the antibody (or immunoglobulin).

There are five major classes of antibodies (IgG, IgA, IgM, IgD and IgE). IgG has four different subclasses (IgG1, IgG2, IgG3, IgG4). IgA has two subclasses (IgA1 and IgA2).

Each immunoglobulin class has distinct chemical characteristics that provide it with specific functions *(Figure 3)*. For example, IgG antibodies are formed in large quantities, last in the circulation for a few weeks, and travel from the blood stream to the tissues easily. Only IgG crosses the placenta and passes some immunity from the mother to the newborn.

Antibodies of the IgA class are produced near mucus membranes and find their way into secretions such as tears, bile, saliva and mucus, where they protect against infection in the respiratory tract and intestines. Some of the IgA also appears in the circulation.

Antibodies of the IgM class are the first antibodies formed in response to infection. They are important in protection during the early days of an infection.

Antibodies of the IgE class are responsible for allergic reactions.

Antibodies protect the body against infection in a number of different ways. For example, some microorganisms, such as viruses, must attach to body cells before they can cause an infection, but antibodies bound to the surface of a virus can interfere with the virus' ability to attach to the host cell. In addition, antibodies attached to the surface of some microorganisms can cause the activation of a group of proteins called the complement system that can directly kill some bacteria or viruses.

Antibody-coated bacteria are also much easier for neutrophils to ingest and kill than bacteria that are not coated with antibodies. All of these actions of antibodies prevent microorganisms from successfully invading body tissues and causing serious infections.

The long life of plasma cells enables us to retain immunity to viruses and bacteria that infected us many years ago. For example, once people have been fully immunized with live vaccine strains of measles virus, they will almost never catch it because they retain the plasma cells and antibodies for many years and these antibodies prevent infection.

T-Cells

T-cells (sometimes called T-lymphocytes and often named in lab reports as CD3 cells) are another type of immune cell. T-cells directly attack cells infected with viruses, and they also act as regulators of the immune system.

T-cells develop from hematopoietic stem cells in the bone marrow but complete their development in the thymus. The thymus is a specialized organ of the immune system in the chest. Within the thymus, immature lymphocytes develop into mature T-cells (the "T" stands for the thymus) and T-cells with the potential to attack normal tissues are eliminated. The thymus is essential for this process, and T-cells cannot develop if the fetus does not have a thymus. Mature T-cells leave the thymus and populate other organs of the immune system, such as the spleen, lymph nodes, bone marrow and blood.

Each T-cell reacts with a specific antigen, just as each antibody molecule reacts with a specific antigen. In fact, T-cells have molecules on their surfaces that are similar to antibodies. The variety of different T-cells is so extensive that the body has T-cells that can react against virtually any antigen.

T-cells have different abilities to recognize antigen and are varied in their function. There are "killer" or cytotoxic T-cells (often denoted in lab reports as CD8 T-cells), helper T-cells (often denoted in lab reports as CD4 T-cells), and regulatory T-cells. Each has a different role to play in the immune system.

