LEARNING OBJECTIVES

1. Become familiar with the barriers the human body has to the entrance of disease producing organisms.
2. Learn the mechanisms of general or non-specific immunity.
3. Learn what an inflammatory reaction is and what purpose it serves.
4. Learn how your immune system operates to provide you with specific immunity, and the difference between active and passive immunity.
5. Learn the roles of B-lymphocytes, T-lymphocytes, and mature Helper T-cells.
6. Learn what an allergic reaction is.
7. Become familiar with the role of the immune system in the case of tissue rejection and autoimmune diseases.

INTRODUCTION

It is said that the science of immunity was born in the year 1876 when a country doctor named Edward Jenner inoculated a young boy with a cowpox virus in an attempt to protect him from a more deadly disease, smallpox. Jenner had observed that milkmaids did not seem to catch smallpox when an epidemic hit a particular area of the country. The milkmaids did catch cowpox, which was very mild. Jenner injected the boy with the cowpox virus and after a period of time injected him with the smallpox virus. The boy did not get smallpox. Based on this Jenner injected people with the cowpox virus and many of them became immune to smallpox.

Today we call the process of injecting a person with a harmless microbe to protect her/him from a pathogen (disease producing organism) vaccination. Some 4 million people, mostly children, die needlessly every year because countries don’t vaccinate enough of their youngest citizens. Although we have learned a lot about immunity and
our immune systems since Jenner’s time we still have a lot to learn. In addition to utilizing the system to protect us from diseases, it also is involved in allergies, transplants, and autoimmune diseases. So a system that has many benefits can also be a hindrance and even a death knoll for some people. In this unit we will examine the immune system, how it functions in providing resistance to foreign materials, including microorganisms, what is an allergy, what is the cause of tissue or organ rejection, and what is an autoimmune disease.

First line of defense—non-specific immunity

The human body possesses certain barriers to the entrance of foreign material, particularly microorganisms. An unbroken skin is the first or most external barrier. In addition to the dead skin layer, the secretion of the sebaceous (oil) glands is toxic to bacteria; they produce a secretion with a pH of 3-5 which inhibits growth of many organisms. Sweat contains a lysozyme which digests bacterial walls. The mucous membrane and cilia in the respiratory tract continually trap and move particles upward toward the mouth where they are usually swallowed. The mucus secreted by the digestive tract and the hydrochloric acid of the stomach serve as barriers in the digestive tract; in addition, saliva contains a lysozyme. A mucous membrane and an acid secretion protect the vagina. Thus, the three openings into the body of a female lead into channels or passageways that are protected by barriers.

Past the barriers—non-specific immunity

Certain white blood cells, macrophages neutrophils and monocytes, engulf foreign material. Phagocytosis (eating by cells) is the process of a cell engulfing a particle. Other white blood cells are involved in a specific type of immunity. Leukocytes (white blood cells) are normally present in a concentration of 5,000 to 10,000 per cubic millimeter of blood. In the case of an infection, leukocytosis occurs and the number of white blood cells increases to 10,000 to 20,000. The specific ratio of different white blood cells in this increase is often diagnostic of the type of infection. An injury that damages cells results in specific cellular exudates (substances released). These include: 1) Opsonins enhance phagocytosis; 2) Lysozymes destroy dead tissue; 3) Lymphokines cause activation and proliferation of white blood cells; 4) Complement is always in the plasma (produced by the liver) and when activated it sets off a series of reactions with the end result that holes are produced in bacterial walls or they are coated so that the bacteria are more attractive to phagocytes (fig. 27-1); and 5) Interferon is released when a virus enters the cell. This binds to the surface of non-infected cells and helps activate the cells to produce substances that prevent viruses from replicating.
Inflammatory response

Figure 27-2 illustrates an acute inflammatory response. Be aware that this response is protective in nature; it is an attempt by the body to get rid of the foreign material. It can be defined as a tissue response to a non-lethal injury. The following reactions take place: 1) Injury to blood vessels causes mast cells to release histamine which causes dilation of the blood vessels and increased permeability of the capillaries. 2) Hyperemia, which is the opening of small arterioles in the skin, occurs with a resulting increase in the redness and temperature of the skin; 3) The mast cells also release bradykinin which stimulates pain nerve endings; 4) Blood vessel permeability is increased and plasma and cells escape into the surrounding tissue, which results in swelling and pain; 5) Fluid exudate contains antibacterial compounds, antibodies, and fibrinogen, which helps form a barrier around the infection; and 6) Neutrophils and monocytes migrate to the area and phagocytize bacteria. Thus the area of infection becomes swollen, red, warm, and painful. There is usually a production of pus that consists of tissue fluid, white blood cells, dead tissue cells, and bacteria. Squeezing the area of infection to get out the pus has two major results, both undesirable: 1) the barrier produced by the fibrinogen that was converted to fibrin is broken and 2) squeezing destroys more tissue cells. The chances are that the infection and the amount of pus will now become considerably greater.

