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The Immune System

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Chapter 7

The Immune System

Zoher F. Kapasi and Catherine C. Goodman

Immunology is the study of the physiologic mechanisms that allow the body to recognize materials as foreign and to neutralize or eliminate them. When the immune system is working properly, it protects the organism from infection and disease; when it is not, the failure of the immune system can result in localized or systemic infection or disease. In fact, the significance of a healthy immune system is apparent in states or diseases characterized by immunodeficiency, as occurs in human immunodeficiency virus (HIV) infection or in people on immunosuppressive medication.

Without an effective immune system, an individual is at risk for the development of overwhelming infection, malignant disease, or both. Not all immune system responses are helpful, as in the case of organ or tissue transplant rejection.

Additionally, excessive or inappropriate activity of the immune system can result in hypersensitivity states, immune complex disease, or autoimmune disease. For a complete understanding of the immune system as it relates to injury, inflammation, and healing, the reader is encouraged to read this chapter along with Chapter 6.

Types of Immunity

◆ *Innate and Acquired Immunity*

Two types of immunity are recognized: innate (natural or native immunity) and acquired immunity (adaptive or specific immunity). *Innate immunity* acts as the body's first line of defense to prevent the entry of pathogens.

Two nonspecific, nonadaptive lines of defense are involved in innate immunity. Nonspecific refers to the fact that this part of the immune system does not distinguish between different types of invaders (e.g., bacteria, fungus, virus, etc.) and is nonadaptive, i.e., does not remember the encounter with specific invaders for future encounters. Each time that potential pathogen is introduced, the innate immune system reacts in the same predictable manner.

The first line of defense is the skin and its mucosal barriers, and the second is a nonspecific inflammatory response to all forms of cellular injury or death. Innate responses occur to the same extent; however, many times the infectious agent is encountered (Fig. 7-1).

Acquired immunity is characterized by specificity and memory. The primary role of the immune system as a more specific line of defense (acquired immunity) is to recognize and destroy foreign substances such as bacteria, viruses, fungi, and parasites and to prevent the proliferation of mutant cells such as those involved in malignant transformation.

This type of immunity results when a pathogen gains entry to the body, and the body produces a specific response to the invader. Acquired immunity has a memory so that when the same organism is encountered again, the body can respond even more rapidly to it and with a stronger reaction. The two components to acquired immunity (humoral immunity and cell-mediated immunity) are discussed in greater detail later in this section.

◆ **Acquired Immunity: Active or Passive Immunity**

Acquired immune responses can occur as a result of active or passive immunity. Active immunity includes natural immunity and artificial immunity, which is intended or deliberate (Table 7-1).

Active acquired immunity refers to protection acquired by introduction (either naturally from environmental exposure or artificially by vaccination) of an antigen (microscopic component of pathogen that causes an immune response) into a responsive host.

The concept of vaccination is based on the fact that deliberate exposure to a harmless version of a pathogen generates memory cells but not the pathologic sequelae of the infectious agent itself. In this way, the immune system is primed to mount a secondary immune response with strong and immediate protection should the pathogenic version of the microorganism be encountered in the future.⁶¹ This type of immunity is expected to last a lifetime, but there are occasional exceptions.

Researchers are developing a new generation of vaccines to fight a variety of diseases. One of the most promising is the deoxyribonucleic acid (DNA) vaccine that allows DNA from a pathogen to be injected into the body where cells accept the added DNA instructions and make antigens that the body can recognize and fight. Genetic manipulation allows researchers to overcome the greatest deterrent to vaccination—the ability of common pathogens such as influenza and pneumococcal bacteria to mutate too rapidly for a vaccine to match the latest version.

Some of the most promising new techniques are being investigated against malaria; cancer; ear infections; acquired immune deficiency syndrome (AIDS); sexually transmitted diseases; asthma; influenza; strep throat; diabetes; and hepatitis C. Improved administration of the vaccine using mucosal sprays, skin patches, time-released pills, and genetically engineered foods to replace needle injections is also under development.

Passive acquired immunity occurs when antibodies or sensitized lymphocytes produced by one person are transferred to another. Preformed antibodies made in a laboratory or made by someone else is another form of passive immunity.

For example, the transplacental transfer of antibodies from mother to fetus, the transfer of antibodies to an infant through breast milk or receiving immune serum globulin (γ -globulin) provides immediate protection but does not result in the formation of memory cells and therefore provides only temporary immunity. This type of immunity (passive acquired) lasts only until the antibodies are degraded, which may be only a few weeks to months.

THE IMMUNE RESPONSE

See Table 7-2. **Editor: this IS the call out for Table 7-2 and should remain here as is rather than incorporated into the text.**

◆ *Antigens*

Any foreign substance in the body that does not have the characteristic cell surface markers of that individual and is capable of eliciting an immune response is referred to as an *antigen* (from antibody generator). Bacteria, viruses, parasites, foreign tissue cells, and even large protein molecules are recognized as antigens or called *antigenic*. On encountering an antigen, the immune system recognizes it as nonself, and the appropriate immune response is mounted against the antigen. A single bacterium contains hundreds of antigenic sites, and therefore has multiple sites capable of stimulating an immune response.

The subunits of an antigen that elicit an immune response are called *epitopes*. These molecules protrude from the surface of an antigen and actually combine with an antibody (Fig. 7-2). Each antigen may display hundreds of epitopes. The more epitopes that are present, the greater is the antigenicity of a substance and the greater the immune response. Antibodies produced in response to an antigen are protein molecules structured in such a way that they only interact with the antigen that induced their synthesis, much as a key is made to fit a lock.

◆ *The Major Histocompatibility Complex*

Since the basis of immunity depends on the immune cells' ability to distinguish self from nonself, all cells of the body contain specific cell surface markers or molecules that are as unique to that person as a fingerprint.

The immune system recognizes these cell markers and tolerates them as self, in other words, produces self-tolerance. These cell markers are present on the surface of all body cells and are known as the major histocompatibility complex (MHC) proteins. They were originally discovered on leukocytes and are commonly called *human leukocytic antigens (HLAs)*. The six specific HLAs within the MHC markers are HLA-A, HLA-B, HLA-C, referred to as *class I antigens*, and HLA-DP, HLA-DQ, and HLA-DR, referred to as *class II antigens*.¹³⁶

Class I antigens are found on nucleated cells and platelets; class II antigens are found on monocytes, macrophages, B cells, activated T cells, vascular endothelial cells, Langerhans' (skin) cells, and dendritic (nerve) cells. There is a third class of antigens (class III) including certain complement proteins (C2, C4, and factor B).

Cell markers are essential for immune function. They not only determine which antigens an individual responds to and how strongly, but they also allow immune system cells to recognize and communicate with one another.

HLA antigens are inherited and can predispose or increase an individual's susceptibility to certain diseases (usually autoimmune) (see Table 40-17) **Au: check this number**. Such diseases encompass many that affect the joints, endocrine glands, and skin, including rheumatoid arthritis, Graves' disease, psoriasis, and many others. Not all people with a certain HLA pattern develop the disease, but they have a greater probability for its development than the general population.

◆ **Innate Immunity**

The innate immune system consists of all the immune defenses that lack immunologic memory. A characteristic of innate responses is that they remain unchanged however often the antigen is encountered. Innate immune responses use phagocytic cells (neutrophils, monocytes, and macrophages); cells that release inflammatory mediators (basophils, mast cells, and eosinophils); and natural killer (NK) cells. The molecular components of innate responses include complement, acute-phase proteins, and cytokines such as the interferons.⁶¹

The strategy of the innate immune response may not be to recognize every possible antigen but rather to focus on a few structures present in large groups of microorganisms. These structures are referred to as pathogen-recognition receptors.¹⁶⁸

A key cellular component of innate immunity and one of the most intensely studied components in the last decade is the interdigitating dendritic cell. Cells of this type (e.g., Langerhans' cells in skin) constantly but quietly endocytose extracellular antigens. Pattern-recognition receptors on these dendritic cells are a part of the innate immune response to differentiate between potentially harmful microorganisms and self-constituents and include toll-like receptors that sense a broad range of microbial products.⁶¹

These types of receptors are specific for structures found exclusively in microbial pathogens (pathogen-associated molecular pattern). This differs from the adaptive immune system, which has a tremendous capacity to recognize almost any antigenic structure but because antigen receptors are generated at random, they bind to antigens regardless of their origin—bacterial, environmental, or self.¹⁶⁸

Exterior Defenses (See Fig. 7-1)

As a covering for the entire body (with the exception of any openings), the skin offers the first and best line of protection, which is clearly demonstrated in cases of significant burns when infection becomes a major problem. The body openings also offer their own unique protection such as lysozyme in tears that can kill bacteria, waxy secretions in the ear canal to prevent bacteria from advancing inside, nasal hair, stomach acid, and unfavorable rapid pH change at gastro-duodenal junction for ingested organisms, protective low pH vaginal secretions, acidic urine, and so on.

When organisms enter the body by penetrating the epithelial surface of the respiratory, gastrointestinal (GI), or genitourinary tract, biochemical defenses offer additional protection such as soluble mediators like complement and cytokines (particularly interferons), phagocytes that engulf and destroy foreign particles, and NK cells that attack and destroy virus-infected cells and tumor cells.

Phagocytes. Phagocytes are involved in nonspecific or innate immunity. These cells readily eat (ingest) microorganisms like bacteria or fungi and kill them as a means of protecting the body against infection.

The two principal phagocytes are neutrophils and monocytes and are part of white blood cells (WBCs) or leukocytes. The five types of leukocytes are: neutrophils, eosinophils, basophils, monocytes, and lymphocyte. Because of their granular appearance, neutrophils, eosinophils, and basophils are collectively referred to as *granulocytes*. Granulocytes are short-lived (2 to 3 days) compared with monocytes and macrophages, which may live for months or years.

Phagocytes emigrate out of the blood and into the tissues in which an infection has developed, and each of these cell types has a specific phagocytic function in the immune system (see the section on Disorders of Leukocytes in Chapter 14). Neutrophils, eosinophils, basophils, and monocytes are classified as phagocytic leukocytes that function in nonspecific or innate immunity. A severe decrease in the blood level of these cells is the principal cause of susceptibility to infection in people treated with intensive radio- or chemotherapy. These treatments suppress blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

Neutrophils, also referred to as polymorphonuclear cells (PMNs), derive from bone marrow and increase dramatically in number in response to infection and inflammation. Neutrophils can directly kill invading organisms but may also damage host tissues. In the process of phagocytosis (Fig. 6-15; AU: check figure number; see also discussion of phagocytosis in chapter 6 and Fig. 6-15 AU: check figure number; formerly 5-15), bacteria or debris is engulfed, and then digested by enzymes contained within the neutrophils. Neutrophils die after phagocytosis; the accumulation of dead neutrophils and phagocytosed bacteria contributes to the formation of pus.

Monocytes circulate in the blood but when they migrate to tissues, they mature into *macrophages*, which means large eaters. The engulfment of a pathogen by a macrophage is an essential first step leading to a specific immune response. After neutrophils kill the invading organism and the process of phagocytosis has begun, macrophages appear to clear up the debris produced by the neutrophils and to kill any damaged but not dead bacteria or bacteria that are too large for neutrophils. Neutrophils and macrophages both have receptors for antibodies and complement so that the coating of microorganisms with antibodies, complement, or both enhances phagocytosis.

After phagocytes digest the pathogens, antigenic material appears on their surface to identify them more specifically as foreign invaders. In this process, phagocytes (primarily macrophages) serve as antigen-presenting cells (APCs) to introduce the pathogen to lymphocytes. The macrophage or APC processes the pathogen and presents a small part of it, the epitope (see Fig. 7-2), to a specific cell of the immune system known as the *helper/inducer lymphocyte*, or T4 lymphocyte (also referred to as *CD4 lymphocyte*).

Microscopically, T lymphocytes appear identical, but they can be distinguished by means of distinctive molecules called *cluster designations (CDs)* located on their cell surface. For example, all mature T cells carry markers known as T2, T3, T5, and T7 (or CD2, CD3, CD5, and CD7). T4 (CD4) are the helper T cells, and T8 (CD8) are cytotoxic T cells. Another group of T lymphocytes are identified as natural killer (NK) cells for their ability to kill certain tumor cells and virus-infected cells without prior sensitization or activation.

To prompt the T4 lymphocyte to recognize the processed pathogen, the macrophage releases interleukin-1 (IL-1), a chemical messenger with many roles. In this way, the macrophage processes the antigen and then signals the lymphocytes to stimulate the specific immune response.

Interleukins are one type of cytokine, a protein released by macrophages to trigger the immune response. See Cytokines, later in this section. Some of the multiple functions of IL-1 include increasing the temperature set-point in the hypothalamus; increasing serotonin in the brainstem and duodenum causing sleep and nausea, respectively; stimulating the production of prostaglandins, leading to a decrease in the pain threshold, resulting in myalgias and arthralgias;

increasing the synthesis of collagenases, resulting in the destruction of cartilage; and most important, kicking the T4 cells into action.

Macrophages also participate in the defense against tumor cells and secrete numerous molecules called *monokines* that assist in the immune and inflammatory response. Stimulation of macrophages can boost the immune response.

Eosinophils are the next group of leukocytes that participate in the innate immunity process. Eosinophils are derived from bone marrow and multiply in both allergic disorders and parasitic infestations. When organisms are too large for neutrophils and macrophages, eosinophils get within close proximity of the invading organisms and release the contents of their granules to kill them.

Basophils are WBCs (leukocytes) that circulate in peripheral blood and function similarly to mast cells in allergic disorders. Basophils and mast cells are located close to blood vessels throughout the body and have similar functional characteristics; *mast cells* contain histamine that dilates blood vessels when released.

Mast cells are derived from stem cells and travel in the blood in such small numbers they are not recognized as blood cells. Arriving basophils and mast cells cause an increase in blood supply in the area where the bacteria or viral antigen is located. This increase in circulation also helps bring more phagocytes to the area thus counteracting bacteria indirectly. The increased circulation is accompanied by the feeling of congestion during an allergic reaction; antihistamines work by neutralizing the histamines and reducing the excessive immune (allergic) response.

The role of erythrocytes and *platelets* in immune responses is sometimes overlooked, but because they have complement receptors, they play an important part in the clearance of immune complexes consisting of antigen, antibody, and components of the complement system.⁶¹

Soluble (Inflammatory) Mediators

The complement system and interferons act as soluble inflammatory mediators along with phagocytes to destroy organisms that breach the first line of defense. The complement system consists of 20 serum proteins, which are key components in the acute inflammatory response designed to enhance immune function.

When activated, these proteins interact in a cascade-like process to assist immune cells by coating microorganisms so they can be more easily phagocytosed and to participate in bacterial lysis. In some cases the invading organisms are eliminated from the body. Sometimes the inflammation produced by the complement cascade (immune response) walls off the microorganism by forming, for example, a cyst or tubercle that protects the rest of the body from infection. (See the section on The Complement System, in Chapter 6; see also Table 6-4.)[Au: check table number](#)

The second group of soluble mediators is the cytokines, especially interferons sometimes referred to as *biologic response modifiers (BRMs)*. They act as messengers both within the immune system and between the immune system and other systems of the body, forming an integrated network that is highly involved in the regulation of immune responses.¹⁷¹

In addition to acting as messengers, some cytokines have a direct role in defense such as the interferons. Interferons are produced by virally infected cells early in infection to limit the spread of the infection by protecting surrounding (noninfected) cells (interferons also inhibit tumor growth). Once a cell becomes infected by a virus, certain genes are turned on in the cell that will produce these interferons that coat the surrounding cells and make them viral resistant.

Natural Killer Cells

NK cells are large granular lymphocytes that are neither T or B lymphocytes. The function of NK cells is to kill viruses, other intracellular microbe infected cells, and tumor cells. NK cells recognize targets by first binding to potential target cells followed by interaction between activating and inhibitory receptors with ligands available on the target, and then integrating signals transmitted by these receptors, which determines whether the NK cells will detach and move on or stay and respond. NK cells respond by releasing cytotoxic granules and by secreting cytokines (Fig. 7-3).¹⁴⁶

◆ Acquired Immunity

To establish an infection, the pathogen must first overcome numerous surface barriers and the innate immune responses (see Fig. 7-1). In these cases, acquired immunity is tailored to recognize each different type of organism and kill it.

The two types of acquired immune responses that occur are *humoral immunity* (also called immunoglobulin-related immunity) and *cell-mediated immunity* (also referred to as T-cell immunity). Although these two responses are often discussed separately, they are two arms of the immune system and work together; failure in one can alter the effectiveness of the other. These two types of responses overlap and interact considerably but the distinction is useful in understanding how the immune system is activated (Fig. 7-4).

The complexity of the cellular interactions that occur during acquired immune responses requires specialized microenvironments in which the relevant cells can collaborate efficiently. Because only a few lymphocytes are specific for any given antigen, T cells and B cells need to migrate throughout the body to increase the probability that they will encounter that particular antigen. In their travels, lymphocytes spend only about 30 minutes in the blood during each trip around the body.¹⁸² More specific information about T-cell function and migration is available.²⁵⁸

Acquired responses involve the proliferation of antigen-specific B and T cells, which occurs when the surface receptors of these cells bind to antigen and initiate the immune response involving immunoglobulins, antibodies, regulatory/suppressor T cells, and cytokines. The acquired immune system generates a highly diverse group of antigen receptors that allows the adaptive immune system to recognize virtually any antigen. However, the price for this diversity is the inability to distinguish foreign antigens from self-antigens.¹⁶⁸

Humoral Immunity

The humoral immune response is mediated by antibodies present in different “humors” (body fluids or secretions) such as saliva, blood, or vaginal secretions. Antibodies produced by B lymphocytes are very effective against organisms that are free floating in the body that can be

easily reached and neutralized. *B lymphocytes*, or B cells, are called such because they originate in the bone marrow and then circulate throughout the extracellular fluid.

The surface of B lymphocytes is coated with immunoglobulin, and each B cell has a receptor (an antibody) that can recognize a specific foreign substance or antigen. When this happens, B cells change into protein-synthesizing cells known as *plasma cells* and *memory B cells*.

The plasma cell produces and secretes into body fluids a specific antibody to that antigen. Memory cells produced in connection with humoral immunity circulate between the blood, lymphoid system, and tissues for about 1 year or even longer. They are responsible for the more rapid and sustained (stronger) immune response that occurs with repeated exposure to the same antigen. This humoral response is particularly useful in fighting bacterial infections.

The B lymphocyte/plasma cell interaction is capable of producing five types of antibodies, or immunoglobulins (Ig), in response to specific antigens. Because of these antibodies the humoral immune response may be referred to as the *antibody immune response*. The five types of antibodies are IgG, IgM, IgA, IgD, and IgE; major functions of immunoglobulins are listed in Box 7-1.

IgM predominates in the primary or initial immune response and is the largest immunoglobulin; because of its size, it is found almost exclusively in the intravascular compartment. *IgG* is the major antibacterial and antiviral antibody and is the predominant immunoglobulin in blood; it is responsible for the protection of the newborn during the first 6 months of life and is the only immunoglobulin to cross the placenta. It is the major immunoglobulin synthesized during the secondary immune response (after *IgM* initially responds to foreign pathogens), conferring long-term or permanent immunity.

IgA defends external body surfaces, is the predominant immunoglobulin on mucous membrane surfaces, and is found in secretions such as saliva, breast milk (colostrum); urine; seminal fluid; tears; nasal fluids; and respiratory, GI, and genitourinary secretions.

IgD is the predominant antibody found on the surface of B lymphocytes, serves mainly as an antigen receptor, and may function in controlling lymphocyte activation or suppression. *IgE* is a primary factor in eliminating parasitic infections such as roundworms and is therefore significant in the immune responses of people in developing countries where adequate nutrition, hygiene, and primary medical care are lacking. *IgE* also functions during allergic reactions by activating the mast cells and releasing histamine in association with allergies, anaphylaxis, extrinsic asthma, and urticaria (hives). This response of *IgE* is a normal reaction but becomes excessive in people with allergies.

The type of antibody produced depends on genetic variability, the specific antigenic stimulus, and whether it is a first or subsequent exposure to that antigen. The humoral immune response is more rapid than the cell-mediated response and is more often a factor in resistance to acute bacterial infections. Humoral immunity can be transmitted to another person, either by inoculation or by maternal transfer via placenta or breast milk. This transfer is called *passive immunity* (see Table 7-1).

Cell-Mediated Immunity

Some organisms (all viruses and some bacteria) actually hide inside the cells where the antibodies cannot reach them. A second arm of the immune system (cell-mediated immunity or

cellular immunity) with more specific cells (T lymphocytes) can recognize these hidden organisms, search them out, and destroy them on a cell-to-cell basis.

Lymphocytes originate from stem cells in the bone marrow and differentiate or mature into either B or T cells (Fig. 7-5; formerly 6-2; see also Fig. 21-6). The B cell (humoral immunity) is thought to mature and become immunocompetent in the bone marrow.

T lymphocytes, or T cells (cell-mediated immunity), are called such because the precursors of these cells start from the bone marrow but then mature in the thymus located right behind the sternum where it learns to discriminate self from nonself (see Fig. 7-8). Both T and B lymphocytes continuously recirculate between blood, lymph, and lymph nodes.

After interaction with a specific antigen, the activated lymphocyte will produce numerous additional lymphocytes called *sensitized T cells*. This T-cell subpopulation has three primary functions. The most numerous of the T cells, *helper T cells*, constituting 75% of all T cells, assist the B cells to mature and produce antibody by secreting protein mediators called *lymphokines*. Many different lymphokines have been identified, including but not limited to, IL-1 and -2, and interferons.

Some of their functions include (1) helping B cells augment the production of antibodies, (2) activating macrophages and helping them destroy large bacteria, (3) helping other T lymphocytes (called *cytotoxic T cells*, or CD8 T cells) recognize and destroy virally infected cells, and (4) helping NK cells kill infected cells (Fig. 7-6).

Helper T cells (CD4 T cells) themselves can be categorized on the basis of their cytokinetic profiles into T-helper type 1 (T_H1) or T-helper type 2 (T_H2) cells. T_H1 produce IFN- γ and TNF- β and are important in assisting CD8 T cell activation, whereas T_H2 produce IL-4, IL-5 and IL-13 and drive B cell activation and antibody generation (Fig. 7-7). HIV destroys or inactivates these helper T cells and leaves the body at risk for infectious agents such as cytomegalovirus (CMV).

The immune system also consists of a regulatory/suppressor T cells (CD4⁺CD25⁺) that suppress activation of the immune system and prevent pathological self-reactivity, i.e. autoimmune disease. Immunosuppressive cytokines TGF-beta and interleukin-10 (IL-10) have been implicated in regulatory T cell function.²³³

Cell-mediated immunity is responsible for the rejection of transplanted tissue; delayed hypersensitivity reactions (e.g., contact dermatitis); and some autoimmune diseases. Cell-mediated immunity is the basis for many skin tests (e.g., tuberculin test, allergy testing). Cellular immunity cannot be transferred passively to another person.

Clinical conditions that compromise the cell-mediated T-lymphocyte function include HIV infection and AIDS, with a progressive reduction in T4 lymphocytes over the duration of the illness. Other conditions known to affect T-cell number or responsiveness include stress, malignancy, general anesthesia, thermal injury, surgery, diabetes, and immunosuppressive drugs (including corticosteroids). Older adults (65 years and older) show reduced numbers of circulating lymphocytes, and malnourished people show defects in most tests of T-cell function.

◆ **Summary of the Immune Response**

Immune responses are initiated according to the type of antigen presented. Adaptive immune responses are generated in the lymph nodes, spleen, and mucosa-associated tissue, referred to as

the *secondary lymphoid tissues*. For example, blood-borne antigens usually initiate responses in the spleen, whereas responses to microorganisms in tissues are generated in local lymph nodes.

Most pathogens are encountered after they are inhaled or ingested. Antigens entering the body through mucosal surfaces activate cells in the mucosa-associated lymphoid tissues (MALTs), including the tonsils, adenoids, and Peyer's patches (see Fig. 7-8⁶²)

Keeping in mind that innate immunity and acquired immunity function in tandem together (Fig. 7-9) and that within the acquired immune system, humoral immunity and cellular immunity are also working simultaneously, a variety of immune responses can occur when an extracellular pathogen approaches the body.

If the pathogenic organism gets past the first line of defense (innate immunity) and is presented to the body, the following can happen: (1) a B lymphocyte recognizes it as a bacteria and produces antibodies that bind to it and neutralize it (humoral response); (2) a T lymphocyte recognizes it as a bacteria and produce cytokines to help the macrophages lyse and phagocytose the bacteria (cell-mediated response); (3) in the case of a virus, a cytotoxic T lymphocyte can recognize the cell and destroy it (cell-mediated response); and (4) the complement system can recognize the invading organism and destroy it (innate immunity).

In some instances, innate and acquired immunity interact with each other, such as when bacteria enters the body and the B lymphocyte recognizes it and produces specific antibodies (acquired immunity). Examples of this interaction include (1) antibodies (acquired immunity) bind to the bacteria coating it and making it available for phagocytosis by the phagocytes of the innate immune system; (2) again, bacteria is recognized by the B lymphocyte (acquired immunity) and coated with the antibody produced by the lymphocyte; the complement (innate immunity) then recognizes it and destroys it; (3) activation of cytotoxic T lymphocytes (acquired immunity) and NK cells (innate immunity) result in a direct attack on cells that have been transformed by a virus or a malignant process; (4) the foreign invader is recognized by a T lymphocyte (from the acquired immune system) and the T lymphocyte then produces hormones (lymphokines) that help the macrophage (from the innate immune system) to destroy it.