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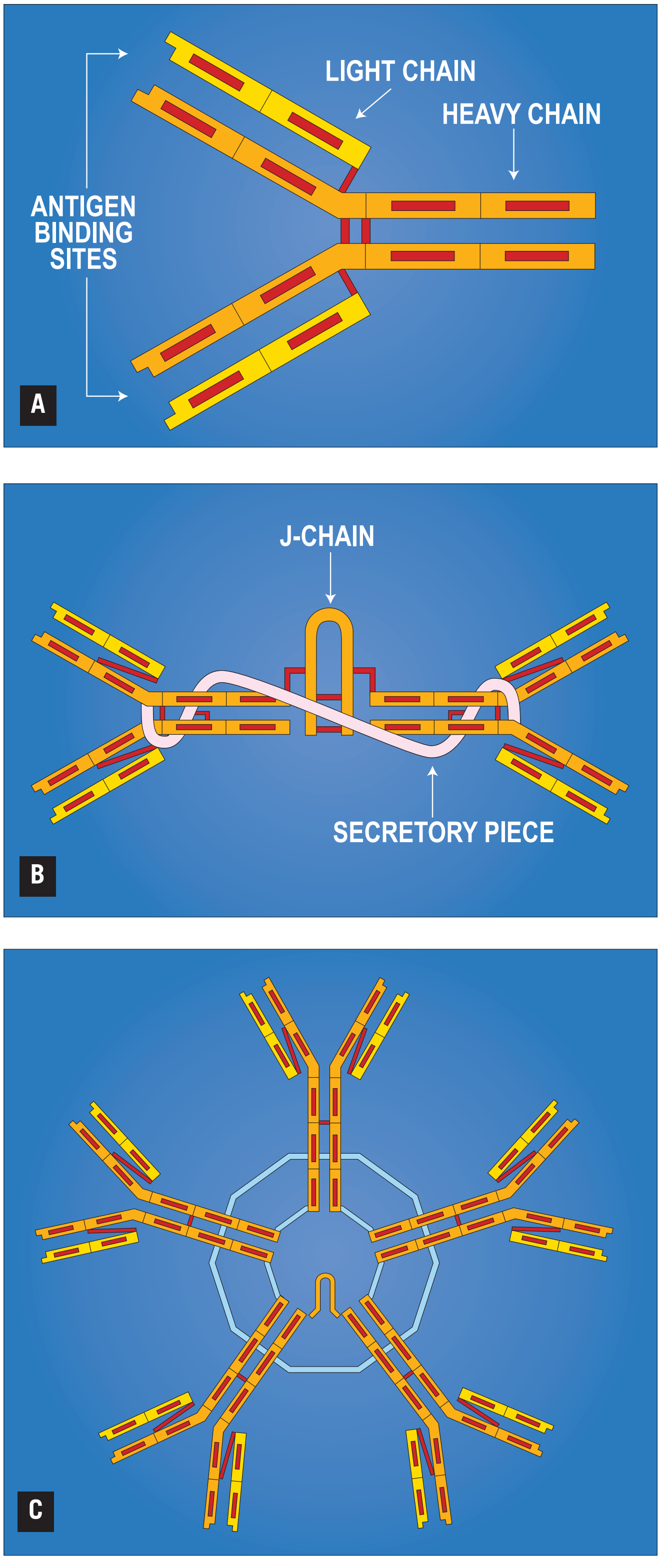
Immunoglobulin Structure

CHAPTER 1; FIGURE 3



Each class or type of immunoglobulin shares properties in common with the others. They all have antigen binding sites which combine specifically with the foreign antigen.

A. **IgG:** IgG is the major immunoglobulin class in the body and is found in the blood stream as well as in tissues.

B. **Secretory IgA:** Secretory IgA is composed of two IgA molecules joined by a J-chain and attached to a secretory piece. These modifications allow the secretory IgA to be secreted into mucus, intestinal juices and tears where it protects those areas from infection.

C. **IgM:** IgM is composed of five immunoglobulin molecules attached to each other. It is formed very early in infection and activates complement very easily.

(Lymphocytes of the Immune System continued)

Killer, or cytotoxic, T-cells perform the actual destruction of infected cells. Killer T-cells protect the body from certain bacteria and viruses that have the ability to survive and even reproduce within the body's own cells. Killer T-cells also respond to foreign tissues in the body, such as a transplanted kidney. The killer cell must migrate to the site of infection and directly bind to its target to ensure its destruction.

Helper T-cells assist B-cells to produce antibodies and assist killer T-cells in their attack on foreign substances.

Regulatory T-cells suppress or turn off other T-lymphocytes. Without regulatory cells, the immune system would keep working even after an infection has been cured. Without regulatory T-cells, there is the potential for the body to "overreact" to the infection. Regulatory T-cells act as the thermostat of the lymphocyte system to keep it turned on just enough—not too much and not too little.

NK Cells

Natural killer (NK) cells are so named because they easily kill cells infected with viruses. They are said to be "natural killer" cells as they do not require the same thymic education that T-cells require. NK cells are derived from the bone marrow and are present in relatively low numbers in the bloodstream and in tissues. They are important in defending against viruses and possibly preventing cancer as well.

NK cells kill virus-infected cells by injecting it with a killer potion of chemicals. They are particularly important in the defense against herpes viruses. This family of viruses includes the traditional cold sore form of herpes (herpes simplex) as well as Epstein-Barr virus (the cause of infectious mononucleosis) and the varicella virus (the cause of chickenpox).

