The Lymphatic System and Immunity

The lymphatic system consists of a fluid, lymph, a network of lymphatic vessels, specialized cells called lymphocytes, and an array of lymphoid tissues and lymphoid organs scattered throughout the body. This system has three major functions: (1) to protect the body through the immune response; (2) to transport fluid from the interstitial fluid to the bloodstream; and (3) to help distribute hormones and nutrients, and transport waste.

The immune response produced by activated lymphocytes is responsible for the detection and destruction of foreign or toxic substances that may disrupt homeostasis. For example, viruses, bacteria, and tumor cells are usually recognized and eliminated by cells of the lymphatic system. Immunity is the specific resistance to disease, and all of the cells and tissues involved with the production of immunity are sometimes considered to be part of an immune system. Whereas the lymphatic system is an anatomically distinct system, the immune system is a physiological system that includes the lymphatic system as well as components of the integumentary, cardiovascular, respiratory, digestive, and other systems.

THE PHYSICAL EXAMINATION AND THE LYMPHATIC SYSTEM

Individuals with lymphatic system disorders may experience a variety of symptoms. The pattern observed varies depending on whether the problem affects the immune functions or the circulatory functions of the lymphatic system (Figure A-45). Important symptoms and signs include:

- **Enlarged lymph nodes** are often found during infection. They also develop in cancers of the lymphatic system, such as lymphoma, or when metastasis is under way from primary tumors in other tissues. The status of regional lymph nodes can therefore be important in the diagnosis and treatment of many different cancers. The onset and duration of swelling, the size, texture, and mobility of the nodes, the number of affected nodes, and the degree of tenderness are all important in diagnosis. For example, nodes containing cancer cells are often large, fixed in place, and nontender. On palpation these nodes feel like dense masses, rather than individual lymph nodes. In contrast, infected lymph nodes are usually large, freely mobile, and very tender.

- **Lymphangitis** consists of erythematous (red) streaks on the skin that may develop with an inflammation of superficial lymph vessels. Lymphangitis often occurs in the lower limbs, with the reddened streaks originating at a site of pathogenic infection and progressing toward the trunk. Before the linkage to the lymphatic system was appreciated, this sign was called “blood poisoning.”

- **Splenomegaly** is an enlargement of the spleen that may result from acute infections, such as endocarditis (p. 104) and mononucleosis (p. 123), or chronic infections such as malaria (p. 99) or leukemia (p. 102). The spleen can be examined through palpation or percussion (p. 12), and the

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**Figure A-45** Disorders of the Lymphatic System
Disorders of the lymphatic system can be sorted into three general categories that are diagrammed in Figure A-45:

1. **Disorders resulting from an insufficient immune response**. This category includes conditions such as AIDS (p. 125) or SCID (p. 32). Individuals with depressed immune defenses may develop life-threatening diseases caused by microorganisms that are harmless to other individuals.

2. **Disorders resulting from an excessive immune response**. Conditions such as allergies (p. 130) and immune complex disorders (p. 130) can result from an immune response that is out of proportion with the size of the stimulus.

3. **Disorders resulting from an inappropriate immune response**. Autoimmune disorders result when normal tissues are mistakenly attacked by T cells or the antibodies produced by activated B cells.

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**Lymphedema** EAP p. 429

Blockage of the lymphatic drainage from a limb produces **lymphedema** (lim-fe-DE-muh). In this usually painless condition, interstitial fluids accumulate, and the limb gradually becomes swollen and distended. If the condition persists, the connective tissues lose their elasticity and the swelling becomes permanent. Lymphedema by itself does not pose a major threat to life. The danger comes from the constant risk that an uncontrolled infection will develop in the affected area. Because the interstitial fluids are essentially stagnant, toxins and pathogens can accumulate and overwhelm the local defenses without fully activating the immune system.

Temporary lymphedema may result from tight clothing. Chronic lymphedema can result from scar tissue formation, which sometimes occurs after lymph node removal as part of cancer treatment, or from parasitic infections. In **filariasis** (fil-a-RI-a-sis), larvae of a parasitic nematode (roundworm), usually *Wuchereria bancrofti*, is transmitted by mosquitoes or blackflies. The microscopic adult worms form massive colonies within lymphatic vessels and lymph nodes. Repeated scarring of the passageways eventually blocks lymphatic drainage and produces extreme lymphedema with permanent distension of tissues. The limbs or external genitalia can become grossly distended, a condition known as **elephantiasis** (el-e-fan-TI-a-sis).

Therapy for chronic lymphedema consists of treating infections by the administration of antibiotics and (when possible) reducing the swelling. One possible treatment involves the application of elastic wrappings that squeeze the tissue. This external compression elevates the hydrostatic pressure of the interstitial fluids and opposes the entry of additional fluid from the capillaries.

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**Infected Lymphoid Nodules** EAP p. 431

Lymphoid nodules may be overwhelmed by a pathogenic invasion. The result is a localized infection accompanied by regional swelling and discomfort.
An individual with **tonsillitis** has infected tonsils. Symptoms include a sore throat, high fever, and leukocytosis (an abnormally high white blood cell count). The affected tonsil (most often the pharyngeal) becomes swollen and inflamed, sometimes enlarging enough to partially block the entrance to the trachea. Breathing then becomes difficult and, in severe cases, impossible. As the infection proceeds, abscesses develop within the tonsilar tissues, and the bacteria may enter the bloodstream by passing through the lymphatic capillaries and vessels to the venous system.