Dysfunction of the immune system can contribute to diseases. For example, two general types of genetic alterations could lead to immunologic abnormalities: mutations that inactivate the receptors or signaling molecules involved in innate immune recognition and mutations that render them active all the time. The first type of mutation would be expected to result in various types of immunodeficiencies. The second type of mutation would trigger antiinflammatory reactions and thereby contribute to a variety of conditions with an inflammatory component (e.g., asthma, allergy, arthritis, autoimmune diseases).¹⁶⁸

AGING AND THE IMMUNE SYSTEM

Aging is accompanied by immune dysregulation as immune function declines with increasing age; this is described as the *Oxidative (Free Radical) Theory of Aging* (see the section Cellular Aging in Chapter 6). Changes are observed in both the innate and acquired immunity defenses; the end result is reduced resistance to pathogens and increased incidence of tumors and autoimmune disorders.

◆ **Changes in Innate Immunity**

Exterior defenses are affected by thinning of the skin, making older adults more prone to pressure ulcers and increasing openings for bacteria to enter the body. Decreased acidity of the GI tract, shallower breathing with decreased air exchange, less acidic urine, and a less elastic bladder that retains more urine are all examples of ways our exterior defenses are affected by aging, thus contributing to reduced effectiveness of the innate immune system.

Phagocytes (neutrophils and monocytes/macrophages) show decreased function with aging. *Eosinophils* accumulate in fewer numbers at sites of infection with age, perhaps predisposing us to parasitic infections as we age. *Basophils* are characterized by reduced degranulation with aging, although *mast cells* show no change in numbers or histamine release with aging. *Platelet aggregation* increases with aging, perhaps contributing to increased clot formation and decreased peripheral circulation.

Soluble mediators are characterized by increased serum levels of complement produced by the liver perhaps a compensatory mechanism but this remains unproved. A decreased production of interferons occurs by monocyte with increasing age.

NK cells (large granular lymphocytes) cytotoxicity is impaired as also production of cytokines by activated NK cells. ⁴⁸

◆ **Changes in Acquired Immunity**

Decline in humoral and cell-mediated immunity occurs with aging. Older adults have particular difficulty in mounting protective immune responses to newly encountered antigens, e.g. West Nile virus. Such responses are dependent upon naïve T and B cells and aging is associated with decline in the production of naïve B and T cells.

Thymic involution and T- and B-lineage specific defects in early lymphoid development in the bone marrow appear to explain this decline. However, it cannot be assumed that changes in the lymphoid compartment are entirely responsible for the poor quality of immune responses in the older adult.

The quality of the immune response may be associated with other cellular changes, such as defective cytoskeletal assembly and hyperglycosylation of proteins, telomerase shortening, replicative senescence, and failed susceptibility to apoptosis.

In humans, CD8 T cells expansions are often accompanied by loss of CD28, an important receptor of accessory signals during T-cell activation. Similar changes are seen in CD4 T cell population with dysregulation of cytokine production. ³¹

Although, B cell-function appears relatively intact, there is a decline in antibody production that may be due to inappropriate or insufficient T-cell help. While this change in antibody is reflected in a decline in the level of antibody upon immunization there may also be decreases in the affinity of the antibodies produced. Any or all of these age-associated changes in immune response may contribute to age-associated changes in response to viral infections resulting in increased morbidity and mortality in older adults. ¹⁷⁶

Older adults are one of the highest risk groups for influenza infection with at least 50% of hospitalizations and greater than 80% of all deaths from influenza occurring in individuals over 65 years of age.

Each year the availability of vaccinations for influenza are prioritized according to age, general health, and comorbidities. However, efficacy of the vaccine in the older adult population is only at 30–40% in comparison to 70–80% in younger individuals. It has also been predicted that pneumonia is the fourth leading cause of death and the first among infectious diseases in the older adult population. Similarly, efficacy of the current pneumococcal vaccine only reaches 44–61% in individuals greater than 65 years of age.²⁵⁶ The diminished cell-mediated immunity can result in the reactivation of dormant infections such as herpes zoster and tuberculosis.

Age-related increase in autoimmune activity is both a cellular and a humoral phenomenon and limited studies suggest that reduced humoral and cellular immunocompetence, reduced suppressor cell activity, and increased autoantibody activity are all associated with reduced survival.

FACTORS AFFECTING IMMUNITY

In addition to the effects of aging, other factors can affect the immune system. These factors may include nutrition; environmental pollution and exposure to chemicals that influence the host defense; prior or ongoing trauma or illnesses; medications; splenectomy (removal of the spleen); influences of the enteric, endocrine, and neurochemical systems; stress; and psychosocial-spiritual well-being and socioeconomic status.

These factors, as well as clinical conditions that contribute to an immunocompromised state, are listed in Box 7-2. Sleep deprivation has also been shown to have important effects similar to stress on the immune system by reducing cellular immunity.^{14, 207} Some factors such as the iatrogenically introduced interventions listed and sexual practices do not alter the immune system directly but increase a person's exposure to pathogens.

New information is being discovered about the sensory functions of the intestine and how neural, hormonal, and immune signals interact. Representatives of all the major categories of immune cells are found in the gut or can be rapidly recruited from the circulation in response to an inflammatory stimulus. The gut immune system has 70% to 80% of the body's immune cells and the protective blocking action of the secretory response in the gut is crucial to the integrity of the GI tract immune function and host defense.¹⁸ Studies suggest that the development and expression of the regional immune system of the GI tract is independent of systemic immunity, but this remains an area of debate and investigation.

Nutritional status can have a profound effect on immune function. Nutrients have fundamental and regulatory influences on the immune response of the GI tract and therefore, on host defense. Reduction of normal bacteria in the gut after antibiotic treatment or in the presence of infection may interfere with the nutrients available for immune function in the GI tract.

Severe deficits in calorie or protein intake or vitamins such as vitamin A or vitamin E can lead to deficiencies in T cell function and numbers. Deficient zinc intake can profoundly depress both T- and B-cell function. Zinc is required as a cofactor for at least 70 different enzymes, some of which are found in lymphocytes and are necessary for their function.

Secondary zinc deficiencies may be associated with malabsorption syndrome, chronic renal disease, chronic diarrhea, or burns or severe psoriasis (loss of zinc through the skin). Dietary

changes may alter aspects of immunity, although research in this area is ongoing. Additionally, morbid obesity may alter the immune system by creating a vulnerability to certain diseases, including cancer.

Some *medications* (e.g., cancer chemotherapeutic agents) profoundly suppress blood cell formation in the bone marrow. Other drugs (e.g., analgesics, antithyroid medications, anticonvulsants, antihistamines, antimicrobial agents, and tranquilizers) induce immunologic responses that destroy mature granulocytes.

Many drugs also affect B- and T-cell function, especially against antigens that require the interaction of helper T cells and B cells for antibody production. These complications have been observed since the advent of potent immunosuppressive (e.g., corticosteroids) and chemotherapeutic drugs as treatment of people with autoimmune diseases, transplants, or cancer. Depression of B- and T-cell formation is manifested as a progressive increase in infections with opportunistic microorganisms (e.g., *P. carinii*, cytomegalovirus, and *Candida albicans* and other fungi).

Surgery and *anesthesia* can also suppress both T- and B-cell function for up to 1-month postoperatively.¹⁶¹ Because of the invasive nature of any surgical procedure and because defects in immunity have been described in most major illnesses, it is logical to assume that the majority of hospitalized surgical clients are immunocompromised to some degree.

Surgery to remove the spleen results in a depressed humoral response against encapsulated bacteria, especially *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, the group A streptococci, and *Neisseria meningitidis* (see Chapter 8).

Burns cause increased susceptibility to severe bacterial infections as a result of decreased external defenses (intact skin); neutrophil function; decreased complement levels; decreased cell-mediated immunity; and decreased primary humoral responses. Blood serum from clients with burns also contains nonspecific immunosuppressive factors that will suppress all immune responses, regardless of the antigen involved.

The relationship between *stress*, *psychosocial-spiritual well-being*, and *socioeconomic status* and susceptibility to disease through depressed immune function has become an area of intense research interest. In the past, there were anecdotal reports of increased incidence of infection, diseases, and malignancy associated with periods of both intense and relatively minor stress (see Box 3-9). [Au: check Box number](#)

In the new and expanding world of psychoneuroimmunology, almost any stress seems capable of altering immune function. The role of stress in the development of pathology is discussed in Chapter 3. Likewise, the role of environmental pollution and exposure to chemicals on susceptibility to immune system dysfunction and development of disease is discussed in Chapter 5.

INTERACTIONS BETWEEN THE IMMUNE AND CENTRAL NERVOUS SYSTEMS

The role of the nervous and endocrine systems in homeostasis has now been shown to include interaction with the immune system. The study of interactions between immune system, endocrine system and the CNS has been called *neuroimmunology*. Newer terms include

neuroimmunomodulation, psychoneuroimmunology, and neuroimmunoendocrinology (see Chapter 1).

Two pathways link the brain and the immune system: the autonomic nervous system (ANS) and neuroendocrine outflow via the pituitary. Immune responses alter neural and endocrine functions, and in turn, neural and endocrine activity modifies immunologic function. ²⁶⁹

Many regulatory peptides and their receptors previously thought to be limited to the brain or to the immune system are now known to be expressed by both. It is now known that endocrine factors can alter immune function, immune responses can alter both endocrine and CNS responses and communication between the central nervous system (CNS) and the immune system is bidirectional. ^{9, 13}

This means the immune system has the capacity not only to sense the presence of foreign molecules, but also to communicate this to the brain and neuroendocrine system. The Interaction between the immune and neuroendocrine systems is termed *bidirectional communication*

Findings that link immune and neuroendocrine function may help explain how emotional state or response to stress can modify a person's capacity to cope with infection or cancer and influence the course of autoimmune disease. Whether emotional factors can influence the course of autoimmune disease, cancer, and infection in humans is a subject of intense research, but studies so far have shown reduced lymphocyte sensitivity with chronic distress. ¹¹

The CNS can be involved in immune reactions arising from within the brain or in response to peripheral immune stimuli. Activated immunocompetent cells such as monocytes, lymphocytes, and macrophages can cross the blood-brain barrier and take up residence in the brain, where they secrete their full repertoire of cytokines and other inflammatory mediators such as leukotrienes and prostaglandins. All aspects of immune and complement cascades can occur in the brain because of these nerve-macrophage communications. The CNS modulates immune cells by direct synaptic-like contacts in the brain and at peripheral sites, such as the lymphoid organs ²⁴⁵ (see Fig. 7-8).

A number of cytokines called *neurocytokines* (e.g., IL-1, -2, -4, and -6, neuroleukin, and TNF- α) are formed by glia, the supporting structure of nervous tissue. The activation of cytokines in the CNS occurs in response to local tissue injury and can lead to profound changes in neural functions, ranging from mild behavioral disturbances to anorexia, drowsiness, sleep disturbances, coma, dementia, and the destruction of neurons. The activation of cytokines in neural tissue by injury or toxins has a positive benefit as well, by stimulating the production of nerve growth factor.

Based on studies using animal models, researchers suggest that the brain can regulate immunocompetence. Much of this neuroimmunomodulation takes place through the hypothalamic- pituitary system and sympathetic nervous system, with the latter by the release of catecholamines at autonomic nerve endings and from the adrenal medulla.

The principal immunoregulatory organs (lymph nodes, thymus, spleen, and intestinal Peyer's patches) are abundantly supplied by autonomic nerve fibers. Sensory neurons contain a variety of neurotransmitters and neuropeptides that can influence lymphocyte function.

EXERCISE IMMUNOLOGY

The effect of physical activity and exercise (aerobic, endurance, and resistance) on the immune and neuroimmune systems has been an area of research interest. A brief summary of the results is presented here, but a more detailed accounting of exercise and the immune system and future direction for studies is available.^{180,187}

Depending on the intensity, activity or exercise can enhance or suppress immune function. In essence, the immune system is enhanced during moderate exercise. Moreover, regular, moderate physical activity can prevent the neuroendocrine and detrimental immunologic effects of stress.⁷⁵

In contrast to the beneficial effects of moderate exercise on the immune system, strenuous/intense exercise or long-duration exercise such as marathon running is followed by impairment of the immune system. Intense exercise can suppress the concentration of lymphocytes, suppress natural killer cell activity, and leave the host open to microbial agents, especially viruses that can invade during this open window of opportunity, and may lead to infections.

Extreme and long-duration strenuous exercise appears to lead to deleterious oxidation of cellular macromolecules. The oxidation of DNA is important because the oxidative modifications of DNA bases are mutagenic and have been implicated in a variety of diseases including aging and cancer.¹⁹⁵

◆ *Effect on Neutrophils and Macrophages*

Exercise triggers a rise in blood levels of neutrophils (PMNs) and stimulates phagocytic activity of neutrophils and macrophages. The exercise-evoked increase in the PMN count is greater if the exercise has an eccentric component, such as downhill running. If the exercise goes beyond 30 minutes, a second, or delayed, rise in PMNs occurs over the next 2 to 4 hours while the exerciser is at rest.

This delayed rise in PMNs is probably the result of cortisol, which spurs release of PMNs from the bone marrow and hinders the exit of PMNs from the bloodstream.¹⁶⁵ After brief, gentle exercise, the PMN count soon returns to baseline, but after prolonged, strenuous exercise, this return to normal may take 24 hours or longer.⁷¹

In many instances, exercise enhances macrophage function and can increase antitumor activity in mice, but many questions still remain regarding the mechanism(s) by which acute or chronic exercise affect macrophage function.²⁶⁷

◆ *Effect on Natural Killer Cells*

Most researchers agree that the number of NK cells and the function or activity of these cells in the blood increases during and immediately after exercise of various types, durations, and intensities.¹⁸⁷

This phenomenon, referred to as *NK enhancement*, is temporary and seems to be the result of a surge in epinephrine levels and from cytokines released during exercise. NK enhancement by exercise occurs in everyone regardless of sex, age, or level of fitness training; however, once a person is accustomed to a given exercise level, the NK enhancement falls off, suggesting it is a response not to exercise, per se, but to physiologic stress.

After intense exercise of long duration the concentration of NK cells and NK cytolytic activity declines below preexercise values. Maximal reduction in NK cell concentrations and lower NK cell activity occurs 2 to 4 hours after exercise.¹⁸⁷ Although this depression in NK cell count seems too brief to have major practical importance for health, there may be a cumulative adverse effect in athletes who induce these changes several times per week. Further study is warranted before specific exercise guidelines are determined.²³¹

◆ **Effect on Lymphocytes**

Brisk exercise (even brief, heavy exertion such as maximal bicycle ergometry for 30 or 60 seconds) increases the WBC count in proportion to the effort.^{99,178} This exercise-induced increase in WBCs (including lymphocytes and NK cells) is largely the result of the mechanical effects of an increased cardiac output and the physiologic effects of a surge in serum epinephrine concentration. Lymphocytes may be recruited to the circulation from other tissue pools during exercise (e.g., from the spleen, lymph nodes, GI tract). The number of cells that enter the circulation is determined by the intensity of the stimulus.¹⁸⁷

The number of lymphocytes in circulation increases during exercise but decreases below the normal levels for several hours after intense exercise. Decreased numbers of lymphocytes are associated with decreased lymphocyte responsiveness and antibody response to several antigens after intense exercise.¹²⁵

The effects of intense exercise on secondary antibody response in older adults remain unknown. In one study with older mice, no adverse effect(s) of multiple bouts of intense exercise on antibody levels occurred.¹²⁵ In contrast to intense exercise, moderate exercise training enhances secondary antibody response in young animals and is mediated in part by endogenous opioids.¹²⁴
¹²⁶ Primary antibody response is not influenced by exercise training.

Effect on Cytokines

Strenuous exercise defined as exercising at a minimum of 80% of maximum oxygen consumption (VO_{2max}) can suppress immune function and damage enough tissue to evoke the *acute phase response* in humans.¹⁸⁶ This complex cascade of reactions can modulate immune defense by activating complement and spurring the release of TNF, interferons, interleukins, and other cytokines.

Plasma-IL-6 increases in an exponential fashion with exercise (without muscle damage) and is related to exercise intensity, duration, the mass of muscle recruited, and endurance capacity. The anti-inflammatory effects of IL-6 are demonstrated by the fact that IL-6 stimulates the production of anti-inflammatory cytokines IL-1ra and IL-10.¹⁸⁹

Furthermore, IL-6 stimulates the release of soluble TNF- α receptors, but not IL-1 β and TNF- α , and appears to be the primary inducer of the hepatocyte-derived acute phase proteins, many of which have anti-inflammatory properties.

Therefore, IL-6 induces an anti-inflammatory environment by inducing the production of IL-1ra and IL-10, but it also inhibits the production of pro-inflammatory cytokine TNF- α . The possibility exists that, with regular exercise, anti-inflammatory effects of an acute bout of exercise will protect against chronic systemic low-grade inflammation, but such a link between the acute effects of exercise and the long-term benefits has not yet been proven.

However, regular exercise protects against diseases associated with chronic low-grade systemic inflammation. This long-term effect of exercise may be ascribed to the anti-inflammatory response elicited by an acute bout of exercise, which is partly mediated by muscle-derived IL-6.

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◆ **Exercise and Apoptosis**

The role of apoptosis, or programmed cell death, in exercise is the focus of much research in the area of exercise science. Apoptotic cell death differs morphologically and biochemically from necrotic cell death, although both appear to occur after exercise.

Accelerated apoptosis has been documented to occur in a variety of disease states, such as AIDS and Alzheimer's disease, and in the aging heart. In striking contrast, failure to activate this genetically regulated cell death may result in cancer and certain viral infections. It is surmised that exercise-induced apoptosis is a normal regulatory process that serves to remove certain damaged cells without a pronounced inflammatory response, thereby insuring optimal body function.

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◆ **Exercise and Infection**

From experimental studies, it is clear that effects of exercise stress on disease lethality varies with the type and time the exercise is performed. In general, exercise or training before infection has either no effect or decreases morbidity and mortality.

Exercise during the incubation period of the infection appears either to have no effect or to increase the severity of infection. Although, a recent study showed that moderate exercise, when performed after influenza virus infection but before flu symptoms, resulted in reduced mortality rates in mice.

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Several epidemiologic studies on exercise and upper respiratory tract infection (URTI) report an increased number of URTI symptoms (based on self-report rather than clinical verification) in the days after strenuous exercise (e.g., a marathon race), whereas moderate training has been claimed to reduce the number of symptoms. However, in neither strenuous nor moderate exercise have these symptoms been causally linked to exercise-induced changes in immune function.

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IMMUNODEFICIENCY DISEASES

In immunodeficiency, the immune response is absent or depressed as a result of a primary or secondary disorder. Primary immunodeficiency reflects a defect involving T cells, B cells, or lymphoid tissues. Secondary immunodeficiency results from an underlying disease or factor that depresses or blocks the immune response.

◆ **Primary Immunodeficiency**

The recognition of impaired immunity in children 50 years ago has resulted in tremendous increase in knowledge of the functions of the immune system. More than 95 inherited immunodeficiency disorders have now been identified. Genetically determined

immunodeficiency can cause increased susceptibility to infection, autoimmunity, and increased risk of cancer (Fig. 7-10).

The defects may affect one or more components of the immune system, including T cells, B cells, NK cells, phagocytic cells, and complement proteins. No further discussion of these conditions is included in this book because the therapist rarely encounters these congenital conditions. A review of the pathophysiology of primary immunodeficiency is available. 26

◆ **Secondary Immunodeficiency**

Secondary immunodeficiency disorders such as leukemia or Hodgkin's disease follow and result from an earlier disease or event. Multiple, diverse, and nonspecific defects in the immune defenses occur in viral and other infections, and also in malnutrition, alcoholism, aging, autoimmune disease, diabetes mellitus, cancer, chronic disease, steroid therapy, cancer chemotherapy, and radiation. More specific causes such as AIDS also contribute to secondary immunodeficiency.

Iatrogenic Immunodeficiency

Immunodeficiency induced by immunosuppressive drugs, radiation therapy, or splenectomy is referred to as *iatrogenic immunodeficiency*. Immunosuppressive drugs fall into several categories, including cytotoxic drugs, corticosteroids, cyclosporine, and antilymphocyte serum or antithymocyte globulin (ATG).

Cytotoxic drugs kill immunocompetent cells while they are replicating, but since most cytotoxic drugs are not selective, all rapidly dividing cells are affected. Not only are lymphocytes and phagocytes eliminated, but these drugs also interfere with lymphocyte synthesis and release of immunoglobulins and lymphokines.

Other effects of this nonselectivity of cytotoxic drugs are discussed in Chapter 5 and may include bone marrow suppression with neutropenia, anemia, and cytopenia; gonadal suppression with sterility; alopecia; hemorrhagic cystitis; and vomiting, nausea, and stomatitis. The risk of lymphoproliferative malignancy is also increased.

Corticosteroids are used to treat immune-mediated disorders because of their potent antiinflammatory and immunosuppressive effects. Corticosteroids stabilize the vascular membrane, blocking tissue infiltration by neutrophils and monocytes, thus inhibiting inflammation. They also kidnap T cells in the bone marrow, causing lymphopenia. Corticosteroids also appear to inhibit immunoglobulin synthesis and interfere with the binding of the immunoglobulin to antigen.

Cyclosporine (immunosuppressive drug) selectively suppresses the proliferation and development of helper T cells, resulting in depressed cell-mediated immunity. This drug is used primarily to prevent rejection of organ transplants but is also being investigated for use in several other disorders. *Antilymphocyte serum* or *antithymocyte globulin* is an anti-T-cell antibody that reduces T-cell number and function, thereby suppressing cell-mediated immunity. It has been used effectively to prevent cell-mediated rejection of tissue grafts or transplants. See the section on Immunosuppressants under Adverse Drug Reactions in Chapter 5.

Radiation therapy is cytotoxic to most lymphocytes, inducing profound lymphopenia, which results in immunosuppression. Irradiation of all major lymph node areas, a procedure known as

total nodal irradiation (TNI), is used to treat disorders such as Hodgkin's lymphoma. It is being investigated for its effectiveness in severe rheumatoid arthritis, lupus nephritis, and prevention of kidney transplant rejection.

Splenectomy increases a person's susceptibility to infection, especially with pyogenic bacteria such as *Streptococcus pneumoniae*. This risk of infection is even greater when the person is very young or has an underlying reticuloendothelial disorder. These people should be observed carefully for any signs of infection (see Table 8-1).

◆ **Consequences of Immunodeficiency**

People who are immunocompromised from any of the immunodeficiency disorders are at increased risk of developing infection because their impaired immune system does not provide adequate protection against invading microorganisms. Normal mechanical defense mechanisms may be affected (respiratory, GI systems). Body flora that are normally harmless, such as *Candida*, may become pathogenic and a source of infection.

Additional risk factors for people who are already immunocompromised include poor physiologic and psychologic health status; old age; coexistence of other diseases or conditions, invasive procedures (e.g., surgery, invasive lines); and treatments (e.g., chemotherapy, radiation therapy, bone marrow transplantation).

The weakened immune system can cause the person to become susceptible to common everyday infectious agents, such as influenza viruses and *S. aureus*, as well as the more exotic organisms, such as *Histoplasma capsulatum* and *Toxoplasma gondii*.

◆ **Acquired Immune Deficiency Syndrome (AIDS)**

Overview. HIV can be considered an infection of the immune system, resulting in progressive and ultimately profound immune suppression. Currently one of the most widely publicized diseases, AIDS was first recognized in homosexual men in 1981 (the earliest sample of HIV-infected blood dates back to 1959,¹¹¹ but computer analysis suggests an emergence date of 1930¹³⁷).

The virus thought to be responsible for the transmission of AIDS was identified as HIV in July 1986. As new discoveries were made the classification scheme later included two subtypes as HIV-1 and HIV-2 with several strains of HIV-1 further identified. This text deals primarily with HIV-1 (the cause of most of the AIDS cases in the United States), hereafter referred to as HIV.

AIDS is characterized by progressive destruction of cell-mediated (T-cell) immunity and changes in humoral immunity and even elements of autoimmunity because of the central role of the CD4+ T lymphocyte in immune reactions (see the section on Monocytes and Macrophages earlier in this chapter for a discussion of CD4+ cells).

The resultant immunodeficiency leaves the affected person susceptible to opportunistic infections, including unusual cancers, tuberculosis, and other abnormalities that characterize this syndrome. For example, HIV-positive individuals are nearly two and a half times more likely than HIV-negative persons to have a recurrence of tuberculosis²³⁹ and 8 to 10 times more likely to develop Hodgkin's disease when compared to the general population.¹⁵²

Additionally, 25 to 40% of Americans with HIV are believed to be infected with the hepatitis C virus (HCV), primarily among injection drug users and those with hemophilia as a result of blood products used to treat the hemophilia.⁷ Mortality is higher and life-expectancy lower in people with hemophilia who are HIV-positive.¹⁹³

Definition. The Centers for Disease Control and Prevention (CDC) revised the definition of AIDS in 1992 to include those who have HIV-1 and a CD4 count below 200/mL (the normal CD4 lymphocyte count is 600 to 1200/mL) or 14% of the total lymphocyte count, even if the person has no other signs or symptoms of infection. The AIDS definition was further expanded in 1993 to include diseases affecting women (e.g., cervical cancer) and people with tuberculosis or depressed immune systems.

The term *HIV infection* includes the entire spectrum of illness from initial diagnosis to full-blown expression of AIDS. Three distinct points identify this continuum: (1) asymptomatic HIV seropositive, (2) early symptomatic HIV, and (3) HIV advanced disease (AIDS).

Not everyone who is exposed to HIV becomes infected, and not everyone who is infected develops AIDS. The explanation for this phenomenon remains unknown, but researchers have shown that infection with HIV and progression to AIDS are controlled by both host genetic factors and viral factors.

