CLINICAL FOCUS

Disorders of the Lymphatic System

It is not surprising that many infectious diseases produce symptoms associated with the lymphatic system. The lymphatic system is involved with the production of lymphocytes, which fight infectious diseases, and the lymphatic system filters blood and lymph to remove microorganisms. **Lymphadenitis** (lim-fad′ĕ-nī′tis) is an inflammation of the lymph nodes, which causes them to become enlarged and tender. This inflammation is an indication that microorganisms are being trapped and destroyed within the lymph nodes. Sometimes the lymphatic vessels become inflamed to produce **lymphangitis** (lim-fan-jī′tis). This often results in visible red streaks in the skin that extend away from the site of infection. If microorganisms pass through the lymphatic vessels and nodes to reach the blood, **septicemia** (sep-ti-sē′mē-ă), or blood poisoning, can result (see chapter 19).

Bubonic (boo-bon′ik) **plague** is caused by bacteria (*Yersinia pestis*), which are transferred from rats to humans by the bite of the rat flea (*Xenopsylla*). The bacteria localize in the lymph nodes, causing them to enlarge. The term *bubonic* is derived from a Greek word referring to the groin because the disease often causes the inguinal lymph nodes of the groin to swell. Without treatment, the bacteria enter the blood, multiply, and infect tissues throughout the body, rapidly causing death in 70%–90% of those infected. In the sixth, fourteenth, and nineteenth centuries, the bubonic plague killed large numbers of people in Europe. Because of improved sanitation and the advent of antibiotics, relatively few cases occur today.

Lymphedema (limf′e-dē′mă) is the abnormal accumulation of lymph in tissues, often the upper or lower limbs due to disruption of lymph flow. **Primary lymphedema** is caused by a developmental defect of the lymphatic system that generally affects the lower limbs; it can be manifested anytime in life. For unknown reasons, it occurs primarily in women (70%–90% of cases). Some primary lymphedemas are inherited. **Hereditary lymphedema type I** (Milroy syndrome) has been mapped to mutations of the vascular endothelial growth factor receptor 3 gene on chromosome 5. Activation of this receptor on endothelial cells causes the proliferation of lymphatic vessels, but not blood vessels. **Secondary lymphedema** is caused by a disease or another pathologic condition that affects an otherwise normal lymphatic system. In the United States, secondary lymphedema is most commonly caused by certain cancer treatments. Worldwide, the major cause is a parasitic infection of the lymphatic system called **elephantiasis** (el-ĕ-fan-tī′ă-sis). Over 120 million people have elephantiasis, which is the most dramatic form of lymphedema. It is caused by long, slender roundworms (*Wuchereria bancrofti*). The adult worms lodge in the lymphatic vessels and block lymph flow. The resulting accumulation of fluid in the interstitial spaces and lymphatic vessels can cause permanent swelling and enlargement of a limb. The affected limb supposedly resembles an elephant's leg, the basis for its name. The offspring of the adult worms pass through the lymphatic system into the blood, from which they can be transferred to another human by mosquitoes.

A **lymphoma** (lim-fō′mă) is a neoplasm (tumor) of lymphatic tissue. Lymphomas are usually divided into two groups: (1) Hodgkin disease and (2) all other lymphomas, which are called non-Hodgkin lymphomas. Typically, lymphomas begin as an enlarged, painless mass of lymph nodes. The immune system is depressed, and the patient has an increased susceptibility to infections. Enlargement of the lymph nodes can also compress surrounding structures and produce complications. Fortunately, treatment with drugs and radiation is effective for many people who suffer from lymphoma.

CLINICAL FOCUS

Immune System Problems of Clinical Significance

HYPERSENSITIVITY REACTIONS

Immune and hypersensitivity (allergy) reactions involve the same mechanisms, but the differences between them are unclear. Both require exposure to an antigen and subsequent stimulation of antibody-mediated immunity or cell-mediated immunity (or both). If immunity to an antigen is established, later exposure to the antigen results in an immune system response that eliminates the antigen, and no symptoms appear. In **hypersensitivity reactions,** the antigen is called an **allergen,** and later exposure to the allergen stimulates much the same process that occurs during the normal immune system response. The processes that eliminate the allergen, however, also produce undesirable side effects, such as a very strong inflammatory reaction. This immune system response can be more harmful than beneficial and can produce many unpleasant symptoms. Hypersensitivity reactions are categorized as immediate or delayed.