In the early stages, antibiotics may control the infection, but once abscesses have formed, the best treatment involves surgical drainage of the abscesses. **Tonsillectomy**, the removal of the tonsil, was once highly recommended and frequently performed to prevent recurring tonsilar infections. The procedure does reduce the incidence and severity of subsequent infections, but questions have been raised concerning the overall cost to the individual. The tonsils represent a “first line” of defense against bacterial invasion of the pharyngeal walls. If they are removed, bacteria may not be detected until a truly severe infection is well under way.

**Appendicitis** usually follows an erosion of the epithelial lining of the appendix. Several factors may be responsible for the initial ulceration, notably bacterial or viral pathogens. Bacteria that normally inhabit the lumen of the large intestine then cross the epithelium and enter the underlying tissues. Inflammation occurs, and the opening between the appendix and the rest of the intestinal tract may become constricted. Mucus secretion accelerates, and the organ becomes increasingly distended. Eventually the swollen and inflamed appendix may rupture, or perforate. If this occurs, bacteria will be released into the warm, dark, moist confines of the peritoneal space (abdominopelvic cavity), where they can cause a life-threatening infection. The most effective treatment for appendicitis is the surgical removal of the organ, a procedure known as an **appendectomy**.

**Lymphomas**

Lymphomas are malignant tumors consisting of cancerous lymphocytes or lymphocytic stem cells. Roughly 64,000 cases of lymphoma are diagnosed in the United States each year, and that number has been steadily increasing. There are many different types of lymphoma. One form, called **Hodgkin’s disease (HD)**, accounts for roughly 12 percent of all lymphoma cases. Hodgkin’s disease most often strikes individuals at ages 15-35 or those over age 50. The reason for this pattern of incidence is unknown; although the cause of the disease is uncertain, an infectious agent (probably a virus) is suspected. Other types are usually grouped together under the heading of non-Hodgkin’s lymphoma (NHL). They are extremely diverse, and in most cases the primary cause remains a mystery. At least some forms reflect a combination of inherited and environmental factors. For example, one form, called **Burkitt’s lymphoma**, most often affects male children in Africa and New Guinea. The affected children have been infected with the Epstein-Barr virus (EBV). This highly variable virus is also responsible for infectious mononucleosis (discussed further below), and it has been suggested as a possible cause of chronic fatigue syndrome and multiple sclerosis.

The EBV infects B cells, but under normal circumstances the infected cells are destroyed by the immune system. EBV is widespread in the environment, and childhood exposure usually produces lasting immunity. Children developing Burkitt’s lymphoma may have a genetic susceptibility to EBV infection; in addition, presence of another illness, such as malaria, may weaken their immune systems to the point that a lymphoma can develop.

The first symptom associated with any lymphoma is usually a painless enlargement of lymph nodes. The involved nodes have a firm, rubbery texture. Because the nodes are painless, the condition is often overlooked until it has progressed to the point that secondary symptoms appear. For example, patients seeking help for recurrent fever, night sweats, gastrointestinal or respiratory problems, or weight loss may be unaware of any underlying lymph node changes. In the late stages of the disease, symptoms can include liver or spleen enlargement, central nervous system (CNS) tumors, pneumonia, a variety of skin conditions, and anemia.

In planning treatment, clinicians consider the histological structure of the nodes and the stage of the disease. When examining a biopsy, the structure of the node is described as nodular or diffuse. A nodular node retains a semblance of normal structure, with follicles and germinal centers. In a diffuse node, the interior of the node has changed, and follicular structure has broken down. In general, the nodular lymphomas progress more slowly than the diffuse forms, which tend to be more aggressive. Conversely, the nodular lymphomas are more resistant to treatment and are more likely to recur even after remission has been achieved.

The most important factor influencing treatment selection is the stage of the disease. Table A-21 includes a simplified staging classification for lymphomas. When diagnosed early (stage I or II), localized therapies may be effective. For example, the cancerous node(s) may be surgically removed and the region(s) irradiated to kill residual cancer cells. Success rates are very high when a lymphoma is detected in these early stages. For Hodgkin’s disease, localized radiation can produce remission lasting 10 years or more in over 90 percent of patients. Treatment of localized NHL is somewhat less effective. The 5-year remission rates average 60 to 80 percent for all types; success rates are higher in nodular forms than for diffuse forms.
Although these are encouraging results, it should be noted that few lymphoma patients are diagnosed while in the early stages of the disease. For example, only 10–15 percent of NHL patients are diagnosed at stages I or II. For lymphomas at stages III and IV, treatment most often involves chemotherapy. Combination chemotherapy, in which two or more drugs are administered simultaneously, is the most effective treatment. For Hodgkin’s disease, a four-drug combination with the acronym MOPP (nitrogen Mustard, Oncovin [vincristine], Prednisone, and Procarbazine) produces lasting remission in 80 percent of patients.

**Bone marrow transplantation** is a treatment option for acute, late-stage lymphoma. When suitable donor marrow is available, the patient receives whole-body irradiation, chemotherapy, or some combination of the two sufficient to kill tumor cells throughout the body. This treatment also destroys normal bone marrow cells. Donor bone marrow is then infused, and over the next 2 weeks the donor cells colonize the bone marrow and begin producing red blood cells, granulocytes, monocytes, and lymphocytes.

