Instructor's Answer Key

Chapter 15: The Immune System

Answers to Test Your Understanding of Concepts and Principles

1. Antibodies (immunoglobulins) bind to antigens on the bacterial target surface and in the process stimulate nonspecific immune processes that destroy the bacteria. Bacteria that are "buttered" with antibodies become targets for phagocytosis by neutrophils and macrophages (opsonization). Immune destruction of bacteria is also promoted by antibody-induced activation of the cascade leading to serum *complement fixation*. Using either the classic pathway that is more rapid and efficient or the alternative pathway, antibodies activate sequences of serum complement proteins that ultimately are inserted into the bacterial cell membrane forming a membrane attack complex. The attack complex is a large pore that can kill the bacterial cell through the osmotic influx of water. Also, free complement fragments participate in various ways: (1) chemotaxis; (2) opsonization; and (3) stimulation of histamine release. [Note: This question is also answered in the Student Study Guide.]

2. There are three major categories of interferons: alpha, beta, and gamma interferons. Almost all cells in the body make alpha and beta interferon. These polypeptides act as messengers that protect other cells in the vicinity from viral infection. The viruses are still able to penetrate these other cells, but the ability of the viruses to replicate and assemble new virus particles is inhibited. Particular lymphocytes and a related type of cell called natural killer cells only produce gamma interferon. The secretion of gamma interferon by these cells is part of the immunological defense against infection and cancer. Alpha interferon is now being used to treat hepatitis C, hairy-cell leukemia, virally induced genital warts, and Karposi's sarcoma. Beta interferon is used to treat relapsing-remitting multiple sclerosis and gamma interferon has been approved to treat chronic granulomatous disease.

3. All cells in the body except red blood cells make class-1 MHC molecules. Class-2 MHC molecules are produced only by macrophages, dendritic cells, and B-lymphocytes as antigen presenting cells to help promote the interactions between helper T cells and B-cell immune response.

4. When a foreign particle infects the body it is taken into macrophages (or dendritic cells) by phagocytosis and partially digested. Within the macrophage, the partially digested virus particles provide foreign antigens that are moved to the surface of the cell membrane. At the membrane, these foreign antigens form a complex with the class-2 MHC molecules. The macrophages thereby "present'' the antigens to the helper T cells that are now able to activate the appropriate T cell response to the specific antigen.

5. There are two subtypes of helper T lymphocytes (with the CD4 surface molecule), designated T_H1 and T_H2. T_H1 lymphocytes produce interleukin-2 and gamma interferon; activate killer T cells and promote cell-mediated immunity. This subtype also stimulates nitric oxide production in macrophages that is required for macrophages to destroy bacteria and tumor cells. T_H2 lymphocytes secrete interleukin-4, interleukin-5, and interleukin-10, and other lymphokines that stimulate B lymphocytes to promote humoral immunity. Research indicates that "uncommitted" helper T lymphocytes are changed into the T_H1 subtype in response to a cytokine called interleukin-12 secreted by macrophages and dendritic cells under certain conditions.

6. Plasma cells are activated B lymphocytes that attack specific antigens by releasing antibodies (~ 2000 antibody proteins per second) into the circulation or interstitial fluid. These antibodies attach themselves to antigens displayed on the surface of the bacteria or pathogenic organism and can then lead to the destruction of these targets in one of two ways. First, "buttering" or coating of an antigen with antibodies makes the antigen more susceptible to phagocytosis by macrophages or neutrophils. This facilitation is known as opsonization. Antibody coating can also activate the complement system. In this system an enzyme cascade results in the formation of pores in the plasma membrane of the invading cells. Presence of these pores leads to lysis of the cells. Similarly killer T lymphocytes destroy target cells through the formation of pores in the membrane of the foreign cell. These pores are composed of a protein known as *perforin*, which is secreted by the killer T lymphocyte upon direct physical contact with the invading cell.

7. Two theories exist as to the method of formation of tolerance. The clonal *deletion* theory says that mostly during fetal life, lymphocytes that produce antibodies against self-antigens are recognized and destroyed. Evidence shows that this occurs in the thymus during the maturation of T lymphocytes (T cell tolerance). The clonal *anergy* theory says that through some not yet understood mechanism cells directed against self-antigens are present throughout life but are suppressed and do not attack those antigens (B cell tolerance). Diabetes mellitus is an autoimmune disease in which antibodies are produced against the beta cells of the pancreatic islets causing these cells to be destroyed. The body can no longer produce insulin if these cells are destroyed and diabetes mellitus results. Rheumatoid arthritis is an autoimmune complex disease where IgM autoantibodies (rheumatoid factor) are produced against IgG antibodies causing inflammation of joints.

8. Vaccinations confer active immunity (secondary response protection) because the person is injected with antigens (killed or attenuated pathogens or their toxins). Each lymphocyte is genetically able to produce one type of antibody, or (for T cells) attack one type of antigen by other means. The antigen that is involved can bind to a receptor protein on the surface of that lymphocyte in a specific manner. Following a vaccination, when such binding occurs, the lymphocyte is stimulated to proliferate and develop a clone of cells competent to attack that antigen. So, upon subsequent exposure to the same antigen, the person has many more competent lymphocytes and is able to combat the infection much more effectively than was possible upon the primary exposure.