The human leukocyte antigen (HLA) region in humans controls immune response functions and influences susceptibility to infectious diseases, including HIV. There are HLA alleles associated with susceptibility to and protection from HIV infection, and these differ among ethnic groups.²¹³ Alleles are situated at one or more sites on chromosomes and carry genetic information that determines a specific genetic characteristic or trait. A single amino acid change in HLA molecules has a substantial effect on the rate of progression to AIDS.⁸⁸

Incidence and Prevalence. Since the first AIDS cases were reported in the United States in 1981, the number of cases and deaths among people with AIDS increased rapidly during the 1980s, followed by substantial declines in new cases and deaths in the late 1990s.

AIDS remains an epidemic of vast proportions in other countries such as in South Africa where the number of deaths has exceeded the estimated 25 million caused by the Black Death in the fourteenth century.^{91, 244} An increase among women has been especially steep in East Asia, Eastern Europe, and Central Asia.⁶⁹

In 2005 there were 4.1 million newly infected individuals worldwide including 700,000 children under the age of 15. Of the 40.3 million people worldwide living with HIV/AIDS 38 million are adults (almost equal between men and women), 2.3 million are children under 15, and two-thirds (25 million) live in the Sub-Saharan Africa area. Twenty percent (7.4 million) are in Asia and the Pacific.⁹¹ [AU: these figures are to be updated and posted on May 30th, recheck data](#)

New infections in the United States has declined to an estimated 40,000 per year (down from a peak of 150,000 per year in the mid-1980s). The number of people living with AIDS in the U.S. is the highest ever reported at more than 1 million.²⁵⁴ Deaths from AIDS declined 63% from approximately 52,000 to 19,000 in the late 1990s.¹⁰³

In the United States the greatest impact of the epidemic is among injection drug users (IDUs), sex workers, and men who have sex with men (MSM) with an 8% increase in this last group.^{91, 223; 353} and among racial/ethnic minorities.³³ Increases have been observed in the number of

cases attributed to heterosexual transmission among minority women and women over age 50. The total number of people living with AIDS has increased as deaths have declined.^{175, 253}

Half of all new cases among adults and adolescents are caused by injection drug use (up from 28% in 2000)³⁵ and almost an equal amount (41%) are infected through MSM. Women account for more than one quarter of all new HIV/AIDS diagnoses. Women of color are especially affected. The rate of AIDS diagnoses for African American women is approximately 23 times the rate for white women and 4 times the rate for Hispanic women;³⁴ women in general are infected through the use of shared injection drug needles and sex with infected men (Fig. 7-12).²⁵³

Most people diagnosed with AIDS in the United States are ages 20 to 49; however, the number of adolescents with HIV in the United States doubles every year. Teens account for one quarter of new sexually transmitted diseases reported each year, and AIDS in older adults accounts for 11% of all AIDS cases.¹⁷⁵

Etiologic Factors, Transmission, and Risk Factors. The primary cause of AIDS is the type 1 retrovirus (HIV). Transmission of HIV occurs by exchange of body fluids (notably blood and semen) and is associated with high-risk behaviors.

High-risk behaviors include unprotected anal and oral sex, including having six or more sexual partners in the past year; sexual activity with someone known to carry HIV; exchanging sex for money or drugs; or injecting drugs. HIV is not transmitted by fomites (e.g., coffee cups, drinking fountains, or telephone receivers) or casual household or social contact.

As mentioned, injection drug use also continues to play a key role in the HIV epidemic. In some large drug-using communities, HIV seroincidence and seroprevalence among injection drug users (IDUs) have declined in recent years.⁶⁵ This decline has been attributed to several factors, including increased use of sterile injection equipment, declines in needle-sharing, shifts from injection to noninjection methods of using drugs, and cessation of drug use.²

However, injection-drug use among young adult heroin users has increased substantially in some areas, an indication that, as with sexual behaviors, changes to less risky behaviors may be difficult to sustain.^{116, 253}

Transmission of HIV varies by gender. In 2004, 57% of male HIV infections were related in men who had sex with men (MSM), 19% were related to injection drug use (IDU), and 17% of the infections resulted from heterosexual sex. In the same year in females, 70% of HIV infections were related to heterosexual sex and 29% resulted from IDU.¹⁷

A woman is twice as likely as a man to contract HIV infection during vaginal intercourse; the presence of some sexually transmitted diseases greatly increases the likelihood of acquiring or transmitting HIV infection. The rates of gonorrhea and syphilis are higher among women of color, especially between the ages of 15 and 24.³⁴

Overall, MSM has been the most common mode of exposure among people reported with AIDS, followed by injection drug use, and heterosexual contact. To avoid social isolation, discrimination, or verbal or physical abuse, many MSM, especially young and minority MSM, do not disclose their sexual orientation.

Young MSM who do not disclose their sexual orientation (nondisclosers) are thought to be at particularly high risk for human immunodeficiency virus (HIV) infection because of low self-

esteem, depression, or lack of peer support and prevention services that are available to MSM who are more open about their sexuality (disclosers).

Additionally, one in three nondisclosers report having recent female sex partners suggesting that nondisclosing MSM might have an important role in HIV/STD transmission to women.²²³ This might be particularly true for black nondisclosing MSM, of whom approximately one in five is infected with HBV and one in seven is infected with HIV.²²⁹

The chief determinant of whether HIV is transmitted during heterosexual intercourse is the viral load in the infected partner's bloodstream. Viral load refers to the number of viral RNA particles present in the blood and correlates strongly with the stage of disease.

Viral load tests measure the amount of HIV-specific RNA and is highest at the time of seroconversion when antibodies appear in the serum and the person is considered positive for HIV. This is a useful measurement for determining the effectiveness of drug treatment and also directly correlates with the risk of perinatal transmission in pregnant women with HIV.

Transmission does not occur when serum HIV-1 ribonucleic [RNA] levels are less than 1500 copies/mL (i.e., low viral load).²⁰³ Uncircumcised men have a greater risk of contracting HIV through sexual contact than do circumcised men. The thinner epithelial lining of the glans penis may be susceptible to increased trauma during sexual activity, increasing the likelihood of viral transmission.¹⁴⁷

Nearly all transmission of HIV through transfusion of blood or blood products occurred before testing of the blood supply for HIV antibody and self-referral programs were initiated in 1985. People with hemophilia were especially vulnerable and susceptible to transmission.

In 1991, approximately 70% of people with hemophilia had seroconverted to being positive for HIV; however, since 1986, no further HIV transmission has occurred via that mechanism. The number of people reported with AIDS who were exposed through blood transfusions was 284 in 2000, down from a peak of 1098 in 1993.¹⁷⁵

The number of perinatally acquired AIDS cases peaked in 1992, followed by a sharp decline since then.¹⁷⁵

Ethnicity is not directly related to increased AIDS risk, but it is associated with other determinants of health status such as poverty, illegal drug use, access to health care, and living in communities with a high prevalence of AIDS. Adolescents are one of the groups at greatest risk for HIV infection, particularly minority inner-city youth. Runaway and homeless youth are especially likely to engage in high-risk sexual activity. The use of amphetamines, ecstasy, and amyl nitrate is associated with increased frequency of unprotected anal sex, especially among homosexual and bisexual individuals under age 23.⁶⁸

The prevalence of HIV infection is nearly five times higher in incarcerated populations than for the general population. HIV transmission among inmates in correctional and detention facilities is associated with male-male sex and tattooing. Sex among inmates occurs and laws or policies prohibiting sexual contact between inmates are difficult to implement and enforce. Condom distribution is unavailable in most correctional facilities.

Although no case of HIV transmission via tattooing has been documented, the procedure carries a theoretical risk for transmission if nonsterile equipment is used. In some instances, receipt of a tattoo is associated with HIV seroconversion.²⁴⁹

Pathogenesis. The rapid convergence of information from diverse areas of AIDS research makes it impossible to present the most up-to-date information. Scientists are reporting new discoveries daily about the pathogenesis of HIV disease.

The natural history of AIDS begins with infection by the HIV retrovirus detectable only by laboratory tests. This retrovirus predominantly infects human T4 (helper) lymphocytes (also known as the CD4 cell), the major regulators of the immune response, and destroys or inactivates them. Macrophages and B cells are also infected (Fig. 7-13).

All human cells contain DNA and RNA, known collectively as *nucleic acids*. The DNA is located in the cell nucleus, and the RNA is located in the cytoplasm of the cell. Viruses contain only one of the nucleic acids and are categorized as belonging to the DNA group (e.g., herpes and mononucleosis) or the RNA group (e.g., measles and mumps). HIV is classified as a lentivirus, a subclass of retroviruses that contain RNA. When the RNA virus initiates replication in the living host cell, it must convert its RNA genetic information into a DNA template to replicate.

HIV is unique in that despite the body's immune responses after initial infection, some HIV invariably escapes. Large amounts of HIV have been discovered hiding in the immune cells lining the surface of adenoids.⁷⁶ This information alters the formally held view that HIV is a slow or covert process, when in fact the virus's growth continues in the period between infection and the onset of AIDS. It is theorized that the use of a preventive vaccine could stop hidden viral production.

Once HIV enters the body, cells containing the CD4 antigen, including macrophages and T4 cells, serve as receptors for the HIV retrovirus, allowing direct passage of the infection into target cells previously identified (e.g., GI tract, uterine cervical cells, and neuroglial cells). After invading a cell, a virus particle called a *virion* injects the core proteins and the two strands of viral RNA into the cell.

As a retrovirus, HIV contains reverse transcriptase, an enzyme required for successful infection by the virus. Before viral replication can occur in the host cell, this enzyme must copy all the genetic information of the virus from viral RNA to viral DNA. Once the viral genome is transcribed, it can be integrated into the host's DNA and duplicated many times (Fig. 7-14).

Replication of the HIV virus can cause cell death, although the person remains asymptomatic. Seroconversion (becoming positive for HIV) usually takes place during the first 3 to 6 weeks of this replication process but can take longer. After a few months, very little virus is found in the blood; only HIV antibodies remain in the serum.

During the asymptomatic period (also called the *early stage*), the virus migrates from the serum into the tissues to infect CD4 cells in lymph tissue. The virus continues to kill the CD4 cells in the lymph nodes, although the CD4 count remains above 500 cells/mm³ (average CD4 cell count is 1000 cells/mm³).

The regulation of HIV expression by modules secreted by immune cells is even more complex than previously realized. The initially expanded clones that can kill HIV-infected cells are found in the bloodstream rather than in the lymph nodes, where the virus is replicating. The gene, *vpr*, within HIV that stops production of the CD4 T lymphocytes and enhances T lymphocyte apoptosis has now been identified.

Research continues to focus on understanding how the *vpr* gene prevents these disease-fighting cells from dividing. New drugs to block the gene's actions and allow immune cells to continue multiplying and fighting HIV may be possible; alternately researchers are studying this phenomenon in hopes of developing a live HIV vaccine.

Once all the cells are depleted, the virus once again enters the blood to infect any remaining lymphocytes and clinically apparent disease occurs. By the time this happens, the immune system has been compromised and is ineffective and unable to mount a specific immune response to these virions. The immune system dysfunction is even more exaggerated if the host has become further immunocompromised by opportunistic diseases.

HIV infection leads to profound pathology, either directly by destruction of CD4+ cells, other immune cells, or neuroglial cells or indirectly, through the secondary effects of CD4+ T-cell dysfunction and resultant immunosuppression.

The decline in CD4 cells results in progressive loss of immune system function and the development of a wide variety of clinical signs and symptoms (see Table 7-3). **Editor: this is NOT the callout for Table 7-3** This describes the middle stage or symptomatic phase of AIDS when CD4 count ranges between 200 and 500 cells/mm³. A decrease in the CD4 count to less than 200 and an elevated viral load occurs during the late-stage or advanced disease associated with the development of opportunistic infections (Fig. 7-15).

This infectious process may result in one or more of the following: (1) immunodeficiency with opportunistic infections and unusual malignancies; (2) autoimmunity such as rheumatoid arthritis, lymphoid interstitial pneumonitis, hypergammaglobulinemia, and production of autoimmune antibodies; and (3) neurologic dysfunction, including AIDS dementia complex, HIV encephalopathy, and peripheral neuropathies.

HIV has an extremely high mutation rate even within a single individual, producing competing strains of the same virus that fight for survival against the weapons produced by the immune system. Researchers are studying how different strains of HIV use cell surface molecules, in addition to the CD4 molecule, to bind to and enter target cells.

Another consideration is how different strains of HIV have a preference for certain cells; strains that infect macrophages and T cells are the main ones found early in the disease. Later, strains appear that replicate efficiently in T cells but not in macrophages. Finally, mutations in the human genes for HIV co-receptors may help explain why some people do not become infected despite repeated exposure and why some who are infected may have different rates of disease progression.

These long-term non progressors (LTNP) are HIV infected individuals characterized by the absence of disease, low viral loads, and stable or even increasing CD4⁺ T cell counts for prolonged periods of time. ¹⁸⁴

Clinical Manifestations. HIV infection manifests itself in many different ways (Table 7-3) and differs between adult and pediatric populations. Great variation exists among individuals as to the amount of time that passes between acute HIV infection, the appearance of symptoms, the diagnosis of AIDS, and death.

Asymptomatic Stage [CD4 >500 cells/mm³]. During the early stage, the person demonstrates laboratory evidence of seroconversion (positive for HIV) but remains asymptomatic. Some

individuals develop an acute, self-limiting infectious mononucleosis-like illness or a subtle, viral-like syndrome, followed by a period of clinical latency that may last a decade or more.

During the asymptomatic period, the infected person is clinically healthy and capable of normal daily activities, normal work habits, and unrestricted level and duration of exercise. Fatigue and generalized lymphadenopathy with swollen and firm lymph glands may be reported during this stage.

Early Symptomatic Stage [$CD4 = 200-500 \text{ cells/mm}^3$]. As the infection progresses and the immune system becomes increasingly more compromised, a variety of symptoms may develop, including persistent generalized adenopathy; nonspecific symptoms such as diarrhea, weight loss, fatigue, night sweats, and fevers; neurologic symptoms resulting from HIV encephalopathy; or an opportunistic infection (e.g., *Pneumocystis carinii* pneumonia [PCP], cytomegalovirus [CMV], toxoplasmosis) or malignancy.

CMV can cause peripheral neuropathy and HIV retinitis (with possible blindness); PCP produces pulmonary symptoms such as dyspnea on exertion, nonproductive cough, and weight loss, and toxoplasmosis is a parasitic disease that affects the CNS. In addition to the symptoms that may occur with opportunistic diseases, treatment with multiple medications can cause adverse side effects, sometimes creating a confusing clinical picture.

More than half the adults with HIV in this stage report fatigue that limits physical and recreational activities. Half the adults who report fatigue are unable to attend school or work at a job. ²²⁶

HIV Advanced Disease (AIDS) [$CD4 < 200 \text{ cells/mm}^3$]. The neurologic manifestations of more advanced HIV disease are numerous and can involve the central, peripheral, and autonomic nervous systems. The CNS appears to be more commonly attacked by HIV than the peripheral nervous system.

HIV or AIDS encephalopathy, also referred to as *HIV-associated dementia* (HAD), formerly AIDS dementia complex, is a primary infection of the brain by HIV. Symptoms can vary and are listed in Table 7-3. In the most advanced stages of the disease, severe dementia, mutism, incontinence, and paraplegia may occur. A detailed summary of nervous system disorders associated with HIV, including treatment, is available. ^{83, 224, 255}

Dermatologic conditions are common and can be extensive including malignancies, bacterial, viral, and fungal infections (Fig. 7-16) or reactions to drug treatment. Cutaneous manifestations of HIV can present as dry flaking skin, telangiectasias, and thinning of the skin (and hair).

The prevalence of conditions such as seborrheic dermatitis, psoriasis, Reiter's syndrome, acquired ichthyosis, Kaposi's sarcoma, and scabies is on the rise. Kaposi's sarcoma (purple nodular skin lesions) predominantly affects homosexual men (Figs. 7-17 and 18). HIV-associated nutritional disorders may also contribute to nail and hair changes. HIV-associated wounds may occur as a result of Kaposi's sarcoma, herpes simplex virus, syphilis, injection drug use ("tracks"), candida/fungal infections, postoperative infections, and herpes zoster (see Fig. 8-7). ¹⁰⁸

Pain Syndromes. Pain syndromes seen in HIV-infected individuals are divided into 3 groups: pain directly related to HIV infection or immunosuppression, pain caused by HIV diagnostic

procedures and treatment, and pain unrelated to AIDS or its treatment (e.g., diabetic neuropathy, discogenic).

Painful sensory peripheral neuropathy is the most commonly reported pain syndrome followed by pain associated with extensive Kaposi's sarcoma and other dermatologic conditions, headache, abdominal pain, chest pain, and arthralgias and myalgias. Women infected with HIV experience pain more often and with greater intensity than men; women also have unique gynecologic syndromes related to opportunistic infections and cancers of the pelvis and genitourinary tract.²⁴⁸

Peripheral neuropathy, disease- or drug-induced myopathy, and musculoskeletal pain syndromes occur most often in advanced stages of HIV disease but can occur at any stage of HIV infection and may be the presenting manifestation. Neuropathic conditions in the AIDS population may develop as a result of neurotoxic antiretroviral medications, vitamin deficiencies resulting from poor nutrition, metabolic abnormalities, and opportunistic infections such as CMV.⁸⁴

Peripheral neuropathies affect a large portion of people with AIDS and are usually distal, symmetric, and predominantly sensory, but other parts of the body may be affected such as the face or trunk. Peripheral neuropathies generally present in a stocking-glove distribution, with the feet and legs most commonly affected. Involvement of the upper extremities is less common and often occurs much later in the disease process.

The pain of peripheral neuropathy is characterized by burning, tingling, contact hypersensitivity, proprioceptive losses, and in severe cases, secondary motor deficits. In the individual with HIV and newly acquired neuropathy with a strong major motor component, vasculitis may be the underlying cause (see the section on Vasculitis in Chapter 12).

AIDS is associated with *neuromusculoskeletal diseases* such as osteomyelitis, bacterial myositis, and infectious (reactive) arthritis. Osteonecrosis, osteopenia, and osteoporosis are increasingly observed in clients with HIV disease. Avascular necrosis (osteonecrosis) of the femoral head(s) has been reported with the use of antiretroviral therapy containing protease inhibitors.⁷⁸

The increased incidence of osteonecrosis in HIV/AIDS may be due to the use of protease inhibitors or possibly as a result of an increased frequency of risk factors previously associated with osteonecrosis such as hyperlipidemia, corticosteroid use, alcohol abuse, and hypercoagulability.²²⁵ It is possible that HIV disease itself may have an independent effect on bone loss regardless of antiretroviral therapy.^{185,166} Others suggest a link between lipodystrophy and bone loss.²⁰²

Musculoskeletal pain syndromes are associated with the wasting process in AIDS referred to as *HIV wasting syndrome*. HIV wasting is characterized by a disproportionate loss of metabolically active tissue, specifically body cell mass (i.e., tissue involved with glucose oxidation, protein synthesis, and immune system function).

These conditions occur secondary to low food intake, altered metabolism, and poor nutrient absorption with manifestations such as extreme weight loss, chronic diarrhea, unexplained weakness, fever, and malnutrition (e.g., mineral and vitamin deficiencies, especially vitamin B deficiency).

Studies have shown a clear relationship between vitamin B₁₂ deficiency and dysfunction of the central and peripheral nervous systems. Some of the clinical abnormalities of the nervous system

seen in people with HIV are similar to those that have been described in those with vitamin B₁₂ deficiency.

Lower genital tract infections and HIV are major causes of morbidity and mortality among women.²⁴⁷ As the HIV epidemic affects more women, increasing cases of pelvic inflammatory disease (PID) are being reported.^{114, 115} Pain is a common symptom in all these conditions. PID is discussed in greater detail in chapter 20.

Rheumatologic manifestations are transient or subtle and appear more often as HIV disease progresses. The arthritis can be severe and does not necessarily respond to conventional medications. Polymyositis involves bilaterally symmetrical proximal muscle weakness and arthritis may precede or accompany seroconversion.

There has been a decline in reactive arthritis, psoriatic arthritis, and various forms of connective tissue disease for adults but new syndromes such as the immune reconstitution infection following HAART may occur months later. Most cases reported resolve without intervention.³⁰ Arthritis with spondyloarthropathy-like features is common in children with HIV infection and may be the presenting symptom.⁴⁶ More detailed information regarding rheumatic disorders in HIV disease is available.²²⁸ [AU: check Primer on Rheumatic Diseases as a possible reference](#)

HIV-associated myopathy presents with a progressive painless weakness in the proximal limb muscles. The weakness is symmetrical and often involves the muscles of the face and neck. This type of myopathy may occur in individuals with HIV at every stage of illness.

Muscle biopsies have shown necrosis of muscle fibers with and without inflammatory infiltrates. No evidence has been found of direct HIV infection of the muscle, and the underlying cause has not been determined. The fact that these clients improve on corticosteroids or plasmapheresis may point to an underlying autoimmune defect. Drug-induced myopathy is discussed in Chapter 6.

Lipodystrophy or Lipodystrophic Syndrome (LDS), a syndrome of defective fat metabolism, dyslipidemia, and insulin resistance manifests as central fat accumulation ([Fig. 7-19](#)) with visceral fat deposition documented by CT scans. It is a common problem that occurs soon after starting HAART. Loss of fat occurs in the arms, leg, or face with concomitant fat deposits in the abdomen, breasts (men and women), and back of the neck (“buffalo hump;” see [Fig. 11-6](#))[Au: check Fig. number.](#)

AIDS-Related Lymphoma (ARL) including Burkitt lymphoma, Non-Hodgkin’s Lymphoma, Hodgkin’s Lymphoma, and other more uncommon types (e.g., primary effusion lymphoma) are more likely to occur in HIV-infected people when compared with the general population. AIDS-related lymphomas (ARL) are now the second most common cancer associated with HIV after Kaposi sarcoma and increase with time following infection. The incidence of NHL appears to be declining with the use of HAART, whereas the incidence of Hodgkin’s disease may actually have increased in the HIV infected population.¹⁵²

ARL can occur at any CD4⁺ level but the risk is increased with declining CD4⁺ lymphocyte counts.^{1, 101} Course of disease is often aggressive with extranodal metastases involving unusual sites such as the jaw, heart, body cavities, gallbladder, skin, and soft tissues. **!**

HAART has had little impact on the incidence of human papilloma virus-associated tumors (e.g., cervical cancer in women and anal cancer most commonly in MSM).²¹ The rising incidence of

anal cancer among men with AIDS may be related to increased longevity with HAART and the consequent increased time at risk for the development of malignancy and/or the result of greater use of cytologic screening. ⁶⁶

Cardiopulmonary diseases continue to be an important cause of illness and death in people with HIV infection. Bacterial pneumonia, bronchitis, tuberculosis (pulmonary and extrapulmonary), and cytomegalovirus are common opportunistic diseases in the HIV/AIDS population. Emphysema, asthma, and pulmonary hypertension are also observed in this population.

Cardiac involvement (heart and blood vessels) occurs as a result of a combination of the HIV infection, medical management, and secondary opportunistic infections. Both HIV infection and HAART can cause changes in lipid and glucose metabolism as well as elevation of blood pressure, promoting the development of atherosclerosis.

Cardiovascular diseases have become a major cause of mortality among HIV-infected people who respond well to antiretroviral therapy. Myocardial infarction, cardiomyopathy, pericardial effusion, and pericarditis are some other cardiovascular conditions that occur as a result of HIV and/or its treatment. There is increasing evidence to suggest that cardiovascular disease appears earlier and more often among HIV-infected adults than in the general public. ^{113, 169}

Medical Management

Prevention. HIV prevention in the U.S. has placed the primary focus on persons who are not HIV infected, to help them avoid becoming infected. Reducing sexual and drug-using risk behavior has been the main emphasis of public health prevention programs. CDC's overarching HIV-prevention goal is to reduce the number of new HIV infections and to eliminate racial and ethnic disparities by promoting HIV counseling, testing, and referral and by encouraging HIV prevention among both persons living with HIV and those at high risk for contracting the virus. ²⁵⁴

However, further reduction of HIV transmission will require new strategies, including increased emphasis on appropriate routine screening, identification of new cases, partner notification, and increased availability of sustained treatment and prevention services for those infected. The addition of a simple rapid HIV test may help overcome some of the traditional barriers to early diagnosis and treatment of infected persons. The CDC also recommends routine HIV testing of all pregnant women and routine screening of any infant whose mother was not screened. ^{22, 118}

Recent reports suggest that behavioral changes often are not maintained and that a substantial number of HIV-infected persons continue to engage in behaviors that place others at risk for HIV infection or revert to risky sexual behavior after adopting safer sexual behavior. ¹¹⁶ This altered behavior is referred to as "fatigue prevention."

Two simple but effective interventions have been shown to limit the horizontal spread of HIV: condoms and counseling. Sex education and the practice of abstinence (or less effectively, the use of condoms) and reducing/eliminating risky drug-abuse behavior including the provision of clean needles has not been enough to stop the spread of AIDS, and no vaccine is available.

Restricting sex to partners of the same serostatus does not protect against transmission of other sexually transmitted diseases or the possibility of HIV coinfection or superinfection (resistant to

two or more classes of antiretroviral drugs) unless condoms are used correctly and consistently.

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Controlling the AIDS epidemic requires sustained prevention programs in all affected communities, particularly programs targeting MSM, sexually active individuals with multiple partners, injection drug users, and minorities. Continuing the ABC (Abstinence, Being Faithful, Condoms) prevention education is important with sexually active individuals undergoing treatment.

Even though potent antiviral treatment can eradicate HIV from the blood, these drugs cannot completely eliminate the virus from the body, especially the semen. Although antiretroviral therapy reduces shedding of HIV in semen thereby reducing HIV transmissibility, a substantial portion of people with HIV may still be infectious and may have drug-resistant strains of the virus.¹⁰ Safe sex practices should continue to be reinforced in all people with HIV.