Potential complications of this treatment include the risk of infection and bleeding while the donor marrow is becoming established. The immune cells of the donor marrow may also attack the tissues of the recipient, a response called **graft-versus-host disease (GVH)**. For a patient with stage I or II lymphoma, without bone marrow involvement, bone marrow can be removed and stored (frozen) for over 10 years. If other treatment options fail, or the patient comes out of remission at a later date, an autologous marrow transplant can be performed. This eliminates the need for donor typing and the risk of GVH disease.

### Disorders of the Spleen

The spleen responds like a lymph node to infection, inflammation, or invasion by cancer cells. The enlargement that follows is called **splenomegaly** (splen-ö-MEG-a-lē: megas, large), and splenic rupture may also occur under these conditions. One relatively common condition causing splenomegaly is **mononucleosis**. This condition, also known as the “kissing disease,” results from acute infection by the *Epstein-Barr virus* (EBV). In addition to splenic enlargement, symptoms of mononucleosis include fever, sore throat, widespread swelling of lymph nodes, increased numbers of atypical lymphocytes in the blood, and the presence of circulating antibodies to the virus. The condition most often affects young adults (age 15 to 25) in the spring or fall. Treatment is symptomatic, as no drugs are effective against this virus. The most dangerous aspect of the disease is the risk of rupturing the enlarged spleen, which becomes fragile. Patients are therefore cautioned against heavy exercise or other activities that increase abdominal pressures. If the spleen does rupture, severe hemorrhaging can occur; death will follow unless transfusion and an immediate splenectomy are performed.

An individual whose spleen is missing or non-functional has **hyposplenism** (hi-pō-SPLÉN-izm). Hyposplenism usually does not pose a serious problem, but such individuals are more prone to some bacterial infections, such as *Streptococcus pneumoniae*, than are individuals with normal spleens, and immunization against this pathogen is recommended. In **hypersplenism**, the spleen becomes overactive and the increased phagocytic activities lead to anemia (low number of RBCs), leukopenia (low number of WBCs), and thrombocytopenia (low number of platelets). Splenectomy is the only known cure for hypersplenism.

### Immunization

**Immunization** is the manipulation of the immune system by providing antigens under controlled conditions or by providing antibodies that can combat an existing infection. In **active immunization** a primary response to a particular pathogen is intentionally stimulated before an individual encounters the pathogen in the environment. The result is lasting immunity against that pathogen. Immunization is accomplished by administering a **vaccine** (vak-SEN), a preparation of antigens derived from a specific pathogen. The vaccine may

<table>
<thead>
<tr>
<th>Table A-21  Cancer Staging in Lymphoma</th>
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<tbody>
<tr>
<td><strong>Stage I</strong>: Involvement of a single node or region (or of a single extranodal site).</td>
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<tr>
<td><strong>Typical treatment</strong>: surgical removal and/or localized irradiation; in slowly progressing forms of NHL, treatment may be postponed indefinitely.</td>
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<tr>
<td><strong>Stage II</strong>: Involvement of nodes in two or more regions (or of an extranodal site and nodes in one or more regions) on the same side of the diaphragm.</td>
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<tr>
<td><strong>Typical treatment</strong>: surgical removal and localized irradiation that includes an extended area around the cancer site (the extended field).</td>
</tr>
<tr>
<td><strong>Stage III</strong>: Involvement of lymph node regions on both sides of the diaphragm. This is a large category that is subdivided on the basis of the organs or regions involved. For example, in stage III, the spleen contains cancer cells.</td>
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<tr>
<td><strong>Typical treatment</strong>: combination chemotherapy, with or without radiation; radiation treatment may involve irradiating all of the thoracic and abdominal nodes plus the spleen (total axial nodal irradiation, or TANI).</td>
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<tr>
<td><strong>Stage IV</strong>: Widespread involvement of extranodal tissues above and below the diaphragm.</td>
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<tr>
<td><strong>Treatment</strong> is highly variable, depending on the circumstances. Only combination chemotherapy is effective; it may be combined with whole-body irradiation. The “last resort” treatment involves massive chemotherapy followed by a bone marrow transplant.</td>
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be given orally or via intramuscular or subcutaneous injection. Most vaccines consist of the pathogenic organism, in whole or in part, living (but weakened) or dead. In some cases a vaccine contains one of the metabolic products of the pathogen.

Before live bacteria or viruses are administered, they are weakened, or attenuated (a-TEN-ū-tä-ted), to lessen or eliminate the chance of a serious infection developing from exposure to the vaccine. The rubella, mumps, measles, smallpox, yellow fever, and oral polio vaccines are examples of vaccines using live attenuated viruses. Despite attenuation, the administration of live microorganisms may produce mild symptoms comparable to those of the actual disease. However, the risks of serious illness developing as a result of vaccination are very small compared with the risks posed by pathogen exposure without prior vaccination. (Live virus vaccines are not recommended for people with immune deficiencies, such as AIDS, or for patients undergoing cancer chemotherapy.)

**Inactivated**, or “killed,” vaccines consist of bacterial cell walls or viral protein coats. These vaccines have the advantage that they cannot produce even mild symptoms of the disease. Unfortunately, inactivated vaccines do not stimulate as strong an immune response and so do not confer as long-lasting immunity as do live-organism vaccines. In the years following exposure, the antibody titer declines and the system eventually fails to produce an adequate secondary response. As a result, the immune system must be “reminded” of the antigen periodically by the administration of boosters. Influenza, cholera, typhus, plague, and injected polio vaccines use inactivated viruses or bacteria. In some cases fragments of the bacterial or viral walls, or their toxic products, can be used to produce a vaccine. The tetanus, diphtheria, and hepatitis B vaccines are good examples. Data concerning attenuated and inactivated vaccines are presented in Table A-22.