Neutrophils

Neutrophils or polymorphonuclear leukocytes (polys or PMN's) are the most numerous of all the types of white blood cells, making up about half or more of the total. They are also called granulocytes and appear on lab reports as part of a complete blood count (CBC with differential). They are found in the bloodstream and can migrate into sites of infection within a matter of minutes. These cells, like the other cells in the immune system, develop from hematopoietic stem cells in the bone marrow.

Neutrophils increase in number in the bloodstream during infection and are in large part responsible for the elevated white blood cell count seen with some infections. They are the cells that leave the bloodstream and accumulate in the tissues during the first few hours of an infection and are responsible for the formation of "pus." Their major role is to ingest bacteria or fungi and kill them. Their killing strategy relies on ingesting the infecting organisms in specialized packets of cell membrane that then fuse with other parts of the neutrophil that contain toxic chemicals that kill the microorganisms. They have little role in the defense against viruses.

Monocytes

Monocytes are closely related to neutrophils and are found circulating in the bloodstream. They make up 5-10 percent of the white blood cells. They also line the walls of blood vessels in organs like the liver and spleen. Here they capture microorganisms in the blood as the microorganisms pass by. When monocytes leave the bloodstream and enter the tissues, they change shape and size and become macrophages. Macrophages are essential for killing fungi and the class of bacteria to which tuberculosis belongs (mycobacteria). Like neutrophils, macrophages ingest microbes and deliver toxic chemicals directly to the foreign invader to kill it.

Macrophages live longer than neutrophils and are especially important for slow growing or chronic infections. Macrophages can be influenced by T-cells and often collaborate with T-cells in killing microorganisms.

Cytokines

Cytokines are a very important set of proteins in the body. These small proteins serve as hormones for the immune system. They are produced in response to a threat and

(Lymphocytes of the Immune System continued)

represent the communication network for the immune system. In some cases, cells of the immune system communicate by directly touching each other, but often cells communicate by secreting cytokines that can then act on other cells either locally or at a distance.

This clever system allows very precise information to be delivered rapidly to alert the body as to the status of the threat. Cytokines are not often measured clinically but can appear on lab slips as IL-2, IL-4, IL-6, etc. Some cytokines were named before the interleukin (IL) numbering convention was started and have different names.

Complement

The complement system is composed of 30 blood proteins that function in an ordered fashion to defend against infection. Most proteins in the complement system are produced in the liver. Some of the proteins of the complement system coat germs to make them more easily taken up by neutrophils. Other complement components act to send out chemical signals to attract neutrophils to sites of infection. Complement proteins can also assemble on the surface of microorganisms forming a complex. This complex can then puncture the cell wall of the microorganism and destroy it.

Examples of How the Immune System Fights Infections

Bacteria

Our bodies are covered with bacteria and our environment contains bacteria on most surfaces. Our skin and internal mucous membranes act as physical barriers to help prevent infection. When the skin or mucous membranes are broken due to disease, inflammation or injury, bacteria can enter the body. Infecting bacteria are usually coated with complement and antibodies once they enter the tissues, and this allows neutrophils to easily recognize the bacteria as something foreign. Neutrophils then engulf the bacteria and destroy them *(Figure 4)*.

When the antibodies, complement, and neutrophils are all functioning normally, this process effectively kills the bacteria. However, when the number of bacteria is overwhelming or there are defects in antibody production, complement, and/or neutrophils, recurrent bacterial infections can occur.