Unfortunately prevention fatigue has made prevention of HIV transmission less attainable as time goes by. Two drugs already used in combination known as Truvada (tenofovir/Viread and FTC/Emtriva) to treat HIV show promise in animal studies as possible preventive treatment.

Human tests are beginning in the United States and Africa to test the safety and effectiveness of this approach.³⁶ The drugs keep the virus from reproducing and are already used to prevent infection in health care workers accidentally exposed to HIV.²⁵³ There is some concern that this kind of use could lead to drug resistance while others encourage chemoprophylaxis research.⁹⁷

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Healthy People 2010 has proposed updates to three primary goals related to reducing the number of AIDS cases: (1) reduce the number of new cases of HIV/AIDS among adolescents and adults to one new case per 100,000 people (from the 19.5 cases reported in 1998 in people age 13 years and older); (2) 25% improvement in the number of new AIDS cases among adolescent and adult men who have sex with men and (3) 25% improvement in the number of new AIDS cases among men and women who inject drugs¹⁰⁶

A new generation of MSM has replaced those who benefited from early prevention strategies. Behavior intervention, the primary prevention tool, includes school-based programs, peer-to-peer interventions, strategies that limit needle sharing, parent-to-child communication, client-centered counseling, and personalized risk-reduction strategies (Box 7-3).

The introduction of routine counseling, voluntary testing for women with HIV, and providing zidovudine (commonly known as AZT) to infected women and their infants has dramatically reduced mother-to-child transmission rates.^{175, 254}

Research efforts on behalf of women infected with HIV via heterosexual contact are investigating genetically engineered bacteria designed to destroy HIV in the vagina. Naturally occurring bacteria present in the vagina are modified to secrete a protein that will attract HIV. Once trapped on the surface, the HIV is destroyed by other natural substances in the vagina that are toxic to the virus.⁴⁴

The search is on to find an HIV-1 microbicide that can neutralize a diversity of HIV-1 strains without causing mucosal inflammation in the lining of the vagina and have a minimum of adverse side effects all while maintaining effectiveness for prolonged periods of time after a single application.²⁰¹

Mycobacterium tuberculosis associated with AIDS is communicable, preventable, and treatable. One in 3 adults with HIV/AIDS is coinfecting with mycobacterium tuberculosis. Tuberculin (TB) skin testing should be available and routinely offered to individuals at HIV testing sites. Highest risk individuals for concomitant HIV and TB infections include the homeless, injection drug users, and incarcerated people⁸² (see Chapter 15). Guidelines for the prevention of other opportunistic infections in people with HIV are also now available.^{89, 198} Au: this is the most recent update. Checked on 5/29/06; leave this note to me, keep ref #39 as is...

Socioeconomic factors (e.g., high rates of poverty and unemployment, lack of access to health care) are associated with high rates of HIV risk behaviors among minority MSM and are barriers to accessing HIV testing, diagnosis, and treatment. Reaching minority MSM who may not identify themselves as homosexual or bisexual with prevention messages remains a challenge.

The development of an HIV vaccine is important to control the global epidemic. However efforts to develop postexposure prophylaxis, microbicides that are safe and effective in reducing HIV transmission through sexual intercourse, and vaccines are collectively unlikely to provide full protection against HIV and offer little or no protection against other STDs such as gonorrhea and chlamydia.²⁵⁴

Effective behavior-change programs will still be needed to address possible behavioral disinhibition (i.e., continuing or returning to high-risk behaviors when one feels protected) among persons who receive these interventions. Prevention counseling that addresses informed choice and consent; the HIV-prevention behaviors of abstinence and delay of sexual debut, being monogamous, having fewer sex partners, and using condoms correctly and consistently; and other reproductive health needs (e.g., STD treatment and family planning) must be incorporated alongside new prevention interventions.²⁵⁴

Diagnosis. Early diagnosis is important so that early and preventive therapies may be initiated and sex partners can be notified of their risk of HIV and the subsequent need for HIV testing. To establish uniformity in reporting AIDS cases, the CDC has established diagnostic criteria for the confirmation of AIDS.

The most commonly performed screening test is the HIV-1 antibody enzyme immunoassay (EIA) test, an antibody test to indicate HIV infection indirectly by revealing HIV antibodies (indicating exposure to the virus). However, antibody testing is not always reliable because the body takes a variable amount of time to produce a detectable level of antibodies. Consequently, a person with HIV could test negative for HIV antibodies. Antibody tests are also unreliable in neonates because transferred maternal antibodies persist for 6 to 10 months. The Western blot test is a more expensive test that may be used when there is a concern about false-positive tests.

The CDC AIDS surveillance definition requires direct testing, including antigen tests (p24 antigen); HIV cultures; nucleic acid probes of peripheral blood lymphocytes; and the polymerase chain reaction (PCR).

Additional laboratory confirmation of HIV infection is required; HIV RNA viral load testing as measured by the plasma HIV RNA assay and a CD4+ T lymphocyte count of less than 200 cells/mm³ is also considered diagnostic. T-cell measurement and viral load are both important indicators of HIV status.

To use a train crash analogy, T-cell values represent the distance to the crash whereas viral load counts represent the speed of the train, i.e., how fast the person is declining. ²²²T-lymphocyte counts monitor the progression of HIV and should be viewed from a broad perspective rather than on a day-to-day basis; the overall trend is more important than single values.

A rapid noninvasive test that uses saliva or a gum swab to detect HIV antibodies is available. The OraQuick Rapid HIV-1 Antibody test can be completed in as little as 10 minutes and has up to 99.6% accuracy. The advantage is in obtaining results quickly. The CDC estimates that one-third of all individuals tested do not return for their test results. Rapid testing means that individuals who are HIV-positive can receive immediate counseling, early treatment to preserve their health, and prompt education on preventing disease transmission. ¹⁵⁰

The disadvantage is that the test cannot detect HIV infection in people who were exposed less than 3 months before taking the test; antibody development can take up to 3 months. Positive results should be followed up with additional test to confirm the results. Concern exists that rapid tests will distract from risk reduction. Although some individuals may be reassured that they are negative for HIV, this does not necessarily translate into reduced risk without continued education.

Treatment. No cure has been found for AIDS, but advances in treatment have successfully transformed AIDS into a manageable chronic condition. The national HIV Vaccine Trials Network has been established to develop and test possible vaccine compounds but an effective vaccine is not imminent. Until a vaccine is available, the goals of intervention are to stop HIV from replicating, increase the number of CD4 cells, and delay HIV disease progression.

Medical management centers on the CD4 cell count and viral load. When CD4 cell counts drop below 500 cells/mm³ highly active antiretroviral therapy (HAART) is initiated. HAART, a protease inhibitor plus two nucleoside-analog reverse transcriptase inhibitors, acts on reverse transcriptase, the enzyme necessary for transcribing HIV RNA to DNA, to achieve sustained suppression of HIV replication reducing the amount of virus in the blood to very low and even nondetectable levels. These drugs do not completely eliminate the virus and lifelong therapy is required until viral complete and permanent eradication is developed.

Current efforts are focused on (1) simplifying the drug regimens to improve adherence (once-daily dosing), (2) developing alternatives for those in whom the current medications have failed, (3) preventing viral rebound (return of high levels of the virus when drugs are discontinued), and (4) managing the wide range of pharmacologic side effects.

A new generation of antiviral drugs emerging will inhibit HIV at several different points in the entry, fusion, and replication cycle of the HIV-1 virus. New classes of HAART include entry inhibitors, attachment inhibitors, fusion inhibitors, and maturation inhibitors to name a few. ¹⁰³ For example entry inhibitors operate early in the viral life cycle by preventing HIV-1 entry into susceptible cells. Fusion inhibitors are effective during the narrow window between virus attachment and the subsequent fusion of viral envelope with the cell membrane. ¹⁴⁸

Development of drug resistance is the inevitable consequence of incomplete suppression of virus plasma levels in individuals with HIV treated with HAART. Noncompliance with the drug regimen that involves taking multiple drugs throughout the day can lead to mutation of the virus and resistance to the treatment. Drug resistance is one of the most significant threats to effective therapy.

Several assays are available for testing HIV for resistance to antiretroviral agents. Genotypic and phenotypic testing has been implemented and should be carried out when the individual is not responding to drug therapy as indicated by an increase in the viral load and a decrease in the CD4+ cell count, especially before the HAART regimen is discontinued. Genotyping detects viral mutation whereas phenotyping detects a decrease in the sensitivity of the virus to the drugs.

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Potential toxicities from drug treatment include metabolic disorders (e.g., lipodystrophy, a syndrome of defective fat metabolism, dyslipidemia, and insulin resistance); avascular necrosis of the femoral head(s); and lactic acidosis. There is no known treatment to stop treatment-induced osteonecrosis.

Palliative treatment may include NSAIDs and pain medications. Surgical procedures to improve blood flow to the affected area or joint replacement to improve function may be considered. When present, dyslipidemia may be associated with accelerated atherosclerosis and insulin resistance contributing to increased cardiovascular morbidity and mortality in the population with HIV. 89,140

The lactic acidosis occurs as a result of injured cell mitochondria, giving off lactic acid in response to the effects of nucleoside reverse transcriptase inhibitors. AZT myopathy, a toxic mitochondrial myopathy is much less often seen today and is limited to people taking high doses of AZT. Both of these conditions are reversible with cessation of the drug therapy. 228

The optimal time at which to initiate intervention remains controversial. When protease inhibitors were first introduced, the strategy was to “hit early, hit hard” because early intervention and the associated reduction of acute viral load might have positive effects on the subsequent course of the disease. 259 However, the development of resistance and the toxic side effects that occur have brought that philosophy into question.

The complete eradication of the infection remains the focus of research today. Some people with HIV are coinfecting with hepatitis C, making treatment more complex because of the hepatotoxicity of antiretroviral medications and the important role the liver has in maintaining health.

The proper treatment of people with both HIV and HCV is still under investigation. The order in which antiretroviral drugs are prescribed is called *sequencing* and is designed to maximize viral suppression for as long as possible and to minimize the development of resistance and hepatotoxicity. Current guidelines advise a drug regimen that saves some categories of medications for future use if and when the person develops resistance to other medications. 92

Structured treatment interruptions (STIs) to improve viral control by stimulating HIV-specific T-lymphocyte immunity in primary HIV infection are also under investigation. If viral suppression is achieved, treatment can be interrupted because of adverse effects, cancer, tuberculosis, or in response to individual preference. It remains to be decided how many doses may be skipped before HIV treatment response is adversely affected. 12; 237

In all treatment situations, dosage adjustments are important considerations. Gender and ethnicity can affect the way a person metabolizes antiretroviral drugs and which adverse reactions occur. Women are especially prone to gender-based response to antiretroviral side effects. Several antiretrovirals are now known to interact with oral contraceptives (e.g., nevirapine [Viraimune]; ritonavir [Navir]; nelfinavir [Viracept]). With HAART treatment,

women are more likely to develop lipodystrophies, experience nausea, vomiting, fatigue, itching, abdominal pain, skin rashes, and perioral numbness while men experience more diarrhea.¹⁰⁷

If, as suspected, multiple variants of HIV are in a single host and the virus is capable of mutating easily, treatment approaches geared toward enhancing host resistance and restoring or building the immune system will be more successful than trying to kill the virus.

This same principle of using drugs to boost the immune system, called biotherapy (immunotherapy), immunodilating, or immunologic therapy, is also being applied in the use of genetically engineered IL-2 to treat cancer. Previous trials using interferon- α resulted in significant toxicity and its use has been limited. Other researchers are investigating the use of gene therapy and immune reconstitution or restoration in relation to AIDS.

Other pharmacologic intervention may be used to treat various clinical manifestations of HIV disease (e.g., antibiotics, nonsteroidal antiinflammatory drugs [NSAIDs]; corticosteroids; immunosuppressives; interferon therapy).

Nonpharmacologic intervention includes nutritional therapy, exercise, mental health support, and alternative or complementary intervention. AIDS-associated weight loss, nutritional deficiencies, loss of muscle mass (wasting syndrome), and other effects contribute to immune dysfunction, faster disease progression in some people, and a variety of complications that can be ameliorated with proper nutrition. The use of alternative and complementary intervention techniques remains an area of controversy and investigation.

Prognosis. AIDS has changed from an acute to subacute chronic illness. The development of combination therapies is extending the lives of AIDS clients, keeping many healthy enough to avoid hospitalization and/or return to their baseline after illness, extending survival, and even resulting in return to work status for some people. People with AIDS are living longer with lower CD4 levels because prophylaxis, improved supportive care, and treatment of PCP, tuberculosis, and ARL saves many who would have died sooner in the earlier days of the AIDS epidemic.

Changes in treatment rather than changes in human behavior accounts for the decline in AIDS-related deaths.¹⁹⁴ Drug combinations with two or more antiretroviral drugs (HAART) have reduced mortality rates from AIDS by more than 80%. Because of HAART 9 out of 10 people with AIDS can expect to live at least 10 years after infection. In the pre-HAART era adults older than 45 years at the time of diagnosis had a much poorer prognosis. Today older adults have the same life expectancy as younger people with AIDS.¹⁰⁰

Highly active antiretroviral therapy is improving survival but at the price of a variety of metabolic (and other) side effects. Patterns of morbidity and mortality are changing: the leading cause of death is now kidney or liver failure (instead of opportunistic infections) as a result of medical treatment (e.g., protease inhibitors are metabolized by the liver) and HCV.²⁹

Prognosis remains poor for anyone who has both HIV and HCV HIV (especially injection drug users) or who is manifesting the wasting syndrome. IDUs have a higher burden of comorbidities of HIV disease possibly contributing to poor response to HAART. Active drug use is most commonly associated with nonadherence to the required antiretroviral treatment regimen and prophylaxis for opportunistic infections.¹⁷⁴

Women are less likely than men to receive prescriptions for the most effective treatments for HIV infection potentially affecting both morbidity and mortality.³⁴

On the other hand, survival has been reportedly prolonged in HIV-positive people who are co-infected with the GBV-C virus. GBV-C does not prevent infection by HIV, but it slows the replication process thereby delaying the progression to AIDS. The GBV-C virus also increases production of various chemokines, chemicals produced by white blood cells to fight infection. Further research may yield new strategies to control HIV-1 replication and progression to AIDS. 90, 241

Clinical presentation in the pediatric population is often more devastating due to the immaturity of the immune system. Children become sicker faster with death within two years in many cases. The immature CNS is very vulnerable to direct infection by HIV. Developmental delays are often the first sign of HIV and contribute to morbidity in this group.

A considerable body of evidence suggests that psychosocial factors play an important role in the progression of HIV infection, its morbidity and mortality. Psychosocial influences relating to faster disease progression include life-event stress, sustained depression, denial/avoidance coping, concealment of gay identity, and negative outlook. Conversely protective psychosocial factors include active coping, collaborative relationship with health care professionals, and stress management.

Biologic factors such as genetics, age of the host, viral strain and virulence, medication, and immune response are also major determinants of disease progression and also impact on outcome. Scientists are continuing to investigate psychoneuroimmunologic pathways by which immune and neuroendocrine mechanisms might link psychosocial factors with health and survival.

◆ **Chronic Fatigue and Immune Dysfunction Syndrome**

Overview. Chronic fatigue and immune dysfunction syndrome (CFIDS); chronic fatigue syndrome (CFS); chronic Epstein-Barr virus (CEBV); myalgic encephalomyelitis; neuromyasthenia; and the “yuppie-flu” all denote a highly publicized but not new illness.

The name *chronic fatigue syndrome* indicates that this illness is not a single disease but the result of a combination of factors and is actually a subset of *chronic fatigue*, a broader category defined as unexplained fatigue of greater than or equal to 6 months’ duration. This distinction is made to facilitate epidemiologic studies of populations with prolonged fatigue and chronic fatigue.

Incidence and Risk Factors.

Two US community based CFS studies found prevalences among adults of 0.23% and 0.42%; the rates were higher in women, members of minority groups, and people with lower educational attainment and occupational status. 119, 210

People of every age, gender, ethnicity and socioeconomic group can have CFS. Demographic data show that in most studies 75% or more of people with CFS are female. The mean age at onset of CFS is between 29 years and 35 years. The mean illness duration ranges from 3 years to 9 years. 28. Although CFS is much less common in children than in adults, children can develop the illness, particularly during the teen years.

Etiologic Factors and Pathogenesis.

Many studies have investigated the etiology and pathogenesis of CFS. ²⁰⁰ More than half of the CFS studies between 1980 and 1995 concentrated on the physical etiology of CFS, with a slight shift towards psychological and psychiatric research in the next few years. ⁵³

Many somatic and psychosocial hypotheses on the etiology of CFS have been explored. Explanations for CFS were sought in viral infections, immune dysfunction, neuroendocrine responses, dysfunction of the central nervous system, muscle structure, exercise capacity, sleep patterns, genetic constitution, personality, and (neuro)psychological processes.

Although several studies found abnormalities, only a few were diagnosed in large groups of people with CFS and were independently confirmed in well-controlled studies, an exception being the subtle changes in the hypothalamopituitary-adrenal axis.

Neuroendocrine challenge tests have found a lower than normal cortisol response to increased corticotrophin concentrations and upregulation of the serotonergic system. Studies of neuroendocrine function in individuals with CFS have found no evidence for uniform dysfunction of the hypothalamopituitary-adrenal axis or stress hormones. ⁵⁴ Increasing evidence points to acquired neuroendocrine dysregulations in people with CFS. ⁸²

However, abnormalities of the neuroendocrine and central nervous systems alone are not sufficient to explain the symptoms of CFS. More complex interactions between regulating systems are assumed to be at work and seem to involve the central nervous system, the immune system, and hormonal regulation system. The etiology and pathogenesis are generally believed to be multifactorial. ^{45, 55}

Personality and lifestyle are presumed to influence vulnerability to CFS. Personality characteristics of neuroticism and introversion have been reported as risk factors for the disorder. ²⁰⁰

Inactivity in childhood and inactivity after infectious mononucleosis have been found to increase the risk of CFS in adults. ^{257, 264} Also, acute physical or psychological stress might trigger the onset of CFS.

Three-quarters of the individuals with this disorder have reported an infection, such as a cold, flulike illness, or infectious mononucleosis, as the trigger. ^{60, 221} and high rates of chronic fatigue after Q fever and Lyme disease have been found. ¹⁵³ Finally, serious life events, such as the loss of a loved one or a job, and other stressful situations have been found to precipitate the disorder. ^{104, 252}

Clinical Manifestations. At illness onset, the most commonly reported CFS symptoms are sore throat, fever, muscle pain, and muscle weakness. As the illness progresses, muscle pain and forgetfulness increase along with prolonged (lasting more than 6 months), often overwhelming fatigue that is exacerbated by minimal physical activity.

Neurally mediated hypotension (NMH) caused by disturbances in the autonomic regulation of blood pressure and pulse is common in people with CFS. This condition is characterized by lowered blood pressure and heart rate accompanied by lightheadedness, visual dimming, or slow response to verbal stimuli. Many people with NMH experience lightheadedness or worsening fatigue as they stand for prolonged periods or when in warm places (e.g., hot shower, sauna, indoor pool environment).

The severity of CFS varies from person to person, with some people able to maintain fairly active lives. By definition, however, CFS significantly limits work, school and family activities.

While symptoms vary from person to person in number, type and severity, all individuals with CFS are functionally impaired to some degree. CDC studies show that CFS can be as disabling as multiple sclerosis, lupus, rheumatoid arthritis, heart disease, end-stage renal disease, chronic obstructive pulmonary disease (COPD) and similar chronic conditions.

CFS often follows a cyclical course, alternating between periods of illness and relative well-being. Some people experience partial or complete remission of symptoms during the course of the illness, but symptoms often reoccur.

This pattern of remission and relapse makes CFS especially hard for clients and their health care professionals to manage. People who are in remission may be tempted to overdo activities when they're feeling better, which can exacerbate symptoms and fatigue and cause a relapse. In fact, postexertional malaise is a hallmark of the illness.³⁸

Medical Management

Diagnosis. There are no physical signs or diagnostic laboratory tests that help identify CFS. People who suffer the symptoms of CFS must be carefully evaluated by a physician because many treatable medical and psychiatric conditions are hard to distinguish from CFS.

Common conditions that should be ruled out through a careful medical history and appropriate testing include mononucleosis, Lyme disease, thyroid conditions, diabetes, multiple sclerosis, various cancers, depression and bipolar disorder.

To aid the identification of this disease, the CDC has developed a working case definition with two criteria to distinguish CFS from other forms of fatigue (Box 7-6). The symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue. Research conducted by the Centers for Disease Control and Prevention (CDC) indicates that less than 20% of the people with CFS in this country have been diagnosed.³⁸

Treatment. Since there is no known cure for CFS, treatment is aimed at symptom relief and improved function. A combination of drug and nondrug therapies is usually recommended. No single therapy exists that helps all individuals with CFS.

Lifestyle changes, including prevention of overexertion, reduced stress, dietary restrictions, gentle stretching and nutritional supplementation, are frequently recommended in addition to drug therapies used to treat sleep, pain and other specific symptoms.

Carefully supervised physical therapy may also be part of treatment for CFS. However, symptoms can be exacerbated by overly ambitious physical activity. A very moderate approach to exercise and activity management is recommended to avoid overactivity and to prevent deconditioning.³⁸ Systematic reviews have investigated the effectiveness of several CFS treatments, and cognitive behavior therapy and graded exercise therapy are the only interventions found to be beneficial.^{199, 209, 265.}

Prognosis. CFS affects each individual differently. Some people with CFS remain homebound and others improve to the point that they can resume work and other activities, even though they continue to experience symptoms.

CDC's research has shown that those who have CFS for two years or less were more likely to improve. It remains unknown if early intervention is responsible for this more favorable outcome; however, the longer a person is ill before diagnosis, the more complicated the course of the illness appears to be.

Recovery rates for CFS are unclear. Improvement rates varied from 8% to 63% with a median of 40% of clients improving during follow-up. However, full recovery from CFS may be rare, with an average of only 5% to 10% sustaining total remission.³⁸

HYPERSENSITIVITY DISORDERS

An exaggerated or inappropriate immune response may lead to various hypersensitivity disorders. Such disorders are classified as types I, II, III, or IV, although some overlap exists (Table 7-4).

Overreaction to a substance, or hypersensitivity, is often referred to as an *allergic response* and although the term *allergy* is widely used, the term *hypersensitivity* is more appropriate. Hypersensitivity designates an increased immune response to the presence of an antigen (referred to as an *allergen*) that results in tissue destruction. The damage and suffering come predominantly from the immune response itself, rather than from the substances that provoke it.

The several types of hypersensitivity reactions include immediate, late-phase, and delayed, based on the rapidity of the immune response. *Immediate hypersensitivity reactions* usually occur within minutes of exposure to an allergen. If the skin is affected, blood vessels dilate and fluid accumulates, causing redness and swelling. In the eyes and nose, increased fluid and mucous secretions cause tearing and a runny nose.

Late phase inflammation and symptoms persist for hours to days after the allergens are removed and can cause cumulative damage (e.g., progressive lung disease) if they persist. *Delayed hypersensitivity reaction* occurs after sensitization to certain drugs or chemicals (e.g., penicillin, poison ivy). These reactions often take several days to cause symptoms.

◆ Type I Hypersensitivity (Immediate Hypersensitivity, Allergic Disorders, Anaphylaxis)

Type I hypersensitivity reactions include hay fever, allergic rhinitis, urticaria, extrinsic asthma, and anaphylactic shock. In this type of immediate hypersensitivity response, IgE, instead of IgG, is produced in response to a pathogen (allergen).

The term *atopy* is often used to describe IgE-mediated diseases. People with atopy have a hereditary predisposition to produce IgE antibodies against common environmental allergens and have one or more atopic diseases.

Allergens are a special class of antigens that cause an allergic response. These normally harmless substances are inhaled (e.g., mold spores, animal dander, dust mites, grasses, weeds); eaten (e.g.,

nuts, fruits, shellfish, eggs); or injected (e.g., venom from fire ants, wasps, bees, hornets), or they come in contact with the skin or mucous membranes (e.g., plants, cosmetics, metals, drugs, dyes, latex).

IgE resides on mast cells in connective tissue, especially the upper respiratory tract, GI tract, and dermis. When IgE meets the pathogen again, an immediate response occurs with histamine release, along with other inflammatory mediators (e.g., chemotactic factors, prostaglandins, and leukotrienes) that enhance and prolong the response initiated by histamine (Fig. 7-20).

If this response becomes systemic, widespread release of histamine (rather than just local tissue response) results in systemic vasodilation, bronchospasm, and increased mucous secretion, and edema referred to as *anaphylaxis*.

Classic associated signs and symptoms are wheezing, hypotension, swelling, urticaria, and rhinorrhea (clear, runny nose often accompanied by sneezing) (Fig. 7-21). Anaphylaxis is a life-threatening emergency and requires immediate intervention with injected epinephrine to restore blood pressure, strengthen the heartbeat, and open the airways. Bee stings remain the number one cause of anaphylaxis; other triggers include penicillin, foods, animal dander, children, semen, and latex.

Marked increase in the prevalence of atopic disease has occurred in the United States during the last two decades, indicating the importance of environmental influences. The mechanisms for this action are outlined in greater detail elsewhere.¹³⁰

◆ **Type II Hypersensitivity (Cytotoxic Reactions to Self-Antigens)**

When the body's own tissue is recognized as foreign or nonself, activation of complement occurs with subsequent agglutination (clumping together) and phagocytosis of the identified pathogens. This means the cellular membrane of normal tissues (e.g., red blood cells [RBCs], leukocytes, and platelets) is disrupted and ultimately destroyed. Self-antigen disorders include blood transfusion reactions, hemolytic disease of the newborn, autoimmune hemolytic anemia, and myasthenia gravis (Fig. 7-22).