Gene-splicing techniques can now be used to incorporate antigenic compounds from pathogens into the cell walls of harmless bacteria. When exposed to these bacteria, the immune system responds by producing antibodies and memory B cells that are equally effective against the engineered bacterium and the pathogen.

**Passive immunization** is usually selected if the individual has already been exposed to a dangerous pathogen or toxin so that there is not enough time for active immunization to take effect. In passive immunization, the patient receives a dose of antibodies that will attack the pathogen and overcome the infection, even without the help of the host’s own immune system. Passive immunization provides only short-term resistance to infection, for the antibodies are gradually removed from circulation and are not replaced.

The antibodies provided during passive immunization have traditionally been acquired by collecting and combining antibodies from the sera of many other individuals. This pooled sera is used to obtain large quantities of antibodies, but the procedure is very expensive, and improper treatment of the sera carries the risk of accidental transmission of an infectious agent, such as the hepatitis or AIDS virus. Antibodies can also be obtained from the blood of a domesticated animal (usually a horse) exposed to the same antigen. Unfortunately, recipients may suffer allergic reactions to horse serum proteins.

At present, antibody preparations are available to prevent or treat hepatitis A, hepatitis B, diphtheria, tetanus, rabies, measles, rubella, botulism, and the venoms of certain fishes, snakes, and spiders. Gene-splicing technology can also be used to reproduce pure antibody preparations free from antigenic or viral contaminants, and this should eventually eliminate the need for pooled or foreign plasma.

It should also be noted that passive immunity occurs naturally during fetal development because maternal IgG antibodies can cross the placental barriers and enter the fetal circulation where they persist for up to six months.

**Transplants and Graft Rejection**

Organ transplantation is a treatment option for patients with severe disorders of the bone marrow, kidneys, liver, heart, lungs, pancreas, or intestine. Finding a suitable donor is the first major problem. In the United States, each day about 60 people receive an organ transplant, but on that same day 15 people on the transplant waiting list die, and another 79 people are added to the transplant waiting list. After surgery has been performed, the major problem is **graft rejection**. In graft rejection, T cells are activated by contact with MHC proteins on cell membranes in the donated tissues. The cytotoxic T cells that develop then attack and destroy the foreign cells.

Significant improvements in transplant success can be made by reducing the sensitivity of the immune system. Until recently the drugs used to produce this **immunosuppression** did not selectively target the immune system. For example, **prednisone** (PRED-ni-sön), a corticosteroid, was used because it has anti-inflammatory effects that reduce the number of circulating white blood cells and depress the immune response. However, corticosteroid use also caused undesirable changes in glucose metabolism.

An understanding of the communication among T cells, macrophages, and B cells has now led to the development of drugs with more selective effects. **Cyclosporin A** (CsA), a compound derived from a fungus, was the most important immunosuppressive drug developed in the 1980s. This compound depresses all aspects of the immune response, primarily by suppressing helper T cell activity while leaving suppressor T cells relatively unaffected.
Acquired immune deficiency syndrome (AIDS), or late-stage HIV disease, develops after infection by the human immunodeficiency virus (HIV), an RNA virus. There are at least three types of HIV, designated HIV-1, HIV-2, and HIV-3. Most people with HIV in the United States are infected with HIV-1; HIV-2 infections are most common in West Africa. Because most of those infected with HIV-1 eventually develop AIDS but not all individuals infected with HIV-2 do so, HIV-2 may be a less dangerous virus. The distribution and significance of HIV-3 infection remain to be determined.

Symptoms of HIV Disease

The initial infection may produce a flulike illness with fever and swollen lymph nodes a few weeks after exposure to the virus. This exposure usually triggers production of antibodies against the virus. These antibodies appear in the serum within 2–6 months of
exposure, and antibody tests can be used to detect infection. Further symptoms may not appear for 5–10 years or more. Over this period the virus content of the blood varies, but the viruses are at work within lymphoid tissues, especially in the lymph nodes.

HIV-1 selectively infects helper T cells (also called CD4 T cells). This impairs the immune response, and the effect is magnified because suppressor T cells are relatively unaffected by the virus. Over time, circulating antibody levels decline, cellular immunity is reduced, and the body is left without defenses against a wide variety of bacterial, viral, fungal, and protozoan invaders.

This vulnerability is what makes AIDS dangerous. The effects of HIV on the immune system are not by themselves life-threatening, but the infections that result certainly are. With the depression of immune function, ordinarily harmless pathogens can initiate lethal infections, known as opportunistic infections. In fact, the most common and dangerous pathogens for an AIDS patient are microorganisms that seldom cause illnesses in humans with normal immune systems. AIDS patients are especially prone to lung infections and pneumonia, often caused by infection with the fungus *Pneumocystis carinii*. They are also subject to a variety of other fungal infections, such as *coccocal meningitis*, and an equally broad array of bacterial and viral infections. Because AIDS patients are immunologically defenseless, the symptoms and time course of these infections are very different from those in normal individuals.

**Incidence**

During 2001, roughly 45,000 new cases of AIDS were diagnosed in the United States, and the number of U.S. deaths attributed to this disorder since its discovery in 1982 exceeds 450,000. AIDS is now the leading cause of death in people aged 25–44. The Centers for Disease Control and Prevention (CDC) in Atlanta, which has been monitoring the spread of AIDS, estimates that the number of AIDS cases in the United States will continue to increase (Figure A-46). As of 2001, there were approximately 900,000 people living with AIDS in the United States.