Immediate Hypersensitivities

An **immediate hypersensitivity reaction** occurs when antibodies interact with allergens and cause symptoms to appear within a few minutes of exposure to the allergens. Immediate hypersensitivity reactions include atopy, anaphylaxis, cytotoxic reactions, and immune complex disease.

Atopy (at′ō-pē) is a localized IgE-mediated hypersensitivity reaction. For example, plant pollens can be allergens that cause hay fever when they are inhaled and absorbed through the respiratory mucosa. The resulting localized inflammatory response produces swelling of the mucosa and excess mucus production. In asthma patients, allergens can stimulate the release of leukotrienes and histamine in the bronchioles of the lung, causing constriction of the smooth muscles of the bronchioles and difficulty in breathing. Hives (urticaria) is an allergic reaction that results in a skin rash or localized swellings and is usually caused by an ingested allergen.

Anaphylaxis (an′ă-fi-lak′sis) is a systemic IgE-mediated reaction that can be life-threatening. The introduction of allergens, such as drugs (e.g., penicillin) and insect stings, is the most common cause. The chemicals released from mast cells and basophils cause systemic vasodilation, a drop in blood pressure, and cardiac failure. Symptoms of hay fever, asthma, and hives may also be observed.

In **cytotoxic reactions,** IgG or IgM combines with the antigen on the surface of a cell, resulting in the activation of complement and subsequent lysis of the cell. A cytotoxic reaction against a bacterial cell can be protective, but against a human cell it can be harmful. Transfusion reactions caused by incompatible blood types, hemolytic disease of the newborn (see chapter 19), and some types of autoimmune disease are examples of harmful cytotoxic reactions.

Immune complex disease occurs when too many immune complexes are formed. Immune complexes are combinations of soluble antigens and IgG or IgM. When too many immune complexes are present, too much complement is activated, and an acute inflammatory response develops. Complement attracts neutrophils to the area of inflammation and stimulates the release of lysosomal enzymes. This release causes tissue damage, especially in small blood vessels, where the immune complexes tend to lodge, and lack of blood supply causes tissue necrosis. Some examples of immune complex disease are serum sickness, some autoimmune diseases, chronic graft rejection, and Arthus reactions.

An **Arthus reaction** is a localized immune complex reaction. For example, suppose an individual has been sensitized to antigens in the tetanus toxoid vaccine because of repeated vaccinations. If that individual were vaccinated again, large amounts of antigen in the vaccine would be present at the injection site. Antibodies could complex with the antigens, causing a localized inflammatory response, neutrophil infiltration, and tissue necrosis. **Serum sickness** is a systemic Arthus reaction in which the antibody–antigen complexes circulate and lodge in many different tissues. Symptoms include fever, hives, swollen lymph nodes and spleen, and arthritis.

Delayed Hypersensitivity

Delayed hypersensitivity is mediated by T cells, and the symptoms usually take several hours or days to develop. Like immediate hypersensitivity, delayed hypersensitivity is an acute extension of the normal operation of the immune system. Exposure to the allergen causes the activation of T cells and the production of cytokines. The cytokines attract basophils and monocytes, which differentiate into macrophages. The activities of these cells result in progressive tissue destruction, loss of function, and scarring.

Delayed hypersensitivity can develop as allergy of infection and contact hypersensitivity. **Allergy of infection** is a side effect of cell-mediated efforts to eliminate intracellular microorganisms, and the amount of tissue destroyed is determined by the persistence and distribution of the antigen. The minor rash of measles results from tissue damage as cell-mediated immunity destroys virus-infected cells. In patients with chronic infections with long-term antigenic stimulation, the allergy-of-infection response can cause extensive tissue damage. The destruction of lung tissue in tuberculosis is an example.

Contact hypersensitivity is a delayed hypersensitivity reaction to allergens that contact the skin or mucous membranes. Poison

ivy, poison oak, soaps, cosmetics, drugs, and a variety of chemicals can induce contact hypersensitivity, usually after prolonged exposure. The allergen is absorbed by epithelial cells, and T cells invade the affected area, causing inflammation and tissue destruction. Although itching can be intense, scratching is harmful because it damages tissues and causes additional inflammation.