A second type of hypersensitivity response occurs when a cross-reaction from exogenous pathogens with endogenous body tissues as occurs in rheumatic fever. For example, group A hemolytic streptococci (the exogenous pathogen) are attacked by the immune system but the body also misinterprets the mitral valve (endogenous body tissue) as a foreign microorganism (i.e., as streptococcus) and attacks normal, healthy tissue in the same way it attempts to destroy the true pathogenic microorganisms. Another example of this type of cross-reaction is an exogenous virus causing the immune system to attack the peripheral nervous system as nonself, as occurs in Guillain-Barré acute syndrome.

◆ **Type III Hypersensitivity (Immune Complex Disease)**

Normally, excessive circulating antigen-antibody complexes called *immune complexes* are effectively cleared by the reticuloendothelial system. When circulating immune complexes (antigen-antibody complexes) successfully deposit in tissues around small blood vessels, they activate the complement cascade and cause acute inflammation and local tissue injury (Fig. 7-23).

The subsequent vasculitis most commonly affects the skin, causing urticaria (wheals); joints, causing synovitis, as in rheumatoid arthritis; kidneys, causing nephritis; pleura, causing pleuritis; and pericardium, causing pericarditis.

Systemic lupus erythematosus (SLE) is the classic picture of vasculitis, occurring in various organ systems. The antigen is the individual's own nucleus of cells; antinuclear antibodies (ANAs) are made, which in turn form a complex with the antigen and are deposited in the skin, joints, and kidneys, causing acute immune injury. Other examples of this hypersensitivity reaction occur in association with infections such as hepatitis B and bacterial endocarditis, malignancies, or after drug or serum therapy.

◆ **Type IV Hypersensitivity (Cell-Mediated Immunity)**

Type IV is a delayed hypersensitivity response such as the reaction that occurs in contact dermatitis after sensitization to an allergen (commonly a cosmetic, adhesive, topical medication, or plant toxin such as poison ivy); latex sensitivity; or the response to a tuberculin skin test present 48 to 72 hours after the skin test.

In this type of reaction, the antigen is processed by macrophages and presented to T cells. The sensitized T cells then release lymphokines, which recruit other lymphocytes, monocytes, macrophages, and PMNs (Fig. 7-24). Graft-versus-host disease (GVHD) and transplant rejection are also examples of type IV reactions (see Chapter 21).

AUTOIMMUNE DISEASES

Definition and Overview. Autoimmune diseases fall into a category of conditions in which the cause involves immune mechanisms directed against self-antigens. More specifically, the body fails to distinguish self from nonself, causing the immune system to direct immune responses against normal (self) tissue and become self-destructive.

More than 56 autoimmune diseases have been identified, affecting everything from skin and joints to vital organs. Autoimmune diseases can be viewed as a spectrum of disorders, some of which are systemic and others of which involve a single organ. A portion of the known diseases most likely to be seen in a rehabilitation setting is listed in Table 7-5.

At one end of the continuum are organ-specific diseases, in which localized tissue damage occurs, resulting from the presence of specific autoantibodies. An example is Hashimoto's disease of the thyroid, characterized by a specific lesion in the thyroid gland with production of antibodies with absolute specificity for certain thyroid constituents.

In the middle of the continuum are disorders in which the lesion tends to be localized in one organ, but the antibodies are not organ specific. An example is primary biliary cirrhosis, in which inflammatory cell infiltration of the small bile ductule occurs, but the serum antibodies are not specific to liver cells.

At the other end of the spectrum are non-organ-specific diseases, in which lesions and antibodies are widespread throughout the body and not limited to one target organ. SLE is an example of this type of autoimmune disease. Identification of ANAs that attack the nucleic acids (DNA and RNA) and other components of the body's own tissues established SLE as an autoimmune disease.

In this book, with the few exceptions included in this chapter (e.g., fibromyalgia, CFS, SLE), autoimmune disorders are discussed individually in the most appropriate chapter. For example, Reiter's syndrome, rheumatoid arthritis, and Sjögren's syndrome are discussed in Chapter 27. Polymyositis, dermatomyositis, and progressive systemic sclerosis are discussed in Chapter 10. Giant cell arteritis is discussed in Chapter 12, sarcoidosis in Chapter 15, and so on. More information is available on autoimmune-related diseases.⁶

Etiologic and Risk Factors. Although the autoimmune disorders are regarded as acquired diseases, their causes often cannot be determined. Autoimmunity is believed to result from a combination of factors, including genetic; hormonal (women are affected more often than men by autoimmune diseases); and environmental influences (e.g., exposure to chemicals, other toxins, or sunlight and drugs that may destroy suppressor T cells).

Although no single gene has been identified as responsible for autoimmune diseases, clusters of genes seem to increase susceptibility. In most autoimmune disorders, a known or suspected genetic susceptibility is evident, and certain HLA types show increased risk, such as ankylosing spondylitis with HLA-B27 (see Table 40-17).**Au: check Table number**

The influence of hormonal factors is confusing since some autoimmune diseases occur among women in their 20s and 30s when estrogen is high, and others develop after menopause or before puberty when estrogen levels are low. During pregnancy, many women with rheumatoid arthritis or multiple sclerosis (MS) experience complete remission, whereas pregnant women with SLE often experience exacerbations.

Other factors implicated in the development of immunologic abnormalities resulting in autoimmune disorders include viruses, stress, cross-reactive antibodies, and various autoimmune diseases occurring in women who have had silicone gel breast implants. This organ-specific autoimmune disease has been associated with musculoskeletal problems.

Pathogenesis. Autoimmune disorders involve disruption of the immunoregulatory mechanism, causing normal cell-mediated and humoral immune responses to turn self-destructive, resulting in tissue damage.

The exact pathologic mechanisms for this process remain unknown. The importance of the innate immune system in determining whether T cells become activated and functional in autoimmune disorders has been shown.¹⁶⁸ Researchers suspect that more than one part of the immune system must be involved for autoimmune disease to develop.

Some autoimmune diseases affect a single organ (e.g., pancreas in type 1 diabetes), whereas others affect a large system or more than one system (e.g., MS). In some cases the autoimmune process overstimulates organ function, as in Graves' disease, in which excess thyroid hormone is produced.

Gene-mapping studies have demonstrated that allergy and autoimmunity must involve not only the recognition of antigen by T cells, but also the very important immunoregulatory effects of cytokines, inhibitory receptors, and survival factors. Linkage analysis of the human genome has revealed candidate loci for susceptibility to MS, type 1 diabetes, SLE, and Crohn's disease. Continued genetic analysis is ongoing to identify the specific genetic link in hopes of finding a more specific treatment.¹²³

Although antibodies and T-cell receptors can accurately distinguish between closely related antigens, they sometimes cross-react with apparently unrelated antigens, either because the two

antigens happen to share an identical epitope (see Fig. 7-2) or because two different epitopes have similar shapes and charges. Such cross-reactions may be the underlying pathogenesis of some autoimmune diseases.⁶²

Many autoimmune diseases are associated with characteristic autoantibodies. In other words, the body begins to manufacture antibodies directed against the body's own cellular components or specific organs. These antibodies are known as *autoantibodies*, in this case, producing autoimmune diseases.

For example, SLE is associated with anti-DNA and anti-splicesosomal (Sm) antigen; Sjögren's syndrome is associated with antiribonucleoproteins (SS-A and SS-B); progressive systemic sclerosis is associated with anticentromere and anti-Scl-70 (DNA topoisomerase); psoriasis and psoriatic arthritis are associated with HLA-B13; and mixed connective tissue disease is associated with antiribonucleoprotein without anti-DNA.

Antibodies specific to hormone receptors on the surface of cells have been found and determined to be partially responsible for some conditions. Examples include myasthenia gravis, in which antiacetylcholine receptor antibodies are involved; Graves' disease, in which antibodies against components of thyroid cell membranes, including the receptors for thyroid-stimulating hormone (TSH), are responsible; and certain cases of insulin-resistant diabetes mellitus, in which the antibodies affect insulin receptors on cells.

Other diseases involving autoimmune mechanisms include rheumatic fever, rheumatoid arthritis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and postviral encephalomyelitis.

Clinical Manifestations. Autoimmune disorders share certain clinical features and differentiation among them is often difficult because of this. Common findings include synovitis, pleuritis, myocarditis, endocarditis, pericarditis, peritonitis, vasculitis, myositis, skin rash, alterations of connective tissues, and nephritis. Constitutional symptoms such as fatigue, malaise, myalgias, and arthralgias are also common.

Medical Management

Diagnosis. Diagnosis can be difficult because autoimmune diseases are poorly understood, mimic one another, and often consist of vague symptoms like lethargy or migratory joint pain. Laboratory tests may reveal thrombocytopenia, leukopenia, immunoglobulin excesses or deficiencies, ANAs, rheumatoid factor, cryoglobulins, false-positive serologic tests, elevated muscle enzymes, and alterations in serum complement. Coombs' test will be positive when hemolytic anemia is present.

Some of the laboratory alterations that occur in autoimmune diseases (e.g., false-positive serologic tests, rheumatoid factor) occur in asymptomatic people. These changes may also be demonstrated in certain asymptomatic relatives of people with connective tissue diseases, in older individuals, those taking certain medications, and people with chronic infectious diseases.

Treatment. Treatment of autoimmune diseases varies with the specific disease. Treatment must maintain a delicate balance between adequate suppression of the autoimmune reaction to avoid continued damage to the body tissues, and maintenance of sufficient functioning of the immune mechanism to protect the person against foreign invaders. In general, autoimmune diseases are

treated by the administration of corticosteroids to produce an antiinflammatory effect and salicylates to provide symptomatic relief.

The wealth of new information gleaned from research in the last decade has been used to improve immunization strategies and hopefully will lead to new approaches to the reinduction of immune tolerance. The development of an effective vaccine is under close scrutiny,¹²³ as is the use of intense immunosuppression (immunoablation), followed by stem cell transplantation for the treatment of autoimmune diseases.

Since autoimmune disease is the result of genetic dysregulation, gene therapy may become a viable alternative in the future. Scientists have been involved in developing new drugs aimed at the mechanism of autoimmunity rather than treating its effects. Based on new information about the function of *Fc* receptors, which bind antibodies that are instructing the immune system in the destructive inflammation characteristic of autoimmune diseases, scientists are looking for blocking compounds to prevent this interaction.

◆ **Systemic Lupus Erythematosus**

Definition and Overview. Lupus erythematosus, sometimes referred to as *lupus*, is a chronic inflammatory autoimmune disorder that appears in several forms, including *discoid lupus erythematosus (DLE)*, which affects only the skin (usually face, neck, scalp) (see Chapter 10), and *systemic lupus erythematosus (SLE)*, which can affect any organ or system of the body.

The clinical picture of SLE presents on a continuum with different combinations of organ system involvement. The most common of these presentations are latent lupus, drug-induced lupus, antiphospholipid antibody syndrome, and late-stage lupus. *Latent lupus* describes a constellation of features suggestive of SLE but does not qualify as classic SLE (Box 7-7). Many people with latent lupus persist with their clinical presentation of signs and symptoms over many years without ever developing classic SLE.

Drug-induced lupus may be diagnosed in people without prior history suggestive of SLE in whom the clinical and serologic manifestations of SLE develop while the person is taking a drug (most often hydralazine used to treat hypertension or procainamide used to treat arrhythmia). The symptoms cease when the drug is stopped, with gradual resolution of serologic abnormalities.

Antiphospholipid antibody syndrome describes the association between arterial and venous thrombosis, recurrent fetal loss, and immune thrombocytopenia with a variety of antibodies directed against cellular phospholipid (lipids in cell membranes containing phosphorus) components. This syndrome may be part of the clinical manifestations seen in SLE, or it may occur as a primary form without other clinical features of lupus.

Late-state lupus is defined as chronic disease duration of greater than 5 years. In such cases, morbidity and mortality are affected by long-term complications of SLE that result either from the disease itself or as a consequence of its therapy. These late complications may include end-stage renal disease, atherosclerosis, pulmonary emboli, and avascular necrosis. In late-stage lupus, when no evidence of active disease exists and the client is on low-dose or no corticosteroids, cognitive disabilities are a common manifestation.

Incidence. SLE is primarily a disease of young women; it is rarely found in older people. It usually develops in young women of childbearing years, but many men and children also develop lupus. Lupus is three times more common in African American women than in

Caucasian women and is also more common in women of Hispanic, Asian, and Native American descent.

SLE also appears in the first-degree relatives of individuals with lupus more often than it does in the general population, which indicates a strong hereditary component. However, most cases of SLE occur sporadically, indicating that both genetic and environmental factors play a role in the development of the disease.

Etiologic and Risk Factors. The cause of SLE remains unknown, but evidence points to interrelated immunologic, environmental, hormonal, and genetic factors. Whether SLE represents a single pathologic entity with variable expression or a group of related conditions remains unknown. Immune dysregulation in the form of autoimmunity is thought to be the prime causative mechanism. SLE shows a strong familial link with a much higher frequency among first-degree relatives. Evidence for genetic susceptibility is present and linkage studies in conjunction with genome scans may delineate this more specifically in the future.

Genetically determined immune abnormalities may be triggered by both exogenous and endogenous factors. Although the predisposition to disease is hereditary, it is likely to involve different sets of genes in different individuals. As the human genome becomes more extensively mapped, a susceptibility gene may be found, although it remains possible that the differences in disease course among ethnic groups relates solely to their environment and other social factors.

Other factors predisposing to SLE may include physical or mental stress, which can provoke neuroendocrine changes affecting immune cell function; streptococcal or viral infections; exposure to sunlight or ultraviolet light, which can cause inflammation and tissue damage; immunization; pregnancy; and abnormal estrogen metabolism.

Whether pregnancy induces lupus flareups has not been established; existing data suggest both that it does and does not. More studies are needed to further determine the effects of pregnancy on this condition.

A higher incidence of SLE exacerbation occurs among women taking even low-dose estrogen contraceptives. Since an increased risk of thrombosis is possible in young women with SLE, estrogen-containing contraceptives are avoided or used at the lowest effective dose.

No evidence exists that postmenopausal estrogen replacement therapy is associated with SLE flareups and since women in this age range are at increased risk for coronary artery disease and osteoporosis, estrogen replacement therapy can be taken. For all women with SLE who have been treated with cyclophosphamide, an increased risk of gynecologic malignancy is evident.

The role of EBV as a possible risk factor for SLE remains under investigation. SLE may also be triggered or aggravated by treatment with certain drugs (e.g., hydralazine, anticonvulsants, penicillins, sulfa drugs, and oral contraceptives), which could modify both cellular responsiveness and immunogenicity of self-antigens.

Pathogenesis. The central immunologic disturbance in SLE is autoantibody production. The body produces antibodies (e.g., ANAs) against its own cells. Deposition of the formed antigen-antibody complexes at various tissue sites can suppress the body's normal immunity and damage tissues.

In fact, one significant feature of SLE is the ability to produce antibodies against many different tissue components such as RBCs, neutrophils, platelets, lymphocytes, or almost any organ or

tissue in the body. This wide range of antigenic targets has resulted in SLE being classified as a disease of generalized autoimmunity. Given the clinical diversity of SLE, the disease may be mediated by more than one autoantibody system and several immunopathogenic mechanisms.

Specific pathologic findings are organ-dependent; for example, repeat biopsies of the kidney show inflammation, cellular proliferation, basement membrane abnormalities, and immune complex deposition comprised of IgM, IgG, and IgA.

Skin lesions demonstrate inflammation and degeneration at the dermal-epidermal junction with the basal layer being the primary site of injury. Other organ systems affected by SLE are usually studied only at autopsy. Although these tissues may show nonspecific inflammation or vessel abnormalities, pathologic findings are sometimes minimal, suggesting a mechanism other than inflammation as the cause of organ damage or dysfunction.

Clinical Manifestations. Generally, SLE is more severe than discoid lupus, and no two people with systemic lupus will have identical symptoms. For some people, only the skin and joints will be involved. For others, joints, lungs, kidneys, blood, or other organs, and/or tissues may be affected.

Musculoskeletal. Arthralgias and arthritis constitute the most common presenting manifestations of SLE, but the onset of SLE may be acute or insidious and may produce no characteristic clinical pattern. Other early symptoms may include fever, weight loss, malaise, and fatigue.

Acute arthritis can involve any joint but typically affects the small joints of the hands, wrists, and knees. It may be migratory or chronic; most cases are symmetrical, but asymmetrical polyarthritis is not uncommon.

Unlike rheumatoid arthritis, the arthritis of SLE is not usually erosive or destructive of bone, and symptoms are not usually severe enough to cause joint deformities, but pain can cause temporary functional impairment. When deformities do occur, ulnar deviation, swan-neck deformity, or fixed subluxations of the fingers often occur as well. Tenosynovitis and tendon ruptures may occur.

Cutaneous and Membranous Lesions. The skin rash occurs most commonly in areas exposed to sunlight (ultraviolet rays) and may be exacerbated by the use of cosmetic products containing alpha hydroxy acids. The classic butterfly rash over the nose and cheeks is common (Fig. 7-25; see also Fig. 10-22).

Discoid lesions associated with DLE are raised, red, scaling plaques with follicular plugging and central atrophy (see Fig. 10-20). This raised edging and sunken center gives them a coin-like appearance (see further discussion, Chapter 10).

Vasculitis (inflammation of cutaneous blood vessels) involving small- and medium-size vessels may cause other skin lesions, including infarctive lesions of the digits (Fig. 7-26), splinter hemorrhages, necrotic leg ulcers, or digital gangrene. Raynaud's phenomenon occurs in about 20% of people.

Diffuse or patchy alopecia (hair loss) may be temporary with hair regrowth once the disease is under control. However, permanent hair loss can occur from the extensive scarring of discoid lesions. Painless ulcers of the mucous membranes are common involving the mouth, vagina, and nasal septum.

Cardiopulmonary System. Signs of cardiopulmonary abnormalities may develop such as pleuritis, pericarditis, and dyspnea. Myocarditis, endocarditis, tachycardia, and pneumonitis (acute or chronic) may also occur. Pulmonary hypertension and congestive heart failure are less common and usually secondary to a combination of factors. Anyone with SLE with the antiphospholipid antibody syndrome is at a high risk of thrombosis. (See the section on Collagen-Vascular Disease in Chapter 12.)

Central Nervous System. A significant number of people with SLE will have CNS involvement at some point in their illness, sometimes referred to as *neuropsychiatric manifestations*. Clinical manifestations may be related to specific autoantibodies that react with nervous system antigens and/ or cytokine-mediated brain inflammation and include headaches, irritability, and depression (most commonly).

Emotional instability, psychosis, seizures, cerebrovascular accidents, cranial neuropathy, peripheral neuropathy, and organic brain syndrome can also occur. Return to the previous level of intellectual function may follow remission of the neuropsychiatric flare, or permanent cognitive impairment may occur.

The pattern of cognitive dysfunction is diverse, intensity can vary within the same person, and can be affected by mood.⁶³ The person may have difficulties with verbal memory, attention, language skills (verbal fluency, productivity), and psychomotor speed. Progressive cognitive impairment, sometimes subtle and sometimes obvious, may develop even in the absence of clinically diagnosed episodes of neuropsychiatric disease.⁶⁴ People with SLE may or may not have other signs of lupus when they experience neurologic symptoms.

Renal System. Pathologic changes may also occur in the kidneys where the glomerulus is the usual site of destruction; other renal effects may include hematuria and proteinuria, progressing to kidney failure. Antiphospholipid antibodies are a significant cause of morbidity and mortality in cases of renal involvement as a result of thrombosis and the development of thrombotic microangiopathy.¹²¹

Other Systems. Anemia from decreased erythrocytes is a common finding with associated amenorrhea (cessation of menstrual flow) among women. Sometimes the spleen and cervical, axillary, and inguinal nodes are enlarged; hepatitis may also develop. Nausea, vomiting, diarrhea, and abdominal pain may occur with GI involvement. All symptoms mentioned in this section can occur at the onset or at any time during the course of lupus. Nearly all people with SLE experience fluctuations in disease activity with exacerbations and remissions.

Medical Management

Prevention. There is no known way to prevent SLE but preventive measures can reduce the risk of flareups. For photosensitive people, avoidance of (excessive) sun exposure and/or the regular application of sunscreen usually prevents rashes. Regular exercise helps prevent muscle weakness and fatigue. Immunization protects against specific infections.

Support groups, counseling, and talking to family members, friends, and health care professionals can help alleviate the effects of stress. Lifestyle choices and personal behavior are very important for people with SLE. These include smoking, excessive consumption of alcohol, too much or too little of prescribed medication, or postponing regular medical checkups.¹⁴⁴

Diagnosis. Diagnosis of SLE is difficult because SLE often mimics other diseases and the symptoms are often vague, varying greatly from individual to individual. The American Rheumatism Association has issued a list of criteria for classifying SLE to be used primarily for consistency in epidemiologic surveys. Usually, four or more of these signs are present at some time during the course of the disease (see Box 7-7).

In addition to the routine history and physical examination, laboratory findings are an important part of the diagnosis of SLE and subsequent monitoring of clinical disease activity. Specific test procedures and their significance are available.¹⁴³ ANA is present in all cases of SLE, but its presence does not make a definitive diagnosis. However, if ANA is absent, SLE is probably not present. Lupus anticoagulant testing and immunologic anti-phospholipid (aPL) establish the presence of antiphospholipid syndrome.

Magnetic resonance imaging (MRI) scans of the head are usually ordered for all people experiencing new episodes of focal neurologic deficits, seizures, altered consciousness, or psychosis. Neuropsychologic assessment may be helpful for identifying subtle, clinically latent sequelae of CNS events such as stroke and in monitoring the response to drug treatment.⁶³

Treatment. The objectives of medical intervention are to reverse the autoimmune and inflammatory processes and prevent exacerbations and complications. At the present time, pharmacologic interventions are the primary means of accomplishing these goals.

Mild symptoms can be managed with NSAIDs to relieve muscle and joint pain while reducing tissue inflammation. Corticosteroid-sparing agents (e.g., methotrexate) used earlier preserve bone and offer protection from premature cardiovascular disease. Anticoagulants for individuals who have antiphospholipid antibody syndrome and coagulopathies will ensure a more favorable outcome.

Antimalarial agents (e.g., chloroquine [Aralen], hydroxychloroquine [Plaquenil]) are useful against the dermatologic, arthritic, and renal symptoms of this disease. Immunomodulating drugs (e.g., azathioprine [Imuran], cyclophosphamide [Cytoxan]) are immunosuppressive drugs used to suppress inflammation and subsequently, the immune system. These are used only with active disease, especially with severe kidney involvement. Corticosteroids and cytotoxic drugs are given in more severe disease that has not responded to these other types of drug therapy.

Treatment in the future may be more specific as knowledge of genes that participate in the predisposition, pathogenesis, pharmacogenetics of, and protection against this disease come to light. Better understanding of the role of sex hormones has allowed trials of weak androgens or prolactin inhibitors.

New immunomodulators or immunosuppressants, immune ablation with subsequent stem cell transplantation, and more precise immunoregulation (e.g., tolerance-induction strategies, intervention at the level of T cell co-stimulation, targeting cytokines, complement and FcγR) may become standard intervention tools.^{23, 134}

Prognosis. The prognosis improves with early detection and intervention that prevents organ damage and improves life expectancy. The overall reduction in the use of large doses of corticosteroids over the past two decades has significantly reduced morbidity and mortality.

People with SLE have an increased prevalence of valvular and atherosclerotic heart disease, apparently because of factors related to the disease itself and to drug therapy necessary in severe cases. Symptomatic large vessel occlusive disease in SLE, occurring several years after the

diagnosis of the disease, is associated with a relatively poor short-term outcome. There is an increased risk of certain cancers in systemic lupus erythematosus; the risk appears to be most heightened for lymphoma.¹⁹

Prognosis is less favorable for those who develop cardiovascular, renal, or neurologic complications, or severe bacterial infections. High-stress, poor social support, and psychological distress are modifiable factors associated with health outcomes for people with SLE.^{67, 261}

◆ **Fibromyalgia**

Definition and Overview. Fibromyalgia or fibromyalgia syndrome (FMS), formerly mislabeled or misdiagnosed as fibrocystitis, fibromyositis, myofascial pain, CFS, or SLE, is a chronic muscle pain syndrome. It is considered a syndrome and not a disease and has now been defined by the American College of Rheumatology as pain that is widespread in at least 11 of 18 tender points (see Clinical Manifestations and Diagnosis in this section).

FMS currently falls under the auspices of rheumatology, having originally been determined to have no known organic basis. However, with the recent advances in understanding of FMS with documented objective biochemical, endocrine, and physiologic abnormalities, it may be best characterized as a biologic (organic) disorder associated with neurohormonal dysfunction of the ANS.

It is commonly associated with many other conditions (e.g., hypothyroidism, rheumatoid arthritis, connective tissue disease, systemic lupus erythematosus, chronic fatigue syndrome); the link between these disorders is under investigation.

Fibromyalgia has been differentiated from myofascial pain (see the section on Myofascial Pain Syndrome in Chapter 27) in that fibromyalgia is considered a systemic problem with widespread multiple tender points as one of the key symptoms.

Myofascial pain is a localized condition specific to a muscle and may involve as few as one or as many as several areas with characteristic trigger points that are painful and refer pain to other areas when pressure is applied. The person with FMS may have both tender points and trigger points requiring specific treatment interventions for each.

The person with myofascial pain syndrome does not exhibit other associated constitutional or systemic signs or symptoms unless palpation elicits a painful enough response to elicit an ANS response with nausea and/or vomiting, increased blood pressure, and increased pulse.