![HIV/AIDS: United States and Global Projections](image)

**Figure A-46** United States and Global Projections for Total Number of HIV and AIDS Cases

Because the virus can remain in the body for years without producing clinical symptoms, the number of individuals infected and at risk is far higher. An estimated 1–2 million Americans are infected with HIV, and all will eventually develop AIDS, probably within the next decade. The numbers worldwide are even more frightening. The World Health Organization (WHO) estimates that as many as 36 million people may be infected, and the number of AIDS patients worldwide is climbing rapidly. Several African nations are already on the verge of social and economic collapse due to devastation by AIDS. For example, in Malawi, one-third of the population is infected and 60 percent of pregnant women there carry the virus; Botswana has similar statistics.

**Modes of Infection**

Infection with HIV occurs through intimate contact with the body fluids of infected individuals. Although all body fluids, including saliva, tears, and breast milk, carry the virus, the major routes of infection involve contact with blood, semen, or vaginal secretions. Four major transmission routes have been identified, and we will consider them individually.

- **Sexual transmission:** In the United States, AIDS was first noted in male patients who had male-to-male sexual contact, but over time more women have become infected. Worldwide, about 80 percent of all infections have resulted from heterosexual intercourse.

  Whether homosexual or heterosexual contact is involved, a sex partner whose epithelial defenses are weakened is at increased risk of infection. This accounts for the relatively higher rate of transmission through anal intercourse, which often damages the delicate lining of the anorectal canal. Genital ulcers from other sexually transmitted diseases, such as syphilis, chancroid, herpes, or trichomoniasis also increases the risk of transmission.

  Because of the predominance of homosexual transmission in the United States, many people still consider AIDS to be a homosexual disease. It is not over time, the number of cases in the heterosexual population has been steadily increasing: since 1987, the percentage of homosexual or bisexual AIDS patients has dropped by roughly 25 percent and the number of cases transmitted by heterosexual contact has steadily increased. It can be anticipated that, over time, the sex ratio will continue to shift toward the 1 to 1 male-to-female ratio typical of the rest of the world.

- **Intravenous drug use:** In the United States, about 25 percent of new infections of both sexes are from intravenous drug use. Although only small quantities of blood are inadvertently transferred when needles are shared, this practice injects the AIDS virus directly into the bloodstream. It is thus a very effective way to transmit the disease. Diabetic drug users who have access to sterile needles have a lower rate of HIV infection.

- **Receipt of blood or tissue products:** About 3 percent of AIDS patients have become infected with the virus after they received a transfusion of contaminated whole blood or plasma, an infusion of blood products, such as platelets or extracts of pooled sera, or an organ transplant from an infected individual. With careful screening of blood and blood products, the rate of new transmission by this route is now essentially zero in the United States.

- **Prenatal exposure:** In the United States, approximately 2000 infants are born each year already infected with AIDS. A pregnant HIV-positive woman may infect her child perinatally (before birth), at birth, or from breast milk in up to 35 percent of pregnancies. Treatment with antiviral drugs around the time of delivery has reduced maternal transmission up to 50 percent.

**Prevention of AIDS**

The best defense against AIDS consists of avoiding exposure to the virus. The most important rule is to avoid sexual contact with infected individuals. All forms of sexual intercourse carry the potential risk of viral transmission. The use of synthetic (latex) condoms has been recommended when the previous history of a sex partner is not known. (Condoms that are not made of synthetic materials are effective in preventing pregnancy but do not block the passage of viruses.) Although condom use does not provide absolute protection, it drastically reduces the risk of infection.

Blood and blood products are now screened for the presence of HIV-1. A simple blood test exists for the detection of HIV-1 antibodies, and a positive reaction indicates previous exposure to the virus. The assay, an example of an ELISA test (enzyme-linked immunosorbent assay), is now used to screen blood donors, reducing the risk of infection by transfusion or the use of blood products from pooled sera. Pooled sera can also be treated with detergents and with heat by exposing it to temperatures sufficient to kill the virus but too low to denature blood proteins permanently.

Most public health facilities will perform the ELISA test on request for individuals who fear that they may have been exposed to the AIDS virus. Unfortunately, the test is not 100 percent reliable, and false positive reactions occur at a rate of about 0.4 percent. In addition, the ELISA test does not detect HIV-2 or HIV-3. In the event of a positive test result, a retest should be performed using the more sensitive Western blot procedure. Because of the variable incubation period, a positive test for HIV infection does not mean that the individual has AIDS. It does mean that the individual is likely to develop AIDS at some time in the future and that the person is now a carrier and capable of
infecting others. In terms of the spread of this disease, the most dangerous individuals are those who appear perfectly healthy and have no idea that they are carrying the virus.

Despite intensive efforts, a vaccine has yet to be developed that will provide immunity from HIV infection. The HIV virus has a high rate of mutation, which results in a changing immunologic target. Current research programs are attempting to stimulate antibody production in response to (1) killed but intact viruses, (2) fragments of the viral envelope, (3) HIV proteins on the surfaces of other, less dangerous viruses, or (4) T cell proteins that are targeted by HIV. (The last approach is based on the hypothesis that the antibodies produced will cover the binding sites, preventing viral attachment and penetration.)