AUTOIMMUNE DISEASE

In **autoimmune disease,** the immune system fails to differentiate between self-antigens and foreign antigens. Consequently, an immune system response is produced against some self-antigens, resulting in tissue destruction. In many instances, autoimmunity probably results from a breakdown of tolerance, which normally prevents an immune system response to self-antigens. In a situation called molecular mimicry, a foreign antigen that is very similar to a self-antigen stimulates an immune system response. After the foreign antigen is eliminated, the immune system continues to act against the self-antigen. It is hypothesized that type I diabetes (see chapter 18) develops in this fashion. In susceptible people, a foreign antigen can stimulate adaptive immunity, especially cell-mediated immunity, which destroys the insulin-producing beta cells of the pancreas. Other autoimmune diseases that involve antibodies are celiac disease, rheumatoid arthritis, rheumatic fever, Graves disease, systemic lupus erythematosus, and myasthenia gravis.

IMMUNODEFICIENCY

Immunodeficiency is a failure of a part of the immune system to function properly. A deficient immune system is not uncommon because it can have many causes. Inadequate protein in the diet inhibits protein synthesis, thereby allowing antibody levels to decrease. Stress can depress the immune system, and fighting an infection can deplete lymphocyte and granulocyte reserves, making a person more susceptible to further infection. Diseases that cause the proliferation of lymphocytes, such as mononucleosis, leukemias, and myelomas, can result in an abundance of lymphocytes that do not function properly. Finally, the immune system can purposefully be suppressed by drugs to prevent graft rejection.

Congenital (present at birth) immunodeficiencies can involve inadequate B-cell formation, inadequate T-cell formation, or both. **Severe combined immunodeficiency disease (SCID)** in which both B and T cells fail to differentiate, although rare, is probably the best known. Unless the person suffering from SCID is kept in a sterile environment or is provided with a compatible bone marrow transplant, death from infection results.

TUMOR CONTROL

Tumor cells have tumor antigens that distinguish them from normal cells. According to the concept of **immune surveillance,** the immune system detects tumor cells and destroys them before a tumor can form. T cells, natural killer cells, and macrophages are involved in the destruction of tumor cells. Immune surveillance may exist for some forms of cancer caused by viruses. The immune response appears to be directed more against the viruses, however, than against tumors in general. Only a few cancers are known to be caused by viruses in humans. For most tumors, the immune system's response may be ineffective and too late.

TRANSPLANTATION

Genes that code for the production of MHC molecules are generally called major histocompatibility complex genes. Histocompatibility is the tissues' ability (Greek, *histo*) to get along (compatibility) when tissues are transplanted from one individual to another. In humans, the major histocompatibility complex genes are often referred to as **human leukocyte antigen (HLA) genes** because they were first identified in leukocytes. The HLA genes control the production of HLAs, also called MHC antigens, which are inserted onto the surface of cells. The immune system can distinguish between self-cells and foreign cells because they are both marked with HLAs. Rejection of a transplanted tissue is caused by a normal immune system response to the foreign HLAs. Millions of possible combinations of the HLA genes exist, and it is very rare for two individuals (except identical twins) to have the same set of HLA genes. The closer the relationship between two individuals, the greater the likelihood of sharing the same HLA genes.

Acute rejection of a graft occurs several weeks after transplantation and results from a delayed hypersensitivity reaction and cell lysis. Lymphocytes and macrophages infiltrate the area, a strong inflammatory response occurs, and the foreign tissue is destroyed. If acute rejection does not develop, **chronic rejection** may occur at a later time. In chronic rejection, immune complexes form in the arteries supplying the graft, blood supply fails, and the graft is rejected.

Graft rejection can occur in two different directions. In **host-versus-graft rejection,** the recipient's immune system recognizes the donor's tissue as foreign and rejects the transplant. In a **graft-versus-host rejection,** the donor tissue recognizes the recipient's tissue as foreign, and the transplant rejects the recipient, causing destruction of the recipient's tissues and death.

To reduce graft rejection, a tissue match is performed. Only tissues with HLAs similar to the recipient's have a chance of acceptance. Even when the match is close, immunosuppressive drugs must be administered throughout the person's life to prevent rejection. Unfortunately, the person then has a drug-produced immunodeficiency and is more susceptible to infections. An exact match is possible only for a graft from one part to another part of the same person's body or between identical twins.

HLAs are important in ways in addition to organ transplants. Because HLAs are genetically determined, characterization of HLAs can help resolve paternity suits. In forensic medicine, the HLAs in blood, semen, and other tissues help identify the person from whom the tissue came.