It has been proposed that fibromyalgia and CFS are two names for the same syndrome with CFS being an early form of FMS, but at present, CFS is thought to differ by the greater degree of fatigue. People with fibromyalgia tend to experience more pain.

In contrast to CFS, fibromyalgia is associated with a variety of initiating or perpetuating factors such as psychologically distressing events, primary sleep disorders, inflammatory rheumatic arthritis, and acute febrile illness.

Fibromyalgia and CFS have similar disordered sleep physiology and evidence suggests a reciprocal relationship of the immune and sleep-wake systems. Interference with either system has effects on the other and will be accompanied by the symptoms of CFS.¹⁷³ A significant number of people with FMS meet the criteria for CFS and vice versa.

Incidence. Fibromyalgia occurs in over 6 million Americans. It has now surpassed rheumatoid arthritis as the most common musculoskeletal disorder in the United States. Women are affected more often than men (90% are women), with symptoms appearing between the ages of 20 and 55 years, although it has been diagnosed in children as young as 6 and adults as old as 85 years.

Risk Factors. Risk factors or triggering events for the onset of fibromyalgia may include prolonged anxiety and emotional stress, trauma (e.g., motor vehicle accident, work injury, surgery), rapid steroid withdrawal, hypothyroidism, and viral and nonviral infections.

Fibromyalgia may also develop with no obvious precipitating events or illnesses. It is more prevalent in minimally to moderately physically fit persons and is not usually found in highly trained athletes; a strong correlation exists between fibromyalgia and anxiety or depression (it remains unclear whether these factors are contributory or a result of this condition).

Women with extracapsular silicone (silicone gel outside of the fibrous scar that forms around breast implants) as a result of rupture are more likely to report having fibromyalgia, but more data is needed to confirm this association.^{24, 25}

Etiologic Factors. Research is now ongoing to determine the cause of fibromyalgia; most likely the initiation of this condition is multifactorial (Fig. 7-27). Debate continues over whether fibromyalgia is even an organic disease and if so, whether it is caused by abnormal biochemical, metabolic, or immunologic pathology.

Possible etiologic theories include diet; viral origin; sleep disorder; occupational, seasonal, or environmental influences; psychologic distress; adverse childhood experiences, including sexual abuse;^{74, 163} and a familial or hereditary link.

Pathogenesis. Both central and peripheral mechanisms may operate in the pathophysiology of impaired muscle function and pain in fibromyalgia. A disturbance in four regulatory systems of the body has been identified in people with FMS: (1) the hypothalamic-pituitary-adrenal axis (HPA); (2) the ANS; (3) the reproductive hormone axis (RHA); and (4) the immune system. Although these systems function independently, each system influences the other, and each helps regulate cellular function. Disruption of one system can influence the other systems, disrupting cellular function.¹¹²

Hypothalamic-Pituitary-Adrenal Axis. The HPA axis is considered the stress system of the body, affecting the body's ability to cope with stress, both psychoemotional and biologic, including dysfunction in metabolic and physiologic processes controlling blood pressure, blood sugar levels, infection control, and so on. The hypothalamus, pituitary, and adrenal glands produce chemical messengers that modulate pain, sleep, mood, sex drive, appetite, energy, and circulation. Many of the HPA axis hormones are found to be at abnormal levels in FMS (see Fig. 7-27).¹¹²

Substance P, a neurotransmitter for pain, may play a role in the transmission of nociceptive information. The inhibitory system acts to lessen or filter out some of the painful signals transmitted to the brain. These pain stimuli are usually transmitted by substance P.

Increased activity of substance P may explain an abnormally decreased pain threshold in fibromyalgia.²⁷¹ Elevated levels of substance P have been found in the cerebrospinal fluid of fibromyalgia clients, resulting in an exaggerated response to normal stimuli and an amplified effect on pain. People with FMS are not just sensitive to pain, they also find loud noises, odors, and bright lights aversive.

The role of other pain-inhibiting neurotransmitters, such as serotonin, gamma-aminobutyric acid (GABA), enkephalins, epinephrine, and norepinephrine has been studied.⁹⁴ Although substance P is elevated, decreased levels of all of these neurotransmitters in the cerebrospinal fluid have been observed.

Serotonin, a CNS neurotransmitter that is made from tryptophan (an essential amino acid obtained from diet), is necessary for restorative sleep and appears to play a role in pain control, immune system function, vascular constriction and dilation, and even emotions that may contribute to such feelings as depression or anxiety. Earlier studies found the concentration of serotonin end products (metabolites) to be lower than normal in clients with fibromyalgia, supporting a hypothesis of aberrant pain perception resulting from a deficiency of serotonin.^{217, 218, 219}

However, clinical trials showed that conventional FMS interventions such as tricyclic antidepressants used to increase the amount of serotonin at synapses were no more effective than placebos in improving or alleviating FMS symptoms.³² This suggests that it is unlikely FMS results primarily from a serotonin deficiency but perhaps another mechanism that causes serotonin deficiency and the other features of this condition.

Available new evidence suggests that impaired metabolism caused by inadequate thyroid hormone regulation at the cellular level may be the underlying pathogenesis. The inadequate regulation of cell function may result from a thyroid hormone deficiency or from cellular resistance to normal levels of thyroid hormone.^{157, 159} Whether this inadequate thyroid hormone regulation is triggered by genetic mutations²⁰⁸ and/or can be attributed to environmental contaminants¹⁶⁷ remains unproved.

Abnormalities in the function of the HPA-kidney-bladder axis may account for the irritable bladder syndrome and the female urethral syndrome characterized by urinary frequency and urgency. Low blood pressure and blood volume (ANS dysfunction) may also contribute to this condition. Studies in this area are very limited at this time.

Autonomic Nervous System. The activity of the skeletal muscles, heart, stomach, intestines, blood vessels, and sweat glands during daily stress tends to be excessive in fibromyalgia. These organs overactivate, resulting in the heart beating faster, the stomach secreting excessive digestive juices and contracting erratically, the smooth muscles of the intestines and bowel contracting abnormally, breathing becoming rapid and shallow, and blood vessels constricting, which decreases blood flow to body parts. These and other ANS responses may occur in response to a relatively mild life stressor and linger even after cognitive memory of the event is gone.

People who do not have fibromyalgia experience these changes, but the autonomic responses occur in smaller amplitude and for a shorter period before returning to normal levels. In fibromyalgia, the nervous system's ability to modulate and return to normal is fragile and lacks the subtle ability to respond quickly; responses are more exaggerated and the return to normal takes more time.^{112, 271}

The enteric system (autonomic nervous control of the digestive system) is often significantly disrupted in fibromyalgia. Digestion is often compromised, and the absorption of nutrients into the bloodstream where it can be used by the body for cell function is often inadequate for healthy daily function. The enteric system's interaction with other systems (e.g., brain, immune system) links effects of nutritional deficits to other functions as well.¹¹²

Sleep disturbances may contribute to fibromyalgia symptoms; researchers are investigating alterations of the neuroimmunoendocrine systems that accompany disordered sleep physiology, resulting in the nonrestorative sleep, pain, fatigue, and cognitive and mood symptoms that people with fibromyalgia (and CFS) experience.

People affected do not enter restorative sleep (phase IV sleep), or rapid eye movement (REM) sleep. Deficiency of non-REM sleep also contributes to sleep disturbance by reducing the amount of time the muscles enter a state of resting muscle tone. Eighty percent of the body's growth hormone is secreted by the pituitary gland (under hypothalamic control) during deep sleep, and it is crucial for normal muscle metabolism and tissue repair. Substantial nighttime decreases in growth hormone have been reported in FMS.¹⁴⁵

These types of sleep disturbances are not unique to fibromyalgia but have been observed in many people with rheumatoid arthritis, osteoarthritis, and other painful rheumatic diseases.

The Reproductive Hormone Axis. Reproductive hormones help regulate the HPA axis in a bidirectional feedback loop (see Fig. 11-2). **Au: check figure number** During chronic stress, a decrease in function in both the HPA and the RHA with diminished reproductive capability, fatigue, sleep disruption, and illness or exacerbation of FMS. Female reproductive hormones, especially estrogen and progesterone, exert influence over menstrual cycle, bowel and bladder function, blood pressure, sleep cycles, endorphins, serotonin levels, thyroid function, digestive activity, sex drive, sense of well-being, and much more.

The onset or exacerbations of fibromyalgia often occur around or during the time of sex hormone-related events (e.g., menses, pregnancy, childbirth, peri-menopause, menopause) but few studies exist to study the relationship between these cycles and fibromyalgia. The possibility of inadequate thyroid hormone regulation of the hypothalamic-pituitary-gonadal axis for men and women has been suggested.¹⁵⁷

Immune System. Finally, a model for pathologic pain syndromes such as FMS and CFS has been formulated based on pain facilitatory effects produced by the immune system. Immune cells, activated in response to infection, inflammation, or trauma release proinflammatory cytokines that signal the CNS to release glia within the brain and spinal cord. Pain has been classically viewed as being mediated solely by neurons, but the discovery that spinal cord glia (microglial and astrocytes) amplify pain has changed this view.

When glial cells become activated by sensory signals arriving from the periphery, they can release a variety of substances known to be involved in chronic pain (e.g., nerve growth factor, excitatory amino acids, nitric oxide), and they can also control the release of neurotransmitters (e.g., substance P).

Once activated, such as when viruses and bacteria enter the CNS, glial cells cause prolonged release of proinflammatory cytokines (e.g., TNF, IL-1 and -6), creating an exaggerated pain state. Glia may be the key driving force for the pain created by tissue inflammation and nerve injury because they can increase the release of pain transmitters and cytokines from the neurons in the surrounding area and they are connected to large networks that allow activation of glia at distant sites.

This pain model emphasizes again the need for anyone with FMS to minimize pain-generating aggravants such as infectious agents, trauma, and inflammation or other triggers (see Fig. 7-27).

Clinical Manifestations. Fibromyalgia is characterized by muscle pain as the major symptom, often described as aching or burning, a “migraine headache of the muscles.” Diffuse pain or tender points is present on both sides of the body in many muscle groups, including the neck, back, arms, legs, jaw, feet, and hands (Fig. 7-28).

Sleep disturbances result in fatigue and exhaustion, even after a night’s sleep. Men with fibromyalgia typically have fewer symptoms and milder tender points (less “hurt-all-over” reports), less fatigue, and fewer incidences of irritable bowel syndrome compared with women who have FMS. ²⁷².

Other symptoms or associated problems occur with a high frequency (Table 7-6) sometimes more incapacitating than the pain and tender points. Symptoms are often exacerbated by stress; overloading physical activity, including overstretching; damp or chilly weather; heat exposure or humidity; sudden change in barometric pressure; trauma; or another illness.

Those people with fibromyalgia who are aerobically fit manifest fewer symptoms than those who remain physically deconditioned and aerobically unfit. Biofeedback specialists have shown that blood circulation to the affected areas is often significantly decreased while at rest and a noticeable decrease in circulation occurs with changes in barometric pressure.

During exercise, when circulation should normally increase to muscles and brain, in fibromyalgia, just the opposite happens, and circulation is decreased significantly. ¹¹² Real-time ultrasonography has confirmed the lower magnitude of muscle vascularity following dynamic and during static exercise. The immediate flow response to muscular activity was lower in magnitude and of a shorter duration in people with fibromyalgia compared to healthy controls. ⁷²

The diaphragm is significantly affected in fibromyalgia to the point that it ceases to function as the major breathing muscle and accessory muscles of the neck and upper chest take over. This overwork results in tender points or tightness of the neck and chest muscles.

In general, the level of muscular activity in fibromyalgia is high, even when the body is sitting or reclining. During daily activities such as cleaning, cooking, typing, and even socializing, the muscles used for these activities are at a higher level of activity than the muscles of a normal person doing the same tasks.

When the activity is over and the person with fibromyalgia is resting, those same muscles continue to repeat the activity over and over at a lower intensity so that no outward movement is apparent. This factor combined with increased central pain processing may lower tender point thresholds. ¹⁷

Medical Management

Diagnosis. No definitive test is currently available to determine the presence of fibromyalgia, and usually the organs involved are not the cause but merely the messenger of a problem originating elsewhere in the body.

According to the American College of Rheumatology (ACR) two criteria must be met before a medical diagnosis of FMS can be made: (1) widespread (four-quadrants) pain both above and below the waist present for at least 3 months and (2) subjective report of pain when pressure is applied to 11 of the 18 common FMS tender points on the body (see Fig. 7-28).

Subjective assessment of tender points can be elicited by the use of an instrument called a *dolorimeter*, which distributes pressure equally over a discrete point. With a dolorimeter, the pressure required to produce pain in a given area can be recorded.

Controversy also exists regarding current use of the ACR's criteria for tender point count in clinical diagnosis of FMS. In fact the original author of the used ACR criteria has suggested that counting the tender points was "perhaps a mistake" and has advised against using it in clinical practice as the only means of diagnosis.²⁶⁶ A proposed survey method that does not require physical examination may be more accurate.¹²⁹

Often, the diagnosis is determined as a process of elimination by ruling out other conditions based on clinical presentation and past medical history (Box 7-8). In addition to the presence of tender points, skin fold tenderness, increased reactive skin hyperemia, and low tissue compliance (in the trapezius and paraspinal regions) provide further diagnostic information.

No special laboratory or radiologic testing is necessary for making a diagnosis of FMS; routine testing for rheumatoid factor or antinuclear antibodies is not recommended. While routine inexpensive tests, including complete blood count (CBC), basic chemistry (blood urea nitrogen, creatinine, hepatic enzymes, serum calcium) and thyroid function, should be undertaken (if not done in the past year), any other test to rule out other conditions, unless clinically indicated (by both symptoms and physical examination), is a waste of time and resources.

A routine CBC test may demonstrate anemia caused by medications or another disease, which may contribute to fatigue, and cytopenia; a base line chemistry tests is useful in monitoring various medication side effects. Because spinal pain in FMS and pain caused by pathologic changes in the spine (e.g., osteoarthritis and osteopenia with vertebral compression fracture) cannot be always distinguished clinically, a spinal X-ray may be necessary for a middle-aged or older adult, especially considering other risk factors for these conditions. It is important not to miss these diagnoses, because management approach is likely to be different from FMS alone. A sleep study should be considered only when history suggests a primary sleep disorder.²⁷³

Treatment.

Despite the chronicity and complexity of FMS, there are pharmacological and nonpharmacological interventions available that have clinical benefit. Helping clients with fibromyalgia must be holistic and multidisciplinary, including education and support; stress management; nutrition and lifestyle training (e.g., coping strategies, applying work simplification and ergonomic principles, and psychotherapy); medications (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, muscle relaxants, analgesics and anticonvulsants); local modalities and techniques for muscle pain (e.g., relaxation techniques, biofeedback, Physiologic Quieting®, or soft tissue techniques); and conditioning and aerobic exercise.

Cognitive behavioral therapy aimed at altering sensory, affective, cognitive, and behavioral aspects of chronic pain (e.g., pain severity, emotional distress, depression, anxiety, pain behavior) have been shown to be effective over a long period, even when the disease process cannot be controlled and symptoms worsen. Based on current evidence, a stepwise program emphasizing education, certain medications, exercise, cognitive therapy, or all 4 should be recommended. ⁹³.

Alternative and complementary intervention (e.g., acupuncture, herbal or vitamin supplements, chiropractic, hypnotherapy, and others) is available and often provides palliative relief from symptoms for periods. Like most interventions (medical or nonconventional), no single intervention is effective all the time, and the person with FMS may cycle through various modalities over time.

Prognosis. Many people with mild symptoms are managed without a specialist and have an expected good long-term outcome, but most people experience persistent symptoms of fibromyalgia for many years or a lifetime. Good therapy must be instituted early in the client's course if there is to be any chance of achieving substantial improvement or a remission.

ISOIMMUNE DISEASE

◆ *Organ and Tissue Transplantation*

With recent advances in technology and immunology, organ and tissue transplantation is becoming commonplace. In fact, transplantation of almost any tissue is feasible, but the clinical use of transplantation to remedy disease is still limited for many organ systems because of the rejection reaction. Transplant rejection, an isoimmune phenomenon, occurs in response to transplantation because the body usually recognizes the donor tissue as nonself and attempts to destroy the tissue shortly after transplantation.

In all cases of graft rejection, the cause is incompatibility of cell surface antigens. The rejection of foreign or transplanted tissue occurs because the recipient's immune system recognizes that the surface HLA proteins of the donor's tissue are different from the recipient's.

For this reason, HLA matching of donor and recipient greatly enhances the probability of graft acceptance. Certain antigens are more important than others for a successful transplant, including ABO and Rh antigens present on RBCs and histocompatibility antigens, most importantly the HLA. As expected, a better chance of graft acceptance is evident with syngeneic or autologous transplants because the cell surface antigens are identical.

For a complete discussion of histocompatibility, graft rejection (acute versus chronic), GVHD, and immunosuppression, see Chapter 21.

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TABLE

7-1

Types of Acquired Immunity

Type of Acquired Immunity* **Method Acquired** **Length of Resistance**

Active

Natural

Artificial

Passive

Natural

Artificial

*Active immunity occurs when a person produces his or her own antibodies to the infecting organism; passive immunity occurs when the antibody is formed in another host and transferred to an individual.

Usually permanent but may be temporary

Usually permanent but may be temporary (occasional exceptions)

Temporary

Temporary

Natural contact and infection with the antigen (environmental exposure)

Inoculation of antigen (vaccination)

Natural contact with antibody transplacentally (mother to fetus) or through colostrum and breast milk

Inoculation of antibody or antitoxin; immune serum globulin

TABLE

7-2

The Immune System and Its Response

Acquired Immunity

Innate Immunity Humoral Cell-mediated

Nonspecific interaction with different antigens; lacks immunologic memory

Exterior defenses: Skin, mucosa, secretions, nasal hair, ear wax

Phagocytes (leukocytes):

Neutrophils (PMNs)

Monocytes/macrophages

Eosinophils

Basophils

Mast cells and platelets (inflammation)

Soluble mediators: Complement and interferons; see Table 6-4

Natural killer (NK) cells or large granular lymphocytes

Specific interaction with different antigens

Mediated by antibody, present as serum globulins

Antibodies are produced by plasma cells (differentiated form of B lymphocytes)

Globulins having antibody activity (immunoglobulins) are produced

Primary and secondary (memory) antibody response

Specific interaction with different antigens

Mediated by T lymphocytes

Production of helper T cells (CD4+) and cytotoxic T cells (CD8+)

Secretion of lymphokines;

Suppressor T cells may be activated

Primary and secondary (memory) T cell response

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FIGURE 7-1 An antigen is recognized on the basis of shape. Epitopes protrude from the surface of an antigen and combine with the appropriate receptor of an antibody, much as a key fits a lock. For small antigens, the binding site on the antibody may be a pocket or cleft but in most cases it more closely resembles an undulating surface.²³² (From Black JM, Matassarin-Jacobs E, editors: *Medical-surgical nursing: clinical management for continuity of care*, ed 5, Philadelphia, WB Saunders, 1997, p 599.)

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FIGURE 7-2 The pathway of lymphocyte maturation. Undifferentiated lymphocyte stem cells are derived from the bone marrow. B cells reach maturity within the bone marrow but T cells must travel to the thymus to complete their development. Activation of either T or B cells by antigens leads to proliferation of immune cells that mediate either cell-mediated immunity or humoral immunity, respectively. (From Black JM, Matassarin-Jacobs E, editor: *Medical-surgical*

nursing: clinical management for continuity of care, ed 5, Philadelphia, 1997, WB Saunders, p 597.)

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Box 7-1

Major Functions of Immunoglobulins*

Immunoglobulins directly attack antigens, destroying or neutralizing them through the processes of agglutination, precipitating the toxins out of solution, neutralizing antigenic substances, and lysing the organism's cell wall.

Immunoglobulins activate the complement system.

Immunoglobulins activate anaphylaxis by releasing histamine in tissue and blood.

Immunoglobulins stimulate antibody-mediated hypersensitivity.

*Globulins with antibody activity are referred to as *immunoglobulins*.

From Thompson JM, McFarland GK, Hirsch JE, Tucker SM: *Mosby's clinical nursing*, ed 3, St Louis, 1993, Mosby.

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FIGURE 7-3 Organs of the immune system referred to as *lymphoid tissues*. The bone marrow and thymus are referred to as primary lymphoid organs since these organs are the central sites of all cells of the immune system and B- and T-cell differentiation, respectively. Immature lymphocytes migrate through the central lymphoid tissues and later reside as mature lymphocytes in the peripheral or secondary lymphoid tissues (e.g., lymph nodes, Peyer's patches, tonsils, spleen, mucosal associated lymphoid tissue or MALT from the mouth to the rectum).

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TABLE

7-3

Factors Affecting Immunity

Factors That Alter the Immune System

Aging

Sex and hormonal influences

Nutrition/malnutrition

Environmental pollution

Exposure to toxic chemicals

Trauma

Burns

Sleep disturbance

Presence of concurrent illnesses and diseases:

- Malignancy
- Diabetes mellitus
- Chronic renal failure
- HIV infection

Medications, immunosuppressive drugs

Hospitalization, surgery, general anesthesia

Splenectomy

Stress, psychospiritual well-being, socioeconomic status

Factors That Increase Exposure to Pathogens

Iatrogenic

- Urinary catheters
- Nasogastric tubes
- Endotracheal tubes
- Chest tubes
- Intracranial pressure monitor
- External fixation devices
- Implanted prostheses

Sexual practices

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Chapter 7 **The Immune System**

Special Implications for the Therapist 7-1

EXERCISE IMMUNOLOGY

Physical therapists employ exercise in treatment of all ages with a variety of clinical problems, thereby influencing immune function. Exercise as a means of preventing illness and attaining a healthy lifestyle and as an intervention tool in immunodeficiency states is becoming a larger part of preventive services. Research in the area of exercise immunology is in its infancy, with many

results based on studies in animals. Keeping abreast of research results is the first step to examining the clinical implications in this area.

Aged adults constitute a growing and important consumer group of therapy services. Since immune function declines with advancing age, it is important that we understand the effects of exercise on immune function. Very few absolute guidelines have been developed; it seems intense or strenuous exercise may be detrimental to the immune system, whereas a lifetime of moderate exercise and physical activity enhances immune function. Further research is needed to clarify or modify this guideline.

It takes 6 to 24 hours for the immune system to recover from the acute effects of severe exercise. Each individual client must be evaluated after exercise to determine the perceived intensity of the exercise or intervention session. For example, in the deconditioned older adult with compromised cardiopulmonary function, reduced oxygen transport, and impaired mobility, ambulating from the bed to the bathroom may be perceived by their body as strenuous exercise.

Although, intense exercise causes suppression of immune parameters in young subjects, data from aged animals ^{125, 127} and humans ¹²⁸ show that intense exercise has no detrimental effect on immune function or rate of infections in older adults. Thus relatively intense exercise programs may be prescribed that could maximize cardiopulmonary and musculoskeletal function without impairing immune function in frail elderly people.

Nevertheless, intense exercise during an infectious episode should be avoided. For anyone, especially competitive athletes, who is wondering whether to exercise in the presence of an acute viral or bacterial infection (e.g., when manifesting constitutional symptoms), a neck check should be conducted.

If the symptoms are located above the neck, such as a stuffy or runny nose, sneezing, or a scratchy throat, exercise should be performed cautiously through the scheduled workout at half speed. If, after 10 minutes, the symptoms are alleviated, the workout can be finished with the usual amount of frequency, intensity, and duration.

If instead the symptoms are worse and the head is pounding or throbbing with every footstep, the exercise program should be stopped and the person should rest. If a fever or symptoms below the neck is evident, such as aching muscles, a hacking cough, diarrhea, or vomiting, exercise should not be initiated.⁷¹ (See the specific exercise guidelines for the person with HIV in this chapter.)

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Special Implications for the Therapist **7-2**

INFECTION CONTROL IN IMMUNODEFICIENCY DISORDERS

Although infection control strategies such as handwashing, standard precautions, and disinfection are important for all people treated in the health care system, they are especially critical for individuals whose immune systems are altered by primary immunodeficiency disorders, secondary immunodeficiency disorders, and HIV infection.

It is important that health care providers stop and think about altered defense mechanisms, infectious agents, reservoirs, modes of transmission, and infection control strategies to prevent infection in this population (Fig. 7-11).

Pulmonary complications are common among the immunocompromised accompanied by poor cough reflexes, an inability to cough effectively, and susceptibility to pulmonary and other opportunistic infections. Additionally, these individuals are often debilitated and easily fatigued. Frequent mobilization and body positioning enhance gas exchange and promote comfort while maintaining strength.⁵⁸

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FIGURE 7-5 Proportion of AIDS Cases by Race/Ethnicity. The highest annual rates remain among blacks, followed by whites, Hispanics, Asian Pacific Islanders and then American Indian/Alaska Natives. Although this illustration does not reflect it, there are a reported 5 to 10 million children infected with HIV-1 (worldwide) and this number is expected to continue to increase in African countries.

Source: HIV/AIDS Surveillance by Race/Ethnicity (2004). Centers for Disease Control and Prevention.

FIGURE 7-4 Factors affecting the immunocompromised person, leading to the selection of the correct infection control strategies to prevent infectious complications. (From Schaffer SD, Garzon LS, Heroux DL et al: *Pocket guide to infection prevention and safe practice*, St Louis, 1996, Mosby, p 222.)

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FIGURE 7-6 Stages of HIV replication cycle. (1) Attachment of the virus to the host cell, (2) Uncoating followed by reverse transcription, (3) Integration of newly synthesized DNA into the host cell DNA, with transcription and translation of the viral genetic message into viral protein; HIV possesses genes that code for proteins with important regulatory functions for the virus such as *tat* (transactivator), *nef* (negative factor), and *rev* (regulator of expression of virion proteins) (4) assembly with release of the virus out of the host cell. (Courtesy Patricia D. Salvato, MD, Houston, Texas, 2000.)