**Treatment**

There is no cure for HIV infection. However, the length of survival for AIDS patients has been steadily increasing because (1) new drugs are available that slow the progress of the disease and (2) improved antibiotic therapies have helped overcome infections that would otherwise prove fatal. This combination is extending the lifespan of patients as the search for more effective treatment continues. It should be noted, however, that overcoming an infection in an AIDS patient with antibiotics may require doses up to 10 times greater than those used to fight infections in normal individuals. Moreover, once the infection has been overcome, the patient may have to continue taking that drug for the rest of his or her life. As a result, some AIDS patients take 50–100 pills per day just to prevent recurrent infections.

In 1995, treatment regimens that included a combination of drugs that attack different stages of the replication of the HIV virus became available. This “Highly Active Anti-retroviral Therapy,” or HAART, reduced that annual death rate in the United States by 67 percent from 1995 (50,877 deaths) to 1999 (16,767 deaths). Viral particles became undetectable, patients got up from their (expected) death beds and started attending informational meetings on “how to prepare for future you didn’t think you’d have.” Hopes of a complete cure were dashed when viable viral particles were detected in lymph nodes. Noncompliance with the difficult treatment schedules (missed doses, side effects, and significant cost around $10,000 per patient per year for medication alone) and viral mutation resulted in relapse and development of drug resistant viral strains. However, innovative drug combinations and newer drugs are simplifying the regimen, and lower-cost generic drugs are becoming available in the developing world.

HAART relies on a variety of antiviral drugs. For example, the antiviral drug **azidothymidine**, or **AZT** (sold as **Zidovudine** or **Retrovir**), can slow the progression of AIDS. Low doses of AZT have now been shown to be effective in delaying the progression of HIV infection to AIDS. Higher doses are used to treat AIDS, but this use can lead to a variety of unpleasant side effects, including anemia and even bone marrow failure. However, **AZT** is effective in reducing the neurological symptoms of AIDS because it can cross the blood-brain barrier to reach infected CNS tissues. By alternating AZT treatment with other antiviral drugs, **dideoxycytidine (ddC)** and **dideoxyinosine (ddI)**, side effects are reduced. **Protease inhibitors**, such as ritonavir, indinavir, and saquinavir mesylate, prevent the assembly and dispersal of new viruses. Alone or in combination with AZT or other drugs, protease inhibitors can dramatically reduce the viral content of blood, although viruses remain within infected immune cells. A third category of anti-HIV drugs include **efavirenz** and **nevirapine**.

**Lyme Disease**

In November 1975, the town of Lyme, Connecticut, experienced an epidemic of adult and juvenile arthritis. Between June and September, 59 cases were reported, 100 times the statistical average for a town of that size. Symptoms were unusually severe; in addition to joint degeneration, victims experienced chronic fever and a prominent rash that began as a bull’s-eye centered around what appeared to be an insect bite (Figure A-47). It took almost 2 years to track down the cause of the problem.

Lyme disease is caused by a bacterium, **Borrelia burgdorferi**, that normally lives in white-footed mice. It is transmitted to humans through the bite of a tick. The high rate of infection among children reflects the fact that they play outdoors during their summer vacations. After 1975, the problem became regional and then national in scope. In 1997, approximately 94,000 people were diagnosed with Lyme disease in the United States. It has also been found in Europe.

Although some of the joint destruction results from immune complex deposition, in a mechanism...
comparable to that involved in rheumatoid arthritis, many of the symptoms (fever, pain, skin rash) develop in response to the release of interleukin-1 (IL-1) by activated macrophages. The cell walls of *B. burgdorferi* contain lipid-carbohydrate complexes that stimulate secretion of IL-1 in large quantities. By stimulating the specific and nonspecific defense mechanisms of the body, IL-1 exaggerates the inflammation, rash, fever, pain, and joint degeneration associated with the primary infection. Treatment for Lyme disease consists of administering antibiotics and anti-inflammatory drugs.

Most cases of Lyme disease are reported from the northeastern coast, the Midwest, and the West Coast of the United States. On the West Coast, the transmission cycle is somewhat different. The bacteria is found in woodrats in the wild, and the disease reaches humans through the bite of a tick. However, few woodrats are infected, and transmission from rat to rat involves a second species of tick. As a result, the disease spreads more slowly.

**Immune Competence**  
*EAP p. 446*

The ability to demonstrate an immune response upon exposure to an antigen is called **immune competence**. Cell-mediated immunity can be demonstrated as early as the third month of fetal development, but active antibody-mediated immunity does not appear until somewhat later.

The first cells that leave the fetal thymus migrate to the skin and into the epithelia lining the mouth, digestive tract, and, in females, the uterus and vagina. These cells take up residence in these tissues as antigen-presenting cells, such as the Langerhans cells of the skin, whose primary function will be the activation of T cells. T cells that leave the thymus later in development populate lymphoid organs throughout the body.

The first B cells to be produced in the liver and bone marrow carry IgM antibodies in their membranes. Sometime after the fourth developmental month, the fetus may produce IgM antibodies if exposed to specific pathogens. Fetal antibody production is uncommon, however, because the developing fetus has natural passive immunity due to the transfer of IgG antibodies from the maternal bloodstream. These are the only antibodies that cross the placenta, and they include the antibodies responsible for the clinical problems that accompany fetal-maternal blood Rh incompatibility, discussed on p. 102. Because the agglutinins anti-A and anti-B are IgM antibodies, and IgM cannot cross the placenta, problems with maternal-fetal incompatibilities involving the ABO blood groups rarely occur.