Chronic inflammatory response occurs in the case of an infection that is not cleared up but continues for a long period of time. Inhalation of insoluble particles, such as asbestos and coal dust, can lead to chronic lung irritation. The lung produces hyaline plaques that may undergo calcification and cuts down on the effectiveness of the alveolar sacs in the lung. Black lung disease was a common disease of coal miners. Most of the coal dust (carbon and silica) is removed by the alveolar macrophages with the remainder accumulating in the macrophages. Over time, these macrophages gather at the perivascular structures, and local fibrosis occurs. Tuberculosis is another example of a chronic inflammatory response. The bacterium that causes tuberculosis causes irritation of the lungs and the lungs in response produces a protective layer around the bacteria, a tubercle.
Immunity is defined as the state of being resistance to injury, particularly by poison, foreign proteins, and parasites. The body responds to the entrance of foreign proteins and parasites by the formation of compounds having specific harmful effects on the protein or organism. It takes steps to rid itself of the unwanted “visitor”, antigen. Antigens are usually protein but occasionally polysaccharides that can elicit an immune response. Antigenicity, the ability to stimulate an immune response, is partly determined by the # and type of specific antigenic sites on the foreign material. These sites are called epitopes. An interesting question is “How does the body know what items are foreign and what items belong in the body?” This ability is referred to as self.
versus nonself. The body has the amazing ability to distinguish its own cells and compounds from those of a foreign body. Virtually every body cell carries distinctive molecules that identify it as self. These compounds are coded for by genes on a specific chromosome and are referred to as MHC, major histocompatibility complex. The immune response has been discussed earlier in this unit. Most people are born with this type of immunity. Acquired immunity is a type of immunity that a person is not born with. Very early it was recognized that people who had recovered from the plague did not get it again. Although not knowing the cause, they were aware that these people had acquired “immunity.” Immunity can be classified as active and passive. Active immunity can be acquired by both having an infection or by vaccination. This results in the individual's body or immune system responding to the infection by producing antibodies against the material or organism. Active immunity is long lasting and the organism produces its own antibodies. Some of the cells involved become memory cells and thus the immunization lasts for a relatively long period of time. It does take a certain period of time for the body to produce a sufficient titer (level of antibodies) so that it can resist any future entrance of the foreign material. Passive immunity is relatively short lasting and some other organism provides the antibodies. It is fast acting and is often used to treat an already existing infection. Infants are born with relatively weak immune responses. They usually have a passive immunity as a result of the antibody IgG crossing the placental barrier from the mother’s blood to theirs. These antibodies would be those that have given immunity to the mother. The child can also receive IgA from the mother’s milk. The U. S. Food and Drug Administration has reported in 2002 that breast-fed babies are more protected from ear infections, the flu and other illnesses. The number of women in Indiana who breast-feed has risen steadily in the past decade. In 1991, about 46% of new mothers in Indiana were nursing when they left the hospital. In 2000, that number had jumped to 58% and estimates for 2001 suggest 60% of women breast-fed immediately after giving birth according to the State Department of Health. An individual can also receive passive immunity by being injected with an antiserum containing antibodies.

**Immune response**

There are four general steps in the immune response (fig. 27-3). The antigen must be recognized as being foreign. The antigen must be processed; its epitopes “read” so that a specific compound can be formed to neutralize it. The processed antigen must be displayed. Plasma cells produce antibodies to neutralize the antigen. Helper T cells stimulate B cells to clone. Some of the B cells become plasma cells and some become memory cells, which retain the ability to secrete antibodies (fig. 27.4). These memory cells can be called into action in a relatively short period of time. The process is referred to as humoral (B-cell) immunity. Humoral refers to the fluid, in this case, the plasma because the antibodies are carried in the blood.
Figure 27-3. Four general steps in the immune response.
**Figure 27-4. Production of clones of plasma cells and memory cells.**