Viruses

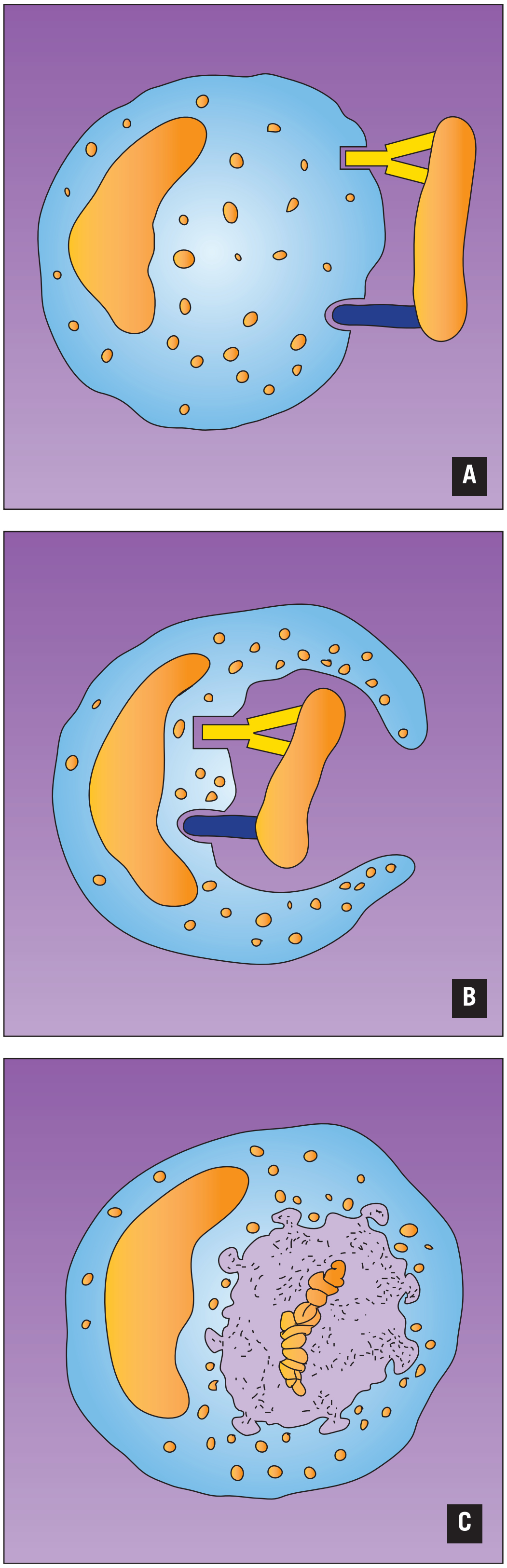
Most of us are exposed to viruses frequently. The way our bodies defend against viruses is different than how we fight bacteria. Viruses can only survive and multiply inside our cells. This allows them to “hide” from our immune system. When a virus infects a cell, the cell releases cytokines to alert other cells to the infection. This “alert” generally prevents other cells from becoming infected. Unfortunately, many viruses can outsmart this protective strategy, and they continue to spread the infection.

Circulating T-cells and NK cells become alerted to a viral invasion and migrate to the site where they kill the particular cells that are harboring the virus. This is a very destructive mechanism to kill the virus because many of our own cells can be sacrificed in the process. Nevertheless, it is an efficient process to eradicate the virus.

At the same time the T-lymphocytes are killing the virus, they are also instructing the B-lymphocytes to make antibodies. When we are exposed to the same virus a second time, the antibodies help prevent the infection. Memory T-cells are also produced and rapidly respond to a second infection, which also leads to a milder course of the infection.

Normal Anti-Bacterial Action

CHAPTER 1; FIGURE 4



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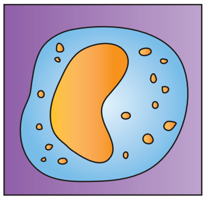
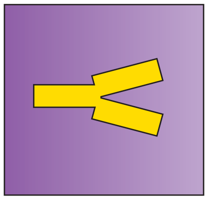
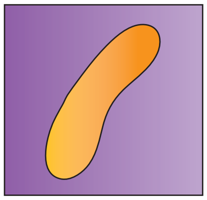


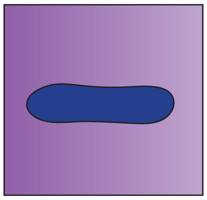
Neutrophil



Antibody



Bacteria



Complement

In most instances, bacteria are destroyed by the cooperative efforts of phagocytic cells, antibody and complement.

A. **Neutrophil (Phagocytic Cell) Engages Bacteria (Microbe):** The microbe is coated with specific antibody and complement. The phagocytic cell then begins its attack on the microbe by attaching to the antibody and complement molecules.