The natural immunity provided by maternal IgG may not be enough to protect the fetus if the pregnant woman becomes newly infected with a bacteria or viral disease. For example, the microorganisms responsible for syphilis and rubella (“German measles”) can cross from the maternal to the fetal bloodstream, producing a congenital infection that leads to the production of fetal antibodies. IgM provides only a partial defense, and infections can result in severe developmental problems for the fetus.

Blood drawn from a newborn infant or taken from the umbilical cord of a developing fetus can be tested for the presence of IgM antibodies. This procedure provides concrete evidence of congenital infection. For example, a newborn infant with congenital syphilis will have IgM antibodies that target the pathogenic bacterium involved (*Treponema pallidum*). Fetal or neonatal (newborn) blood may also be tested for antibodies against the rubella virus or other pathogens.

In the case of congenital syphilis, antibiotic treatment of the mother can prevent fetal damage. In the absence of antibiotic treatment, fetal syphilis can cause liver and bone damage, hemorrhaging, and a susceptibility to secondary infections in the newborn infant. There is no satisfactory treatment for congenital rubella infection, which can cause severe developmental abnormalities. For this reason rubella immunization has been recommended for young children (to slow the spread of the disease in the population) and for women of childbearing age. The vaccination, which contains live attenuated virus, must be administered before pregnancy to prevent maternal infection during pregnancy, with resulting fetal damage.

Delivery eliminates the maternal supply of IgG, and although the mother provides IgA antibodies in the breast milk, the infant gradually loses its passive immunity. The amount of maternal IgG in the infant’s bloodstream declines rapidly over the first 2 months after birth. During this period, the infant becomes vulnerable to infection by bacteria or viruses that were previously overcome by maternal antibodies. The infant also begins producing IgG on its own, as the immune system begins to respond to infections, environmental antigens, and the vaccinations administered by pediatricians. It has been estimated that children encounter a “new” antigen every 6 weeks from birth to age 12. (This fact explains why parents exposed to the same antigens when they were children usually remain healthy while their children develop runny noses and colds.) Over this period, the concentration of circulating antibodies gradually rises toward normal adult levels, and the populations of memory B cells and T cells continue to increase.

Skin tests can determine whether an individual has been exposed to a particular antigen. Small quantities of antigen are injected into the skin, usually on the anterior surface of the forearm. If resistance exists, the region will become inflamed over the next 2–4 days. Many states require a tuberculin test, called a *tuberculin skin test*, when someone applies for a job in the food-service industry. If the test is positive, the individual has been exposed to the disease and has developed antibodies. Further tests must be performed to
determine whether an infection is under way. (Anyone with tuberculosis may accidentally transmit the bacteria when preparing or serving food.) Skin tests are also used to check for allergies to environmental antigens.

Immediate Hypersensitivity

Immediate hypersensitivity begins with the process of sensitization. Sensitization is the initial exposure to an allergen that leads to the production of antibodies, specifically large quantities of IgE. The tendency to produce IgE antibodies in response to specific allergens may be genetically determined. In drug reactions, such as penicillin allergies, IgE antibodies are produced in response to a hapten (partial antigen) bound to a larger molecule inside the body.

Because of the lag time needed to activate B cells, produce plasma cells, and synthesize antibodies, the first exposure to an allergen does not produce symptoms. It merely sets the stage for the next encounter. After sensitization, the IgE antibodies become attached to the cell membranes of basophils and mast cells throughout the body. When exposed to the same allergen at a later date, the bound antibodies stimulate these cells to release histamine, heparin, several cytokines, prostaglandins, and other chemicals into the surrounding tissues. The result is a sudden, massive inflammation of the affected tissues.

Basophils, eosinophils, T cells, and macrophages are drawn to the area by the cytokines and other secretions of the mast cells. These cells release chemicals of their own, extending and exaggerating the responses initiated by mast cells.

The severity of the allergic reaction depends on the sensitivity of the individual and the location involved. If allergen exposure occurs at the body surface, the response may be restricted to that area. If the allergen enters the systemic circulation, the response may be more dramatic and occasionally can be lethal.

ANAPHYLAXIS In anaphylaxis (a-na-fi-LAK-sis; ana-, again + phylaxis, protection) a circulating allergen affects mast cells throughout the body (Figure A-48). The entire range of symptoms can develop within a matter of minutes. Changes in capillary permeabilities produce swelling and edema in the dermis and raised welts, or hives, appear on the surface of the skin or the respiratory mucosa. Smooth muscles along the respiratory passageways contract, and the narrowed passages cause wheezing and make breathing extremely difficult. In severe cases of anaphylaxis, an extensive peripheral vasodilation occurs, producing a fall in blood pressure that may lead to a circulatory collapse. This response has been called anaphylactic shock.

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Under normal circumstances, immune complexes are promptly eliminated by phagocytosis. But when an antigen appears suddenly, in high concentrations, the local phagocytic population may not be able to cope with the situation. The immune complex then enlarges further, eventually forming insoluble granules that are deposited in the affected area. The presence of these complexes triggers extensive activation of complement, leading to inflammation and tissue damage at that site. This condition is known as an immune complex disorder. The process of immune complex formation is further enhanced by neutrophils, which release enzymes that attack the inflamed cells and tissues. The most
serious immune complex disorders involve deposits within blood vessels and in the filtration membranes of the kidney.

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Delayed hypersensitivity begins with the sensitization of cytotoxic T cells. At the initial exposure, macrophages called antigen-presenting cells (APCs) present antigens to T cells. On subsequent exposure, the T cells respond by releasing cytokines that stimulate macrophage activity and produce a massive inflammatory response in the immediate area. Examples of delayed hypersensitivity include the many types of contact dermatitis, such as poison ivy, a form of dermatitis (p. 44).