T-cells are responsible for cell-mediated immunity. Mature Helper T-cells are necessary to activate cytotoxic T-cells, which then destroy infected cells. The mature cytotoxic T-cells produce chemicals (perforin, granzymes, and hydrolytic enzymes which produce apoptosis (Apoptosis is a distinctive type of cell death in which single or small groups of cells are deleted from their tissue or organ.) Figure 27-5 shows the reactions necessary to produce a mature Helper T-cell and an activated cytotoxic cell. From this information, you should be aware that Helper T-cells are necessary for both humoral and cell mediated responses. Later when we discuss AIDS, you will better understand the reason that the AIDS virus is so deadly when it destroys the Helper T-cells.
**Allergies**

Reaction to a normally harmless environmental substance—dust, pollen, food, drug, etc—is called an allergic reaction (fig. 27-6) The substance producing the reaction is called an allergen. Upon the first exposure to the allergen, B-cells produce and release large amounts of IgE (antibody). The IgE molecules attach themselves to the surface of mast cells in tissues or basophils in the circulation. Mast cells are abundant in the lungs, skin, tongue, and linings of the nose and intestinal tract. A subsequent exposure of a sensitized individual to some allergen elicits an immune attack, which may vary from a mild annoying reaction to a severe, body damaging reaction that may cause death, by what is called anaphylactic shock. This is due to the IgE stimulating the mast cells or basophils to release chemicals from within the cells.

These chemicals include histamine, heparin, and substances that activate blood platelets and attract cells such as eosinophils and neutrophils. The cells also synthesize prostoglandins and leukotrienes. These chemical mediators cause wheezing, sneezing, runny eyes and itching. These changes are referred to as immediate B-cell responses. May result in anaphylactic shock which is life threatening. It results from swelling of body tissues (throat) and a sudden fall in blood pressure due to increased permeability of capillaries. Injection of epinephrine can reverse this reaction.
Slow hypersensitivity response is the result of T cells migrating to the tissues. Usually occurs about 48 hours after exposure. Induces prolonged and profound contraction of smooth muscle, and increased permeability of capillaries. Delayed hypersensitivity responses usually are caused by infectious agents, such as mycobacteria, protozoa, and fungi. These organisms present a chronic antigenic
stimulus, and the T cells and macrophages react and sometime confer protective immunity against later exposure. Usually antihistamines will alleviate the symptoms. Poison ivy is another type of delayed hypersensitivit response. Chemicals in the plants, not proteins, bind to cell membrane proteins and are recognized by antigen-specific lymphocytes. Greatest effect seen in about 24 to 48 hours after exposure. Antihistamines have no affect on the symptoms but corticosteroids do.

**Tissue transplants**

Since organ transplant was introduced over 30 years ago, it has been accepted as a life-saving method for persons suffering from certain diseased organs. A problem is that the transplant is a foreign tissue and the recipient’s body tends to reject this foreign material. For a transplant to take, the immune system of the recipient must be made to suppress its natural tendency to reject the transplant. Remember that each individual has specific markers on her/his cells; therefore the transplant has different markers. Before a transplant is undertaken, tissue typing or histocompatibility testing is done. Because the testing is usually done on white blood cells the markers are referred to as HLA, human leukocyte antigens. There are number of different HLA antigens in different individuals in as many as 20 varieties. The number of possible HLA types is about 10,000. The testing is to determine if the donor and the recipient share HLAs. The larger the number of matched HLAs the better the chance for a successful transplant. Identical twins are the best match and next close relatives such as brothers and sisters. In addition to getting the best HLA match, it is possible to suppress the immune system of the recipient; this is called **immunosuppression**. Steroids suppress lymphocyte function. The drug cyclosporine holds down production of lymphokine (interleukin), which is necessary for T-cell growth. If this fails, another treatment, KOT3 is used. It is a monoclonal antibody that seeks out the T3 marker on all mature T cells. By destroying the T cells or incapacitating them, KOT3 can stop an acute rejection.

**Autoimmune diseases**

Sometimes the immune system’s recognition apparatus breaks down and the body begins to make antibodies and T cells against the body’s own constituents. These are called **autoantibodies**. These diseases include: 1) anemia as the result of autoantibodies against red blood cells; 2) juvenile diabetes as the result of autoantibodies against the cells of the pancreas; 3) myasthenia gravis as the result of autoantibodies against nerve and muscle cells; 4) rheumatoid arthritis as the result of autoantibodies against tissues in the joints; and 5) lupus erythematosus as the result of autoantibodies against many components, including DNA, RNA, and proteins. Autoimmune diseases affect the immune system at several levels. B-cells may become hyperactive or/and the suppressor cells become underactive. Or suppressor cells for T-cells may be defective; this is the case in certain types of rheumatoid arthritis.