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6-4

Clinical Manifestations of HIV Disease

Musculoskeletal Neurologic/Neuromuscular Cardiopulmonary Integumentary Other
Myalgia/arthritis

Rheumatologic manifestations:

- Inflammatory joint disorders (e.g., Reiter's syndrome, reactive arthritis, psoriatic arthritis)
- Myositis/pyomyositis
- Connective tissue disease

Avascular necrosis (osteonecrosis)

Musculoskeletal pain syndrome/HIV wasting syndrome

Myopathy (disease or drug-induced)

Pelvic pain (e.g., pelvic inflammatory disease [PID])

Extrapulmonary tuberculosis

Constitutional symptoms:

- Flulike symptoms
- Fever, sore throat
- Generalized adenopathy
- Weight loss
- Lethargy, fatigue
- Night sweats, fevers

Opportunistic infections:

- Cytomegalovirus
- Bacterial pneumonia
- Tuberculosis
- Toxoplasmosis
- *Pneumocystis carinii* pneumonia
- Sinusitis
- Vaginal infection

Malignancy (most common forms):

- Non-Hodgkin's lymphoma
- Kaposi's sarcoma
- Cervical cancer

GI disturbance, including wasting syndrome

Lymphedema

Lipodystrophy

Renal (kidney) failure

Hepatic (liver) failure

Oral thrush

Gingivitis

Visual disturbance (CMV)

HIV-related psychiatric disorders

Alopecia (hair loss)

Basal cell carcinoma

Kaposi's sarcoma

Mucocutaneous ulcers

Rash

Urticaria (diffuse skin reaction, wheals)

Dyspnea, especially on exertion

Nonproductive cough

Hypoxia

Symptoms associated with opportunistic infections of the pulmonary system

Pericardial effusion

Cardiomyopathy

Endocarditis

Vasculitis

HIV encephalitis:

- Gait disturbance
- Intention tremor
- Delayed release of reflexes

HIV-associated dementia:

- Behavioral: Apathy, lethargy, social withdrawal, irritability, depression
- Cognitive: Memory impairment, confusion, disorientation
- Motor: Ataxia, leg weakness with gait disturbances, loss of fine motor coordination, incontinence, paraplegia (advanced stage)

Guillain Barré syndrome

Headache, seizures (toxoplasmosis)

HIV myelitis (osteomyelitis)

Radiculopathy

Peripheral neuropathy:

- Pain (burning, tingling, hypersensitivity)

- Sensory loss
- Secondary motor deficits, gait disturbances

Brachial neuropathy

Vacuolar spinal myelopathy

TABLE

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Chapter 7 **The Immune System**

Section II **Clinical Medicine**

Box 7-2

Risk Reduction Behaviors for the Prevention of HIV Transmission

Obtain testing for HIV* if any of the following is true:

- You received blood or blood products before 1985.
- You have (or have had) multiple sex partners.
- You inject drugs and share needles.
- You have sexual intercourse (vaginal, anal, or oral) with someone else who injects drugs and shares needles.
- You have sex without a condom (“rubber”) with someone who has HIV.
- You share used needles for tattooing or body piercing.

Protect yourself during sexual activities as follows:

- Abstinence or a monogamous relationship (sex with only one partner; both partners must be HIV free) is the only known prevention for the transmission of HIV.
- Use latex glove when inserting finger(s) into vagina or rectum.
- Use a new condom each time you have oral, anal, or vaginal sex.
- Latex or polyurethane is best because HIV can pass through lambskin or natural condoms
- Do not use outdated condoms (check expiration date).
- Use the new condom with each sexual act from beginning to end (i.e., put on the condom before genital contact with partner and when the penis is erect; hold the condom firmly against base of penis during withdrawal; withdraw penis while still erect).
- Use water-based lubricants (e.g., KY jelly), NOT oils, lotions, or vaseline that can cause a condom to tear or break.
- Ensure that no air is trapped in tip of condom.

Protect yourself as follows if you use drugs:

- Never share drug needles or “works.”
- Participate in clinic needle exchange programs or clean drug needles with 100% bleach, leave 30 seconds, repeat three times and then rinse three times with water between uses.
- Mixing sex, drugs, and alcohol increases your risk. If you are drunk or high, it is harder to make good decisions about sexual practices.

Protect yourself as follows if you are pregnant:

- You can pass on HIV to your unborn child during pregnancy, birth, or breastfeeding. If you are pregnant and you have engaged in HIV risk–behaviors, obtain HIV testing and appropriate treatment if you test positive for HIV.
- Medications taken during pregnancy can reduce your risk of HIV transmission to the fetus during pregnancy.

*A simple blood test (some centers offer a saliva test) can determine HIV infection 6 months after exposure. This test can be obtained anonymously (without giving out your name) and is free or low cost in most states. Contact your local Health Department.

From Montana Department of Health and Environmental Sciences, Doc No 20858 MT 4-98, Helena, Mont, 1998.

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Special Implications for the Therapist 7-3

ACQUIRED IMMUNE DEFICIENCY SYNDROME

Preferred Practice Patterns

Many other patterns may apply according to individual clinical manifestations.

4C: Impaired Muscle Performance

5A: Primary Prevention/Risk Reduction for Loss of Balance and Falling

5E: Impaired Motor Function and Sensory Integrity Associated With Progressive Disorders of the Central Nervous System

5G: Impaired Motor Function and Sensory Integrity Associated With Acute or Chronic Polyneuropathies

6A: Primary Prevention/Risk Reduction for Cardiovascular/Pulmonary Disorders (decreased functional work capacity and maximum aerobic capacity)

6B: Impaired Aerobic Capacity/Endurance Associated With Deconditioning

6C: Impaired Ventilation, Respiration/Gas Exchange and Aerobic Capacity/Endurance Associated With Airway Clearance Dysfunction

6D: Impaired Aerobic Capacity/Endurance Associated with Cardiovascular Pump Dysfunction or Failure

With advances in treatment, improved care, and longer survival, therapists can expect to see increasing numbers of people in their practices who may have HIV. Maximal effectiveness from physical therapy requires a therapist who is knowledgeable about HIV disease and the unique rehabilitation issues surrounding individuals with HIV/AIDS.²²⁰

It is possible for individuals with HIV infection or AIDS to come to a therapy practice undiagnosed or unwilling to provide this information. Women who have been attacked or the victim of domestic violence have an increased risk of HIV transmission and do not always report this information.

It is important to include questions in the history that consider the possibility of sexual violence and HIV-related disease and correlate this information with objective evaluation results. For example, anyone presenting with musculoskeletal or neuromuscular symptoms of unknown origin, with or without constitutional symptoms, should be interviewed more specifically about the presence of past or current HIV risk behaviors. This may potentially lead to early medical referral, early diagnosis, and early, appropriate therapy. Early treatment choices will also determine future therapies because of viral resistance and other factors.

Health-care providers who routinely assess the HIV/STD risks of their clients can encourage at-risk MSM to test annually for HIV, syphilis, gonorrhea, and chlamydia, and to accept or seek vaccination against hepatitis A and B.²⁶⁸ Providing a discrete and nonjudgmental environment with assurance of confidentiality while emphasizing the importance of disclosing accurate risk information may help facilitate risk disclosure from young MSM.

Clients at all stages of HIV infection need psychosocial support to deal with depression, anxiety, and other emotional problems that can develop as the person's condition changes. Screening for depression and anxiety is essential; referral for further treatment may be indicated. Selective serotonin reuptake inhibitors (SSRIs) are usually well-tolerated and safe for anyone with hepatitis or other hepatic impairment. Antidepressants should be prescribed in conjunction with counseling or support groups.¹³²

Therapists also may have a role in osteoporosis education, prevention, and screening. Risk factor assessment is advised for anyone with HIV infection. Anyone at high risk for osteopenia or osteoporosis should be referred for DXA measurement of bone mineral density. Clients should be encouraged to minimize risk for developing osteoporosis with dietary calcium and vitamin D intake, maintaining a normal BMI, avoiding tobacco and alcohol abuse, and maintaining a long-term weight bearing exercise program.²⁰²

Prevention of Transmission

Health care workers (HCWs) may be concerned about potential contact in the workplace with clients who have AIDS; however, the risk of transmission of the virus from client to health care worker is exceedingly small. The health care worker is at far greater risk for the transmission of the hepatitis B virus (HBV) and should consider prophylactic vaccination for HBV or become familiar with postexposure prophylaxis (PEP) for HBV (see Chapter 17).

Health care workers at potential risk of contact with HIV-containing body fluids include blood bank technologists, dialysis technicians, emergency department personnel, morticians, dentists, medical technicians, surgeons, and laboratory workers. Therapists are not considered at risk

unless working in one of these capacities or performing wound care or débridement with a client with the virus.

The reported cases of occupational HIV transmission have been helpful in developing a definition of what constitutes exposure that could result in HIV transmission. Exposure routes implicated in occupational HIV transmission include (1) percutaneous injury (e.g., needle puncture or cut caused by a needle or other sharp object); (2) mucous membrane contamination with blood; and (3) nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) contamination.¹⁸³

Contact of intact skin when the duration of contact is prolonged (i.e., several minutes or more) has not been associated with HIV transmission but is considered a potential exposure, in part because the skin may have unrecognized areas of disruption that could serve as portals of entry.¹⁶²

Sources of HIV that may pose a risk of transmission through these routes include blood, visibly bloody fluids, tissues, and other body fluids including semen; vaginal secretions; and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids. In addition, any direct cutaneous or mucosal contact, without barrier protection, to concentrated HIV in a research laboratory or production facility is considered to be an exposure.¹⁶²

Although one nonoccupational episode of HIV transmission has been attributed to contact with blood-contaminated saliva, this incident was not analogous to the contact with saliva that occurs during dental or medical care.

In the absence of visible blood in the saliva, exposure to saliva from a person with HIV is not thought to pose a risk for HIV transmission. Exposure to tears, sweat, or nonbloody urine or feces from individuals with the virus does not constitute exposure to HIV. Occupational exposure to breast milk does not constitute an exposure unless ingested directly.¹⁶²

Health care considerations are primarily directed at preventing the transmission of the virus when caring for someone with AIDS by avoiding occupational blood exposure. Recommendations for preventing the spread of the virus consist of the use of standard precautions (e.g., using barriers for working with any liquid that comes from another person, excluding sweat [see Appendix A]).

Specific recommendations for health care professionals working with AIDS and HIV-positive clients are included in Box 7-4. Everyone with AIDS is immunodeficient, and every precaution must be taken to prevent infection for that person.

An individual with HIV does not need a private room unless he or she has a communicable disease that requires respiratory isolation (e.g., tuberculosis) (see specific recommendations made in Chapter 15). Hepatitis would require standard precautions but not isolation. The virus is not transmitted through casual nonintimate contact or social encounters such as eating in restaurants or using public transportation or public bathroom facilities because the virus does not live long or replicate outside the body.

There are no documented cases of HIV being transmitted during participation in sports. The very low risk of transmission during sports participation would involve sports with direct body contact in which bleeding might be expected to occur. There is no risk of HIV transmission

through sports activities where bleeding does not occur. Athletes in contact and collision sports are at greater risk of hepatitis B transmission and should be vaccinated against this virus. ¹³⁸

Postexposure Prophylaxis¹⁸³

HIV postexposure prophylaxis (PEP) is a form of secondary HIV prevention that may reduce the incidence of HIV infections. The two types of PEP are occupational and nonoccupational. Occupational exposure should be considered an urgent medical concern requiring timely postexposure management. ⁸⁹

Occupational HIV PEP is an accepted form of therapy for health care workers exposed to HIV through their jobs. ⁴¹ Health-care providers caring for persons with occupationally acquired HIV infection or who have acquired HIV themselves through occupational exposure can report these cases to CDC by telephone (800-893-0485) or to their state health departments.

Well-established U.S. national guidelines for occupational HIV PEP exist. No national guidelines are available for nonoccupational HIV PEP, after nonconsensual sexual intercourse (sexual abuse and assault), injected drug use or needle-stick and sharp injuries (i.e., in non-health care individuals). ¹⁷⁰ HCP with occupational exposure to HIV should receive follow-up counseling, postexposure testing, and medical evaluation regardless of whether they receive PEP.

The presumed mechanism for HIV PEP comes from animal and human work suggesting that shortly after an exposure to HIV, a window period exists during which the viral load is small enough to be controlled by the body's immune system.

Antiretroviral medications given during this period may help to diminish or end viral replication, thereby reducing the viral inoculum to a more potentially manageable target for the host's defenses. HIV PEP is accepted practice in the perinatal setting and for health care workers with occupational injuries. Determining level of risk and appropriateness of drug selection should be conducted as soon as possible after an exposure has occurred. HIV PEP should be administered within 1 hour of exposure.

HCP who are exposed and choose to take PEP must complete the prescribed regimen. Information should be provided about potential drug interactions and drugs that should not be taken with PEP, side effects of prescribed drugs, measures to minimize side effects, and methods of clinical monitoring for toxicity during the follow-up period. Symptoms of rash, fever, back or abdominal pain, pain on urination or blood in the urine, or symptoms of hyperglycemia (e.g., increased thirst or frequent urination) should be reported to the physician immediately.

HCP may fail to complete the recommended regimen because of side effects such as nausea and diarrhea. These symptoms often can be managed with antimotility and antiemetic agents or other medications that target specific symptoms without changing the regimen. Modifying the dose interval (i.e., administering a lower dose of drug more frequently throughout the day) might help encourage adherence to the regimen.

Follow-up care provided to exposed HCP is important including follow-up testing, monitoring, and counseling especially psychologic counseling for those with needlestick exposure or exposure to blood or body fluid. Exposed HCP are advised to use precautions to prevent

secondary transmission, especially during the first 6 to 12 weeks postexposure (e.g., avoid blood or tissue donations, breastfeeding, or pregnancy). Other guidelines for HIV PEP are available.^{39,170,183}

Guidelines for Health Care Workers with HIV

Any health care worker with HIV and/or HBV or HCV should not perform exposure-prone procedures in which blood contact might occur. Permission and guidance from special review committees is required before an infected health care worker can perform such procedures.

For the therapist, this would primarily exclude internal pelvic floor examination and wound care, including débridement and dressing changes. According to guidelines drafted by the CDC, at a minimum the potential client must be informed of the worker's HIV, HBV, or HCV status if the therapist is to engage in high-risk activity such as vaginal examination of the pelvic floor muscles, debridement, or other wound care.⁴⁰

HIV and Rehabilitative Therapy

Over the past twenty years, the rehabilitation of the person with HIV/AIDS has changed significantly. In the middle of the 1980's, the person with AIDS often developed *Pneumocystis carinii* (PCP) pneumonia and/or other opportunistic infections and quickly succumbed.

During this period, the physical therapist's role was primarily that of pain control, energy conservation, and instruction in the use of adaptive equipment to maximize functional ability. Today, prophylactic medications are highly effective in the prevention of PCP and many other opportunistic infections and HIV-associated conditions.

Chronic conditions such as cardiovascular disease related to lipodystrophy and rheumatologic and musculoskeletal conditions are much more common in those living with HIV. Therefore, physical therapists are generally focused on assisting the individual with the management of physical dysfunctions related to this chronic disease.

From a rehabilitation point of view, HIV is considered a chronic illness on a continuum (i.e., from being asymptomatic to exhibiting mild to severe symptoms) rather than as a terminal illness. The individual with HIV disease may demonstrate clinical manifestations of overlapping pathologic processes and HIV-related physical disabilities that need appropriate rehabilitation intervention.

For example, lesions of the CNS can be the site of more than one opportunistic disease process simultaneously⁸³ or the individual may experience a stroke in addition to an already existing peripheral neuropathy or other neuromusculoskeletal manifestations. The therapist may be involved in wound intervention when integumentary impairment is caused by HIV opportunistic infections while also providing intervention to relieve problems associated with rheumatologic dysfunctions.²²⁰

In addition to physical fitness and strength training, therapists must look at quality of life (QOL) issues; work simplification; and activities of daily living (ADLs), including community management skills such as access to transportation, socialization opportunities, shopping, banking, ability to negotiate health care, and insurance systems⁸³; and participation in church, synagogue, or other spiritual network. Home programs must be simple and easily incorporated into ADLs.

Often individuals with AIDS are overwhelmed by the disease process, the complicated treatment, the multiple health care appointments, and scheduling to manage all of these tasks. Adding an exercise program may result in frustration and noncompliance unless the person can see a clear benefit and way to manage yet another aspect of the treatment program.

Rehabilitative therapy may help the client with neurologic involvement optimize functional ability. These clients may respond to an eclectic blend of rehabilitation strategies such as those for individuals with strokes or head-injuries. Proprioceptive neuromuscular facilitation (PNF) and Bobath techniques may be more beneficial for the lower-level functioning clients.¹³¹

The therapist must be prepared for seizures, which may occur as a result of nervous system involvement, sometimes for the first time during a therapy session. Cognitive deficits in attention, concentration, and memory require consistency, structure, and environmental cues to minimize confusion.⁸³

Quickly progressive peripheral neuropathy is one of the most common types of pain experienced by people with HIV, sometimes as a result of drugs used to treat HIV or possibly related to HIV-induced immune complexes.⁸⁵

The use of conventional transcutaneous electrical nerve stimulation (TENS) may exacerbate peripheral pain in HIV-related peripheral neuropathies and should not be utilized. Joint and soft tissue mobilization, stretching, gait and balance training, and desensitization techniques can also be very effective. The alternate use of microcurrent, electroacupuncture has been reported to reduce pain, improve functional status, and increase perceived strength. Discussion of the possible mechanisms for these effects is available.⁸⁵

The presence of peripheral neuropathies may also signal nutritional deficiencies requiring nutritional counseling. This is especially true for the client who has the wasting syndrome that often accompanies HIV infection and AIDS.

The body may begin to draw from its own stores of fat, affecting the myelin sheaths of nerves, which are protected by fat. Without proper nutrition, therapy involving balance training, extremity strengthening and stretching, and motor skills, although extremely important, may be limited in benefit.

Diminished sensory information associated with peripheral neuropathies of the lower extremities makes balance and gait control more difficult. Clients with AIDS may have balance deficits at lower movement speeds compared to healthy adults. Motor slowness is associated with both neuropathy and myopathy.¹⁵⁵ Formulating a rehabilitation approach must be based on the underlying neurophysiologic deficit(s) present.⁸⁴ Other guidelines for management of the lower extremity complications, balance, and postural derangements associated with distal symmetrical polyneuropathy (DSP) are available.^{86,227}

For individuals with painful myopathy in the large muscle groups, progressive resistance training with weights or elastic band/tubing to strengthen specific muscles may be beneficial. Muscle spasms accompanying myopathy may respond well to gentle but consistent stretching exercises. Postexercise soreness is common in the AIDS group experiencing muscle pain. A longer rest period between exercises may be necessary.

Improper body mechanics, poor postural alignment and postural instability, balance and gait problems, and other biomechanical changes may occur in the person who has developed muscle weakness and fatigue following progression of the disease process, malnutrition, or the wasting

syndrome. Again, postural awareness, stretching and strengthening of specific muscles, and attention to nutrition may be part of the treatment plan.

Cardiopulmonary complications (see Table 7-3) in advanced stages of AIDS contribute to morbidity and mortality. Oxygen transport mechanisms can be adversely affected. Muscle and joint mobilization techniques and breathing exercises are essential for the person who has been immobilized for any length of time as a result of respiratory or other disease involvement. The rib cage is one area where normal respiratory and accessory movements are essential for adequate lung ventilation, energy conservation, correct posture, and balance reactions.

For the client with malignancy, guidelines for the management/treatment intervention of the oncologic client are discussed in Chapter 9 (see also the section on Kaposi's Sarcoma in Chapter 10).

Exercise and HIV/AIDS

Unlike other infections, HIV directly affects the immune system. As discussed in the section on Exercise Immunology in this chapter, since exercise has clinically significant effects on immune responsiveness, then a potential exists to alter the natural history of HIV infection in a beneficial manner through the use of exercise. A growing number of studies are now addressing the issue of the relationship between exercise and HIV infection.^{70, 133} The results are summarized here.

Early Stage HIV Disease. Exercise is considered safe for people with HIV and an important way to increase the CD4 cells at earlier stages of the disease, possibly delaying symptoms while increasing muscle strength and size. During stage I (asymptomatic HIV) metabolic parameters are within normal limits with no limitations placed on the individual. Individuals with asymptomatic HIV disease should be encouraged to exercise regularly including both an aerobic and resisted exercise component.¹³³

The effect of HIV and its treatment with protease inhibitors on exercise and activity tolerance has been reported. Physical activity intolerance resulting in functional limitations may be caused by diminished aerobic capacity (decreased peak VO₂) far below that occurring as a result of physiologic deconditioning alone. Individuals who receive HAART may have a reduced ability to extract and use oxygen from the muscle during exercise limiting their ability to increase the intensity of activity.²⁷

Advanced Stages or Chronic HIV Disease. During stages II and III, functional capacity is reduced, requiring more individualized exercise prescription and lower intensities.¹⁴⁹ Neurologic dysfunction and deconditioning are common. Regular physical activity and exercise is just as important in this group but more difficult and symptom-limited. Among people with HIV who have known cardiovascular disease, pulmonary limitations, or muscle dysfunction, exercise prescription should address impairments and limitations. Collaboration with the physician to determine any contraindications for exercise is advised.

Strenuous exercise training is not recommended; aerobic exercise at moderate levels of intensity is suggested with medical clearance.²⁴⁶ Constant or interval aerobic exercise for at least 20 minutes, at least 3 times per week for 4 weeks may lead to improved cardiopulmonary fitness and improved psychologic status, with an accompanying maintenance of immunologic function.¹⁸¹ Supervised aerobic exercise training safely decreases fatigue, weight, BMI, fat and central fat in HIV-1 infected individuals. It may not affect dyspnea.²³⁶

Clients with advanced disease may be at greater risk for exercise-related injuries due to chronic myopathic and neuropathic tissue changes. Recovery periods after exercise may be prolonged compared to asymptomatic or early stage individuals. Response to exercise should be carefully monitored. ¹³³

Anyone with acute myopathy and myositis should not perform strenuous or resisted exercises until CPK levels normalize. Bouts of acute inflammatory arthralgia may require periods of joint protection and relative rest, as well as medical management. ¹³³

Likewise, exercise has beneficial effects for those with the AIDS-related wasting syndrome. In either condition, the goal is to exercise enough to gain muscle and build lean body mass without causing degeneration with acidosis. Progressive resistive exercise can increase lean body mass significantly without increasing circulating HIV RNA concentrations. ^{214, 215}

The role of exercise in the treatment of lipodystrophy syndrome is important ²⁰ and has been shown to have potential in normalizing insulin resistance, which is under investigation; to be effective in managing metabolic abnormalities without causing further side effects ⁵⁶; and to reduce trunk fat mass with fat redistribution. ²¹⁶ Short-term intervention of aerobic exercise combined with a low-lipid diet can increase functional capacity but may not change plasma lipid levels. ²⁵¹

All Stages. Exercise in all stages may provide pain relief; improve appetite, reduction of muscle atrophy, and regular bowel activity; and improve function; it can also enhance immune function by increasing T helper/inducer (CD4) cells and the inducer subset, which activate suppressor/cytotoxic (CD8) cells. Exercise can improve overall cardiovascular and pulmonary function to improve endurance and cardiac function and help prevent pneumonia and other respiratory infections.

Moderate exercise often reduces anxiety and improves mood state, which may be the mechanism by which it enhances or stabilizes the immune system. Exercise can benefit psychoneuroimmunology interactions by reducing stress and improving mood, potentially improving quality of life, which in turn can influence disease progression.

Results of group aerobic exercise and t'ai chi on functional outcomes and quality of life for persons living with chronic AIDS showed improved physiologic and physical changes along with improved functional outcomes and quality of life. Group intervention provides a socialization context for the management of chronic HIV disease with enhanced psychologic coping and improved social interactions. ⁸⁷

Exercise training at 70% to 80% of maximal heart rate is recommended to achieve the benefits listed. Higher intensities increase strength and aerobic fitness but have not been shown to change total lymphocyte cell counts or ratios. ²¹¹ A rate of perceived exertion (RPE) no greater than 14 is recommended ¹⁴⁹ (AU: check table number Table 11-13); other recommendations established by the American College of Sports Medicine (ACSM) are available for all three stages of HIV disease.

Monitoring vital signs (see Appendix B) and laboratory values (see Chapter 40) is an important part of determining exercise intensities especially in the presence of co-morbidities such as anemia, vitamin deficiency, wasting syndrome, or opportunistic infections. Proper caloric intake is also important in setting the standard for each type of exercise to meet energy expenditure

required for the activity. Seeking the advice of a nutritionist is recommended.⁸³ [AU: check for updated edition of this text](#)

The effects of exercise demands on a high-level athlete with HIV in competition on levels of psychologic stress and immune function remain unclear. Potential adverse effects of the stresses of competition include increased upper respiratory infections in marathon runners.¹⁷⁹ Exercise recommendations for athletes with HIV are summarized in Box 7-5.

Exercise programs to increase strength and body mass are particularly relevant to HIV because wasting is one of the most devastating aspects of this infection. In contrast to people experiencing simple starvation who lose adipose tissue but initially retain lean body mass, people with HIV infection lose lean body mass too.