9. Passive immunity is a type of immunity where the antibody is produced by one individual and then given to protect another individual. An example of passive transfer occurs with antibodies found in a baby that were produced by the mother. The baby receives these antibodies either by them crossing the placenta prenatally or by breast-feeding postnatally. Passive immunity can also be conferred by the injection of serum containing a certain antibody. These sera are known as antisera or antitoxins. To produce an antitoxin an animal is exposed to a pathogen by injection. After a period of time long enough for this animal to begin producing antibodies against this toxin, blood is taken from this animal and the antibodies are isolated from the blood and prepared as antitoxins to be used clinically to immediately protect people who have been exposed that toxin, or infectious agent.

10. *Immediate* hypersensitivity is a process mediated by IgE antibodies due to an abnormal B lymphocyte response to an allergen (producing symptoms within seconds or minutes). These IgE antibodies attach to tissue mast cells and basophils, and when exposed to the same allergen results in the release of histamine. The release of histamine from mast cells and basophils leads to such allergic symptoms as runny or stuffy nose, conjunctivitis, allergic asthma, hives, sneezing, itching, and inflammation. *Delayed* hypersensitivity, by contrast, is mediated by an abnormal T cell response (producing symptoms between 24 and 72 hours after exposure). When these T lymphocytes come in contact with an allergen they release lymphokines, which lead to the development of inflammation characteristic of such an allergic reaction. Examples of delayed hypersensitivity are contact dermatitis caused by poison oak, poison ivy, and poison sumac; and skin tests for tuberculosis (Mantoux test). Immediate hypersensitivity is treated with antihistamine drugs which block the action of histamine released by the mast cell (block the H_1-histamine receptor). Delayed hypersensitivity cannot be treated with antihistamines, because it is not caused by the release of histamine but by the release of lymphokines. At present, corticosteroids are the only drugs that can effectively treat delayed hypersensitivity.

Answers to Test Your Ability to Analyze and Apply Your Knowledge

1. The innate (nonspecific) defense mechanisms distinguish between the kinds of carbohydrates that are produced by mammalian cells and those produced by bacteria. The bacterial carbohydrates that "flag" the cell for phagocytic attack are part of the glycoproteins and lipopolysaccharides on the bacterial cell wall. This immune defense against the invasion by bacteria is inherited as part of our genome and therefore is limited in its ability to combat the spectrum of foreign pathogens. By contrast, the specific T lymphocyte immune response is usually directed against only selected protein antigens and can complement the protection provided innately. Unlike B cells, T cells do not make antibodies and thus do not have antibodies on their surfaces to serve as receptors for these protein antigens. These T cells do, however have a different type of antigen receptor (coreceptor) on their membrane surfaces that cannot bind to free antigens. In order for T lymphocytes to respond to foreign antigens, the antigens must be presented to the T cells on the membrane of antigen-presenting cells, such as macrophages or dendritic cells - a killing process that is highly evolved and highly specific against protein antigens.

2. Fever may be a component of the nonspecific defense system. Divide a random group of lizards into three groups: one at "normal" lizard temperature, one at "mild" fever temperature, and a third group of "high" fever lizards. Inject the lizards with an infectious agent, fever-inducing pyrogen, or endotoxin from bacteria to promote the fever response and return the animals into the three different temperature environments. Observe and compare the recovery time for the three groups. The hypothesis is that the "mild" fever temperature group should recover the fastest.

3. By being composed of four different protein chains, antibodies can present themselves in different combinations that exhibit tremendous diversity of responses to different antigen molecules. Although limited in their numbers, antibodies that bind to particular antigens can cross-react with closely related antigens to some extent, ensuring that there will be some antibodies that can combine with almost any antigen a person might encounter. Despite the enormous number of antibodies present in the body, there are only a few hundred genes that code for different H chains and a few hundred that code for different L chains. The number of possible combinations is partly responsible for the tremendous diversity in antibodies produced. Furthermore, different segments of DNA code for different segments of the heavy and light chains. Three segments in the antigen-combining region of a heavy chain and two in a light chain are coded by different segments of DNA and can be combined in different ways to make an antibody molecule. Finally, somatic mutations that occur with age as lymphocyte populations divide producing an increase in number and diversity of lymphocyte progeny. If each antibody were coded for by one gene there would be only one protein configuration possible and antibody diversity would not exist.

4. Allergy (immediate hypersensitivity) is produced when antibodies of the IgE subclass attach to tissue mast cell membrane receptors and stimulate histamine release. A drug that destroys all mast cells would interrupt immediate hypersensitivity responses and help prevent the unpleasant symptoms of allergies. Mast cells would not degranulate with the release of various chemicals, including histamine. The symptoms of hay fever such as itching, sneezing, tearing, and runny nose that are the result of histamine vasodilation, would be absent. Also, the normal histamine-related discomfort and difficulty in breathing due to bronchoconstriction would no longer be present. However, the exaggerated blood vessel smooth muscle relaxation and subsequent drop in blood pressure could result in negative side effects. Mast cells also contain heparin, an important anticoagulant molecule. The lack of mast cells therefore increases the risk of spontaneous blood clotting and hemostasis. There would also be a lack of other chemicals normally released from mast cells including inflammatory prostaglandins and leukotrienes, a variety of cytokines that promote inflammation, and tumor necrosis factor$_{\alpha}$ (TNF$_{\alpha}$)

5. After few days of battling an infection, the FAS ligand molecule begins to be expressed on the surface of activated T lymphocytes. The binding of normal FAS surface receptors to newly formed FAS ligand on the same or different activated T lymphocytes triggers the apoptosis (cell suicide) of the aggressive lymphocytes. The discovery of this mechanism in the placenta helps to maintain mother-fetus boundary as an immunologically privileged site. The fetus is sheltered from immune attack by the mother's T lymphocytes because the presence of FAS ligand in the placenta will trigger the apoptosis of any T lymphocytes that may enter the area.