Lack of one or more components of the immune system results in an **immunodeficiency disease**. These can be inherited or acquired as a result of a disease. Very rarely, infants are born lacking all the major immune defenses. This is known as severe combined immunodeficiency disease, SCID. These are the children referred to as “bubble” children because they have to live in a sterile environment to protect them from all pathogens. We will refer to the treatment of some SCID patients in the unit on New Methods of Disease Treatment.
OBJECTIVE QUESTIONS OVER IMMUNITY AND DISEASE

1. A low pH (acid condition) serves as a barrier in the (A) respiratory and digestive systems (B) respiratory and reproductive systems (C) digestive and reproductive systems.

2. (A) Opsonins (B) Lysozymes (C) Lymphokines (D) Complement (E) Interferon cause(s) holes in bacterial cell walls.

3. The normal white blood cell count is about (A) 1,000-5,000 (B) 5,000-10,000 (C) 10,000-15,000 (D) 15,000-20,000 per cubic milliliter of blood.

4. The pain associated with an acute inflammatory response is due to (A) bradykinin (B) excess fluid (C) both A and B (D) neither A or B.

5. Phagocytes are (A) tissue cells (B) red blood cells (C) white blood cells (D) platelets.

6. Histamine is secreted by (A) lymphocytes (B) neutrophils (C) mast cells (D) platelets.

7. MHC stands for (A) major histocompatibility complex (B) measured hemoglobin content (C) minimum hemoglobin count (D) multiple health counts.

8. Passive immunity (A) lasts longer (B) is effective more rapidly (C) is due to self produced antibodies (D) two of the preceding (E) all the preceding than/as active immunity.

9. An infant may have obtained passive immunity from (A) its mother’s blood (B) its mother’s milk (C) both A and B (D) neither A or B.

10. Most antigens are (A) carbohydrates (B) lipids (C) proteins.

11. The first step in developing an immune response is (A) displaying a processed antigen (B) processing an antigen (C) producing antibodies (D) recognizing an antigen.

12. (A) B-cells (B) T-cells (C) Both A and B (D) Neither A or B produce antibodies.

13. T-Helper cells are necessary for the production of (A) antibody producing plasma cells (B) activated cytotoxic T-cells (C) both A and B (D) neither A or B.
14. Allergens result in B-cells producing (A) IgA (B) IgB (C) IgD (D) IgE antibodies.

15. The slow response to an allergen is the result of (A) B-cell action (B) T-cell action (C) both A and B (D) neither A or B.

16. There about (A) 10 (B) 100 (C) 1,000 (D) 10,000 possible HLA types.

17. Cyclosporine acts to (A) increase B-cell production (B) increase red blood cell production (C) suppress the immune response (D) destroys T-cells.

18. Which of the following autoimmune diseases is the result of T-cell action? (A) juvenile diabetes (B) lupus erythematosus (C) rheumatoid arthritis (D) myasthenia gravis.

19. SCID is the result of (A) no white blood cells (B) no red blood cells (C) inability of the blood to clot (D) lacking all elements of the immune system.

20. The immune system is involved in (A) resistance to disease producing organisms (B) transplant rejection (C) allergies (D) two of the preceding (E) all the preceding.

DISCUSSION QUESTIONS OVER IMMUNITY AND DISEASE

1. Smoking decreases or destroys the ciliary action of the respiratory tract. Explain how this results in smoker’s cough in the morning.

2. The female reproductive system has an acid secretion, which serves as a barrier to entrance of microorganisms. The male system does not. What might be the evolutionary significance of this difference?

3. An acute inflammatory response is defined as a tissue response to non-lethal injury. What is the overall biological result of this response?
4. Both having an infection and getting a vaccination can result in a person developing active immunity to a disease. What is the difference between the two in so far as the effect(s) on the individual?

5. Do all humans possess the same MHCs? Explain.

6. List some of the ways the body communicates with white blood cells (leukocytes).

7. What historic perspective is there to the inflammatory response as it responds to a bacterial invasion?

8. Based upon the concepts of epitopes, how would it be possible to provide immunity to a disease produced by a virus without subjecting the patient to a virus that could cause the disease?

9. Of what value are B memory cells?

10. How is it possible for a person to develop an allergy later in life when he/she did not have the allergy earlier?

11. Knowing the mechanisms of fast response to an allergen, how can these result in anaphylactic shock?
12. What is one of the problems with taking immunosuppression drugs?

13. My sister suffers from rheumatoid arthritis; she takes steroids as a treatment. This does not cure her but it does diminish the symptoms. Explain.

14. Where is the record or history involved in an allergic reaction recorded in the human being?

15. In the case of the body producing autoantibodies, what aspect(s) of the immune system is not working properly?