Skin tests can be used to check for delayed hypersensitivity. The antigen is administered by shallow injection, and the site is inspected after a period of minutes to days. Most skin tests inject antigens taken from bacteria, fungi, viruses, or parasites. If the individual was previously exposed to the antigen, in 2–4 days the injection site will become red, swollen, and invaded by macrophages, T cells, and neutrophils. These signs are considered a positive test that indicates previous exposure but does not necessarily indicate the presence of the disease. The skin test for tuberculosis, the ppd, is the most common.

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It is possible to identify an individual B cell responsible for producing a specific antibody. That B cell can then be isolated and fused with a cancer cell. This produces a hybridoma (hi-bri-DÔ-ma), a cancer cell that produces large quantities of a single antibody. Hybridomas undergo rapid mitotic divisions, like other cancer cells, so culturing that original hybridoma cell soon produces an entire population, or clone, of genetically identical cells. This particular clone will produce large quantities of a monoclonal (mo-nô-KLÔ-nal) antibody.

Monoclonal antibodies are useful because they can be made free of impurities. One important use for this technology has been the development of antibody tests for the clinical analysis of body fluids. Labeled antibodies can be used to detect small quantities of specific antigens in a sample of plasma or other body fluids. For example, a popular home pregnancy test relies on monoclonal antibodies that detect small amounts of a placental hormone, human chorionic gonadotrophin (HCG), in the urine of a pregnant woman. Other monoclonal antibodies are used in standard blood screening tests for venereal diseases and urine tests for ovulation.

Monoclonal antibodies can also be used to provide passive immunity to disease. Passive immunizations using monoclonal antibodies do not cause any of the unpleasant side effects associated with antibodies from pooled sera, for the product will not contain plasma proteins, viruses, or other contaminants. The antibodies can be made to order by exposing a population of B cells to a particular antigen, then isolating any B cells that produce the desired antibodies.

Genetic engineering techniques can also be used to promote immunity in other ways. One interesting approach involves gene-splicing techniques. The genes coding for an antigenic protein of a viral or bacterial pathogen are identified, isolated, and inserted into a harmless bacterium that can be cultured in the laboratory. The clone that eventually develops will produce large quantities of pure antigen that can then be used to stimulate a primary immune response. Vaccines against malaria and hepatitis were developed in this manner, and a similar strategy may be used to design an AIDS vaccine.

A more controversial experimental technique involves taking a pathogenic organism and adding or removing genes to make it harmless. The modified pathogen can then be used to produce active immunity without the risk of severe illness. Fears that the engineered organism could mutate or regain its pathogenic habits have so far limited the use of this approach.

Hybridomas that manufacture other products of the immune system can also be produced. Interferons are not effective against all viruses, but many patients with chronic hepatitis caused by the hepatitis B and C viruses respond to interferon treatment. Interferons can also control certain forms of virally induced cancers. Interleukins may prove useful in increasing the intensity of the immune response.

As our understanding of the immune system grows, complex therapies involving combinations of lymphokines, interleukins, and monoclonal antibodies are appearing. For example, in a recent clinical trial, cytotoxic T cells were removed from patients with malignant melanoma, a particularly dangerous cancer discussed in Chapter 5 (p. 113). These lymphocytes were able to recognize tumor cells, and they had migrated to the tumor. However, for some reason they were unable to kill the tumor cells. The extracted lymphocytes were cultured, and viruses were used to insert multiple copies of the genes responsible for the production of tumor necrosis factor. The patients were then given periodic infusions of these “super-charged” T cells. To enhance T cell activity further, the researchers also administered doses of interleukin-2. Although the outcome of this particular therapy remains uncertain, it is clear that the ability to manipulate the immune response will revolutionize the treatment of many serious diseases.
CRITICAL-THINKING QUESTIONS

7-1. Matthew, a 17-year-old hemophiliac, reports to Dr. M. that he has recently lost weight for no apparent reason and has had a flu disorder “on and off” for the last month. Matthew has a fever of 37.8°C (100°F), cervical lymph node swelling, and a persistent cough. Dr. M. is worried about Matthew’s immune state and recommends tests to detect the cause of the respiratory problems. The cultured specimen from Matthew’s lungs contains the bacteria *Pneumocystis carinii*. Matthew is diagnosed with PCP or *Pneumocystis carinii pneumonia*. What further tests might you order for Matthew?

7-2. Paula’s grandfather is diagnosed as having throat cancer. His physician orders biopsies of several lymph nodes from neighboring regions of the body. Paula wonders why, since his cancer is in the throat. What would you tell her?

7-3. Teresa, an 18-year-old college student, goes to her physician with symptoms that have persisted for 2 weeks. Anne has been fatigued and feverish, with a temperature as high as 38.6°C (101°F). She has inflamed tonsils and enlarged cervical lymph nodes. On palpation, her spleen is slightly enlarged; the physician notes no other signs or symptoms.

Teresa’s lab results are as follows:

- RBC count: 4.2 million/mm³
- Hct: 37
- Hb: 12 g/dl
- MCV: 80 µm³
- MCH: 27 pg
- Reticulocytes: 1% of total RBCs
- WBC count: 4500/mm³
- Diff. count:
  - 40% neutrophils
  - 60% lymphocytes
  - 2% monocytes
  - 1% eosinophils
  - 0.5% basophils
- Platelets: 200,000/mm³

Based on the lab results, what is a likely diagnosis?