B. **Phagocytosis of the Microbe:** After attaching to the microbe, the phagocytic cell begins to ingest the microbe by extending itself around the microbe and engulfing it.

C. **Destruction of the Microbe:** Once the microbe is ingested, bags of enzymes or chemicals are discharged into the vacuole where they kill the microbe.

The Immune System and Primary Immunodeficiency Diseases

Immune deficiencies are categorized as primary immune deficiencies or secondary immune deficiencies. Primary immune deficiencies are “primary” because the immune system is the primary cause and most are genetic defects that may be inherited. Secondary immune deficiencies are so called because they have been caused by other conditions.

Secondary immune deficiencies are common and can occur as part of another disease or as a consequence of certain medications. The most common secondary immune deficiencies are caused by aging, malnutrition, certain medications and some infections, such as HIV.

The most common medications associated with secondary immune deficiencies are chemotherapy agents and immune suppressive medications, cancer, transplanted organ rejection or autoimmune diseases. Other secondary immune deficiencies include protein losses in the intestines or the kidneys. When proteins are lost, antibodies are also lost, leading to low immune globulins or low antibody levels. These conditions are important to recognize because, if the underlying cause can be corrected, the function of the immune system can be improved and/or restored.

Regardless of the root cause, recognition of the secondary immune deficiency and provision of immunologic support can be helpful. The types of support offered are comparable to what is used for primary immune deficiencies.

The primary immunodeficiency diseases are a group of disorders caused by basic defects in immune function that are intrinsic to, or inherent in, the cells and proteins of the immune system. There are more than 250 primary immunodeficiency diseases. Some are relatively common, while others are quite rare. Some affect a single cell or protein of the immune system and others may affect two or more components of the immune system.

Although primary immunodeficiency diseases may differ from one another in many ways, they share one important feature. They all result from a defect in one or more of the elements or functions of the normal immune system such as T-cells, B-cells, NK cells, neutrophils, monocytes, antibodies, cytokines or the complement system. Most of them are inherited diseases and may run in families, such as X-Linked Agammaglobulinemia (XLA) or Severe Combined Immune Deficiency (SCID). Other primary immunodeficiencies, such as Common Variable Immune Deficiency (CVID) and Selective IgA Deficiency are not always inherited in a clear-cut or predictable fashion. In these disorders, the cause is unknown, but it is believed that the interaction of genetic and environmental factors may play a role in their causation.

Because the most important function of the immune system is to protect against infection, people with primary immunodeficiency diseases have an increased susceptibility to infection. This may include too many infections, infections that are difficult to cure, unusually severe infections, or infections with unusual organisms. The infections may be located anywhere in the body. Common sites are the sinuses (sinusitis), the bronchi (bronchitis), the lung (pneumonia) or the intestinal tract (infectious diarrhea).

Another function of the immune system is to discriminate between the healthy tissue (“self”) and foreign material (“non-self”). Examples of foreign material can be microorganisms, pollen or even a transplanted kidney from another individual. In some immunodeficiency diseases, the immune system is unable to discriminate between self and non-self. In these cases, in addition to an increased susceptibility to infection, people with primary immunodeficiencies may also have autoimmune diseases in which the immune system attacks their own cells or tissues as if these cells were foreign, or non-self.

There are also a few types of primary immunodeficiencies in which the ability to respond to an infection is largely intact, but the ability to regulate that response is abnormal. Examples of this are autoimmune

(The Immune System and Primary Immunodeficiency Diseases continued)

lymphoproliferative syndrome (ALPS) and IPEX (an X-linked syndrome of immunodeficiency, polyendocrinopathy and enteropathy).

Primary immunodeficiency diseases can occur in individuals of any age. The original descriptions of these diseases were in children. However, as medical experience has grown, many adolescents and adults have been diagnosed with primary immunodeficiency diseases. This is partly due to the fact that some of the disorders, such as CVID and Selective IgA Deficiency, may have their initial clinical presentation in adult life. Effective therapy exists for several of the primary immunodeficiencies, and many people with these disorders can live relatively normal lives.

Primary immunodeficiency diseases were initially felt to be very rare. However, recent research has indicated that as a group they are more common than originally thought. It is estimated that as many as 1 in every 1,200–2,000 people may have some form of primary immunodeficiency.