Exercise training, including strength training, may have the potential to (possibly only temporarily) arrest and/or reverse the wasting effects. In the nonacute stage, improved muscle function and increased body dimensions and mass can occur following progressive resistive exercises three times per week for 6 weeks.^{73,240}

Clients coinfectd with HIV and HCV who also have hemophilia face some difficult musculoskeletal and orthopedic problems. Joint arthroplasty can relieve pain and improve quality of life but postoperative complications are a concern due to the poor health status that many of these people experience. The therapist can play a vital role in the multidisciplinary hemophilia team in weighing the potential risks and benefits before endorsing a surgical procedure.²¹²

Continued

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Section II **Clinical Medicine**

Box 7-3

Standard AIDS/HIV Precautions for Health Care Workers

Use protective barriers (gloves, eye shields, gowns) when handling blood, body fluids, and infectious fluids.

Wash hands, skin, and mucous membranes immediately and thoroughly if contaminated by blood or other body fluids.

Prevent needle or scalpel sticks.

Ventilation devices are available for resuscitation.

Any health care worker (HCW) with open wounds or skin lesions should not treat clients or handle equipment until the lesion(s) heals.

Pregnant health care workers should take extra precautions. See Appendix A for additional information.

Occupational exposure to HIV should be followed immediately by evaluation of exposure source and postexposure prophylaxis.

U.S. Public Health Service: Updated guidelines for the prevention of HIV and hepatitis virus transmission and the management of occupational exposures to HIV, BHV, and HCV, *MMWR* 50(RR-11):1-67, 2001.

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Chapter 7 **The Immune System**

Continued

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Section II **Clinical Medicine**

Box 7-4

Exercise Recommendations for Athletes with Human Immunodeficiency Virus* Disease

Before initiating any exercise program, the athlete must have a complete physical examination.

A graded exercise test may be a necessary part of the evaluation to determine how much exercise the person can tolerate and what baseline of exercise should be established to start.

Exercise is a safe and beneficial activity for the HIV-infected person.

For healthy individuals who are asymptomatic of HIV, unrestricted exercise activity and competition are acceptable; overtraining should be avoided.

For people with more advanced HIV infection, who are experiencing mild to moderate symptoms, athletic competition is not considered advisable given the stress of competition and its effect on the immune system; training may continue without competition.

Symptomatic people should avoid exhaustive exercise but may be able to continue exercise training under close supervision.

Exercise training programs may need to be modified to include mild exercise and energy conservation techniques for anyone during the acute stage of an opportunistic infection.

For the noncompetitive person, exercise should begin while healthy with strategies to help maintain an exercise program throughout the course of the illness.

People with HIV, through the use of exercise, can play an important role in the management of their illness while improving quality of life.

Exercise has the potential to offer subtle and effective behavioral therapeutic benefits regardless of ethnicity, exposure category, or gender.

*General principles included here apply to all individuals with HIV, including those who are not athletes or competitive in athletics or sports.

Modified from Calabrese LH, LaPerriere A: Human immunodeficiency virus infection, exercise, and athletics, *Sports Med* 15:6, 1993.

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Chapter 7 **The Immune System**

Box 7-5

CDC Revised Case Definition: Chronic Fatigue Syndrome

1. Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is any of the following:

- New or definite onset (i.e., not lifelong)
- Not the result of ongoing exertion
- Not substantially alleviated by rest
- Results in substantial reduction in previous levels of occupational, educational, social, or personal activities

2. The concurrent occurrence of four or more of the following symptoms:

- Substantial impairment in short-term memory or concentration
- Sore throat
- Tender lymph nodes
- Muscle pain
- Multiple arthralgias without swelling or redness
- Headaches of a new type, pattern, or severity
- Unrefreshing sleep
- Postexertional malaise lasting more than 24 hours

These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

Centers for Disease Control and Prevention: Chronic fatigue syndrome: the revised case definition, 2006. Available at <http://www.cdc.gov>.

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Section II **Clinical Medicine**

Special Implications for the Therapist 7-4

CHRONIC FATIGUE SYNDROME

Preferred Practice Patterns

4B: Impaired Posture (fatigue-related)

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated With Connective Tissue Dysfunction

5A: Primary Prevention/Risk Reduction for Loss of Balance and Falling (neurogenic hypotension)

6B: Impaired Aerobic Capacity/Endurance Associated With Deconditioning

The client with CFS is treated following guidelines and protocols for autoimmune disorders such as fibromyalgia (see the section on Fibromyalgia in this chapter). Pacing; energy conservation (see Box 9-2) **Au: check box number; formerly 8-2**; Physiologic Quieting®; stress management; and balancing life activities are extremely helpful in preventing worsening of fatigue and maintaining an even flow of energy from day to day. Support groups may be beneficial in providing emotional and psychologic support and in helping the individual keep up with latest research results and progress in medical intervention.

Exercise and Chronic Fatigue Syndrome

Carefully controlled and graded exercise is the center of effective intervention for CFS. **80, 81, 188,**

196 Many affected individuals fear a relapse and avoid physical activity and exercise but deconditioning and muscle atrophy increases fatigue and makes other symptoms even worse.

The physical therapist can be very instrumental in providing a prescriptive program of regular, moderate exercise to avoid deconditioning while advising against overexertion during periods of remission. During the acute onset or during flareups people with CFS are unable to sustain physical activity or exercise. Beginning with low-level, intermittent physical activity throughout the day to accumulate 30 minutes of exercise has been shown to be effective without exacerbating symptoms. **50**

People with CFS may also have a significantly reduced exercise capacity. Always assess for conditioning before initiating even a simple exercise program with anyone who has had CFS longer than 6 months. Athletes and sports participants may require special help to develop a progressive exercise regimen. Impairments of peak aerobic power and muscle strength may occur with self-imposed or physician-imposed inactivity. **230**

Although abnormal lung function or low concentration of oxygen with accompanying dyspnea or shortness of breath is not a clinical feature of this disease, anyone who is severely deconditioned and then tries to do even light exercise may experience dyspnea. Reaching age-predicted target heart rates may be limited by autonomic disturbances. **59** It may be better to begin a strengthening program before challenging the cardiovascular system.

The therapist must evaluate for altered breathing patterns, components of poor posture, and inefficient or biomechanically faulty movement patterns contributing to pain. Addressing these areas is an important part of the rehabilitation process.

Stretching, strengthening, and cardiovascular training are essential aspects of therapy. Like people with fibromyalgia, those diagnosed with CFS must progress slowly and avoid overexertion since they often do not have the internal mechanism to alert them to stop an activity.

Soft tissue and joint mobilization combined with stretching are important components of intervention, especially in the presence of postural components or faulty mechanics. Prolonged inactivity, rest in poorly supported positions for long periods, and assuming postures dictated by pain can contribute to muscles shortening (see the sections on Modalities and Fibromyalgia in this chapter).

Over time, some individuals can be progressed to graded aerobic exercise therapy (some can begin at this level depending on the individual clinical presentation). Continuous exercise must be started at a short duration appropriate to the client's baseline ability. A more specific

description of how to deliver a graded exercise therapy program to people with CFS is available.⁷⁹ This has been shown to be significantly more effective than just stretching and relaxation exercises.^{80,263}

Monitoring Vital Signs

Assessment of vital signs in adults with CFS may demonstrate very large fluctuations in pulse rate and blood pressure, which are not consistent with the person's position or movement. Whereas the blood pressure and pulse rate normally show a slight increase as a physiologic response to a change in position from sitting to standing, orthostatic hypotension is marked in the CFS population. Vital signs may stay the same or even decrease, resulting in dizziness, lightheadedness, or loss of balance. The symptoms may result in decreased self-confidence in the ability to pursue activities.

During the initiation of an exercise program, it is advised to monitor blood pressure; RPE (see Table 12-13)^{AU: check table number}; heart rate; and respiratory rate for any signs of physiologic distress. Although the RPE may not change during the exercise session, the individual may perceive fatigue as worse after initiating exercise. However, if this increase in fatigue does not exceed 1 unit on a scale from 1 to 5 from the baseline level established before exercise, symptom exacerbation following exercise can potentially be avoided.⁵⁰ ■

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TABLE

7-5

Clinical Manifestations of Hypersensitivity Disorders

Type I **Type II** **Type III** **Type IV**

Varies according to the allergies present

Classic symptoms

- Wheezing
- Hypotension
- Swelling
- Urticaria
- Rhinorrhea

Anaphylaxis

General: malaise, weakness

Dermal: hives, erythema

Respiratory: sneezing, rhinorrhea, dyspnea

Upper airway: hoarseness, stridor; tongue and pharyngeal edema

Lower airway: dyspnea, bronchospasm, asthma (air trapping), chest tightness, wheezing

Gastrointestinal: increased peristalsis, vomiting, dysphagia, nausea, abdominal cramps, diarrhea

Cardiovascular: tachycardia, palpitations, hypotension, cardiac arrest

Central nervous system: anxiety, seizures

Headache

Back (flank) pain

Chest pain similar to angina

Nausea and vomiting

Tachycardia

Hypotension

Hematuria

Urticaria

Fever

Arthralgias

Lymphadenopathy

Urticaria

Anemia

Special Implications for the Therapist 7-5

HYPERSENSITIVITY DISORDERS

Preferred Practice Pattern

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

Immediate action is required for any client experiencing a type I hypersensitivity reaction or anaphylaxis. When a severe reaction occurs, the health care professional must call for emergency assistance.

Type IV reactions may occur in response to lanolin added to lotions, ultrasound gels, or other preparations used in massage or soft tissue mobilization, requiring careful observation of all people for delayed skin reactions to any of these substances.

With the first exposure, no reaction necessarily occurs, but antigens are formed and on subsequent exposures, hypersensitivity reactions are triggered. Anyone with known hypersensitivity should have a small area of skin tested before use of large amounts of topical agents in the therapy setting. Careful observation throughout treatment is recommended.

Beginning in the 1980's, use of latex gloves to protect health care workers against exposure to blood and body fluids increased. Since then, the number of reported cases of latex sensitivity

also has increased. Reactions to latex range from contact dermatitis (Type IV hypersensitivity) to anaphylactic shock (Type I hypersensitivity).

Therapists who are allergic to latex should avoid contact with latex gloves and other products that contain latex. Use of low-powder, powder-free, and non-latex gloves provides therapists with a strategy for preventing exposure to latex allergens. 154.

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Chapter 7 The Immune System

TABLE

7-6

Autoimmune Disorders

Organ-Specific Systemic

Addison's disease

Crohn's disease

Chronic active hepatitis

Diabetes mellitus

Giant cell arteritis

Hemolytic anemia

Idiopathic thrombocytopenic purpura

Polymyositis/dermatomyositis

Postviral encephalomyelitis

Primary biliary cirrhosis

Thyroiditis

Graves' disease

Hashimoto's disease

Ulcerative colitis

Amyloidosis

Ankylosing spondylitis

Mixed connective tissue disease

Multiple sclerosis

Myasthenia gravis

Polymyalgia rheumatica

Progressive systemic sclerosis (scleroderma)

Psoriasis (psoriatic arthritis)

Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Sjögren's syndrome
Systemic lupus erythematosus
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Section II **Clinical Medicine**

Box 7-6

American Rheumatism Association Diagnostic Criteria for Systemic Lupus Erythematosus

A person is considered to have SLE if four or more of the following 11 criteria are present, serially or simultaneously, during any interval of observation:

1. Abnormal titer of antinuclear antibodies (ANA)
2. Butterfly (malar) rash
3. Discoid rash
4. Hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
5. Neurologic disorder: seizures or psychosis
6. Nonerosive arthritis of two or more peripheral joints characterized by tenderness, swelling, or effusion
7. Oral or nasopharyngeal ulcerations
8. Photosensitivity
9. Pleuritis or pericarditis
10. Positive lupus erythematosus cell preparation, anti-DNA, or anti-Sm test or chronic false-positive serologic test for syphilis
11. Renal disorder: profuse proteinuria (>0.5 g/day) or excessive cellular casts in urine

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Section II **Clinical Medicine**

Special Implications for the Therapist **7-6**

SYSTEMIC LUPUS ERYTHEMATOSUS

Preferred Practice Patterns

Other patterns may apply depending on individual clinical manifestation and presentation.

4A: Primary Prevention/Risk Reduction for Skeletal Demineralization (osteoporosis as a side effect of some medications; prolonged bedrest)

4B: Impaired Posture (fatigue related)

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated With Connective Tissue Dysfunction

6B: Impaired Aerobic Capacity/Endurance Associated With Deconditioning

7A: Primary Prevention/Risk Reduction for Integumentary Disorders (vasculitis)

7E: Impaired Integumentary Associated With Skin Involvement Extending Into Fascia, Muscle, or Bone and Scar Formation

Like fibromyalgia, physical and occupational therapy intervention can be important components of the overall treatment plan. Recurrence of disease can be managed with carefully controlled and sometimes restricted activities. After an exacerbation, gradual resumption of activities must be balanced by maximum rest periods, usually 8 to 10 hours of sleep a night and several rest periods during the day.

Most of the principles and reference materials outlined in the following section, Fibromyalgia, also apply to SLE. Management of joint involvement follows protocols for rheumatoid arthritis (see Special Implications for the Therapist: Rheumatoid Arthritis, 27-6 [Au: check number](#)). Clients with skin lesions should be examined thoroughly at each visit. The therapist can be instrumental in teaching and assisting with skin care and prevention of skin breakdown.

Functional limitations among people with SLE vary according to the type and degree of the disease. Generalized fatigue defined as “the inclination to rest, even though pain and weakness are not limiting factors,” is a common problem and can be very debilitating, especially for those individuals with both SLE and fibromyalgia. ⁴

The therapist can be very instrumental in teaching clients how to pace activities and conserve energy (see Box 9-2) [Au: check number](#), follow a prescriptive exercise plan, avoid excessive bed rest, and protect joints. Excessive bedrest can worsen fatigue, promote muscle disuse and atrophy, and promote osteoporosis. Prescriptive exercise should strengthen the muscles and improve endurance while avoiding undue stress on inflamed joints.

Septic arthritis or osteonecrosis may develop as a complication of SLE or its treatment. Septic arthritis is uncommon in SLE, but it should be suspected when one joint is inflamed out of proportion to the others. People with SLE may develop a drug-related myopathy secondary to corticosteroids or as a complication of antimalarials (see the section on Corticosteroid Myopathy in Chapter 5).

Anyone taking corticosteroids or immunosuppressants must be monitored carefully for signs of infection, especially people at heightened risk of infection such as those with renal failure, cardiac valvular abnormalities, or ulcerative skin lesions. (See specific side effects and Special Implications for the Therapist: Corticosteroids in Chapter 5.) The client should contact the physician if a fever or any other new symptoms develop. The therapist can provide osteoporosis prevention and intervention management.

High-dose oral corticosteroid treatment remains the major predisposing cause of avascular necrosis in SLE and other autoimmune disorders. The most common site is the femoral head of

the hip; less commonly, the femoral condyle of the knee is affected. Although the condition may be bilateral, it most often presents with an insidious onset of unilateral hip or knee pain that is worse with ambulating but often present at rest. Symptoms are progressive over weeks to months.

Observe carefully for any sign of renal involvement such as weight gain, edema, or hypertension. Take seizure precautions if there are signs of neurologic involvement. The therapist may recognize signs of cognitive dysfunction or decline, either directly observed in the client or by family report. These manifestations should be reported to the physician for consideration in evaluating medications. If Raynaud's phenomenon is present, teach the client to warm and protect the hands and feet. (See Special Implications for the Therapist: Peripheral Vascular Disease/Raynaud's Phenomenon, 12-23.) Au: check number

A discussion of pregnancy and SLE is beyond the scope of this text but may be of importance to the therapist involved in women's health issues. More detailed information is available elsewhere. 172,205, 206 ■

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FIGURE 7-7 Multifactorial Causes of Fibromyalgia Syndrome. There are many hypotheses and models of how multiple factors contribute to the development of fibromyalgia syndrome (FMS). This model represents data thus far to support FMS as a biologic (organic) disorder caused by neurohormonal dysfunction of the ANS. The physiologic effects of four primary systems dysfunction are listed.

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FIGURE 7-8 Anatomic locations of tender points associated with fibromyalgia, according to the American College of Rheumatology 1990 classification of fibromyalgia. Digital palpation should be performed using the thumb or the first two fingers. Apply a steady, uniform pressure with an approximate force of 4 kg/cm² (approximately the pressure needed to indent a tennis ball; enough to blanch the examiner's thumbnail). Using the Tender Point Index, a composite score can be assessed by adding up the individual scores for each of the 18 fibromyalgia tender point sites.

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TABLE

7-7

Clinical Manifestations of Fibromyalgia

Sign/Symptom	Incidence (%)*	Sign/Symptom	Incidence (%)*
Muscle pain (myalgia), tender points	99†		
Visual problems (e.g., blurring, double vision,		95 bouncing images)	
Mental and physical fatigue	85		
Sleep disturbance/morning fatigue	80		
Morning stiffness (persists >30 min)	75		
Mitral valve prolapse	75		
Global anxiety	72		
Cognitive (memory) problems (e.g., decreased memory, decreased concentration, increased distractibility)		71 attention span, impaired short-term	
Irritable bowel syndrome	70		
Inflammatory bowel disease (Crohn's disease,		50-60 ulcerative colitis)	
Headaches	70		
Hypersensitivity to noise, odors, heat, or cold		50-60 (cold intolerance)	
Paresthesias	50		
Swollen feeling (joint or soft tissues)	50		
Muscle spasms or nodules	50		
Reactive hypoglycemia (e.g., weakness, irritability,		45-50 disorientation)	
Pelvic pain	43		
Irritable bladder syndrome, female urethral syndrome		40	
Hypotension (low blood pressure, elevated heart rate); neurally mediated hypotension or vasopressor syncope	40		
Raynaud's phenomenon	38		
Sicca syndrome (dry eyes/mouth)	33		
Respiratory dysfunction (e.g., dyspnea, erratic breathing patterns during exertion)		33	
Restless leg syndrome, nocturnal myoclonus, (PLMD)		30-60 periodic leg movement disorder	
Auditory problems	31		
Temporomandibular dysfunction	25		
Depression	20		
Allergies	Unknown		
Lack of libido	Unknown		
Skin discoloration	Unknown		

Sciatica Unknown

*These figures were compiled from a variety of sources but represent a fairly accurate clinical perspective.

†Although the American College of Rheumatology requires the identification of at least 11 out of 18 tender points to qualify for a diagnosis of FMS, some clinicians report isolated individuals without pain but characterized by the physiologic effects and manifestations of FMS or patients with fewer than 11 tender points.

Modified from Hulme J: *Fibromyalgia: a handbook for self-care and treatment*, ed 3, Missoula, Mont, 2000, Phoenix.

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Box 7-7

Differential Diagnosis of Fibromyalgia

Endocrine Disorders

Hypothyroidism

Hypopituitary

Hyperparathyroidism

Growth hormone deficiency

Diabetes Mellitus

Adrenal Insufficiency

Pregnancy

Menopause

Menstrual Disorders

Illness

Rheumatoid arthritis

Systemic lupus erythematosus

Sjögren's syndrome

Polymyositis/dermatomyositis

Polymyalgia rheumatica/ giant cell arteritis

Metabolic myopathy (e.g., alcohol)

Metastatic cancer

Chronic fatigue syndrome

Infection/Inflammation

Subacute bacterial endocarditis

Lyme disease
Hepatitis C
AIDS
Chronic syphilis
Tuberculosis
Other
Temporomandibular joint dysfunction
Disk disease
Myofascial pain syndrome
Silicone breast implant
Neurosis (depression/ anxiety)
Substance Abuse
Malnutrition
Allergies

Special Implications for the Therapist 7-7

FIBROMYALGIA

Preferred Practice Patterns

4A: Primary Prevention/Risk Reduction for Skeletal Demineralization (osteoporosis as a side effect of some medications)

4B: Impaired Posture (metabolic-based fatigue)¹⁵⁷

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated With Connective Tissue Dysfunction

5A: Primary Prevention/Risk Reduction for Loss of Balance and Falling (neurogenic hypotension)

6B: Impaired Aerobic Capacity/Endurance Associated With Deconditioning

Therapists are often the first to recognize the history and clinical manifestations suggestive of fibromyalgia and then request medical diagnosis and intervention. Efforts to assess the accuracy of thumb nailbed blanching as a means of determining the presence of tender points suggest that the therapist can quickly learn to use the 4 kg/cm² of force required to administer a tender point examination (Manual Tender Point Survey or MTPS).²³⁸

Accurate assessment allows the therapist to establish a baseline sensitivity to aid in determining progress and direct intervention.⁴⁷ Specific procedures for identifying and palpating each site are available.^{141,243} A complete compendium of blank assessment forms and information on how to obtain assessment instruments for FMS is also available.^{112,157}

Rehabilitative therapy is an important component in managing fibromyalgia. Many people with FMS have undergone unnecessary exploratory or corrective surgery and have residual functional limitations. Chronic musculoskeletal conditions that are sources of noxious neural input to the CNS often involve the shoulder(s) and spine.

Therapy is helpful first in directing individuals to reach goals of lessening pain and fatigue, and eliminating sleep disturbance. Outcomes can be measured in a variety of ways, not only by reduction in tender points but also by global scores of pain, fatigue, sleep, reduction of other distressing symptoms, improved quality of life, reduced visits to the physician, reducing or eliminating medications, increased sexual activity, improved work performance, and so on.

Many people with FMS have been told they must “learn to live with it.” A more positive approach is to suggest working together to learn how to move forward with FMS, respecting limitations but not being controlled by them. The therapist can be very instrumental in guiding that person to understand how to manage this condition. Prevention programs for osteoporosis and falls related to low blood pressure are additional services the therapist can provide.

Strategies for work modification and applying ergonomic techniques to increase efficiency and decrease pain are important interventions. A chronic pain program may be appropriate. The reader is referred to more specific literature for treatment regimens, self-stabilizing techniques, and therapy protocols for this condition.^{43,112,204 188}

Monitoring Vital Signs

Monitoring tests provide an indication of the present physiologic status but cannot predict future status so regular monitoring is necessary. Depending on the current status, the individual may have to self-monitor every 2 hours, whereas others are able to maintain a balance by monitoring twice daily or less often. For most people with FMS, the sensory system and the ANS are overactive. Monitoring tests are a helpful tool in developing techniques to quiet these hypersensitivities and achieve a state of physiologic quiet.¹¹²

Blood pressure and heart rate are indicators of cardiac and circulatory system function and should be monitored. Most people with FMS have low blood pressure and usually an elevated pulse rate even at rest (some individuals have a slow pulse). Hypotension in people with FMS is now referred to as *neurogenic hypotension* (see Chapter 12). It has been suggested that thyroid hormone regulation will normalize the heart rate and contractility and often normalizes the blood pressure.¹⁵⁹

For some individuals with a hypoglycemic component, blood glucose assessment may be necessary. Hand temperature is one indicator of ANS function and can be easily assessed using a handheld biofeedback device (e.g., Thermister®)¹⁹² designed to measure hand temperature. This tool provides a mean of modulating the ANS, improving circulation, and reducing pain levels. The therapist can monitor medical and physical therapy intervention outcomes by assessing vital signs and documenting results.

Modalities and Fibromyalgia

Very little research is available to determine the outcomes of modality use (i.e., physical therapy intervention with thermal or mechanical properties such as physical agents, cryotherapy, moist heat, massage, manual therapy, soft tissue treatment) with FMS.

Investigation into the use of cranial electrotherapy stimulation (sending minicurrents of electricity through the brain) is under investigation. Limited study shows that this treatment intervention provided a significant improvement in tender point scores and in self-rated scores of general pain level, along with dramatic gains in six stress-related psychologic test measures.^{135,151}

Ultrasound can be an effective therapeutic modality for the treatment of pain in people with FMS when combined with connective tissue manipulation and high-voltage pulsed galvanic stimulation.⁴⁹ Also, pulsed ultrasound has been shown to be effective in treatment of pain in FMS as combined therapy with interferential current.⁵

There have been some reports on the use of ultrasound as an effective therapeutic modality for its thermal effects and for the treatment of myofascial trigger points often present in people with FMS. Continuous ultrasound is preferable to pulsed ultrasound and should be combined with a complete trigger point (TrP) protocol.²⁵⁰ The intensity must be reduced from standard settings to accommodate hypersensitivity in most people with FMS. Specific positions, tissue effects, intervention techniques, and treatment parameters are available.^{109, 110}

Again, additional steps must be taught to sustain pain relief (e.g., using biofeedback or Physiologic Quietening®¹¹² to avoid contracting the involved muscle, gentle stretching combined with moist heat several times each day, appropriate changes in work style, patterns of movement, postures, and over-the-counter analgesics such as ibuprofen or naproxen when approved by the physician).¹¹⁰

Soft tissue techniques may correct the neurocirculatory abnormality and thereby reduce or eliminate the nociceptive signal transmission from the muscle. The result should be to relieve pain and improve Tender Point Index scores or other FMS pain scores assessed.

Given the proposed mechanism of muscle pain (hyperresponsive myofascial mechanoreceptors/impaired CNS pain-inhibiting system), soft tissue techniques must be applied gently and slowly to increase circulation while avoiding an increase in nociceptive signal transmission. With the typical FMS client, posttreatment discomfort can be avoided by keeping the discomfort level during treatment between 1 and 5 on a self-assessment scale from 1 to 10. Cross-friction massage is not advised.¹⁵⁸

Exercise and Fibromyalgia

The primary nonpharmacologic modality in the management of FMS is prescriptive exercise. Improvement in both subjective pain and objective measurement has been demonstrated with cardiovascular fitness training or simple flexibility training.¹⁶⁴ Increases in β -endorphin; adrenocorticotrophic hormone (ACTH); and cortisol levels in response to exercise at aerobic levels (i.e., 60% of maximal oxygen consumption) have also been shown in this population.¹⁷⁷

Aerobic exercise also contributes by increasing the metabolic rate of the lean tissues for those individuals with a thyroid component.²³⁴ Resistance exercise contributes to the increase in metabolism by increasing lean tissue mass, which has a higher metabolic rate than fat tissue.¹⁹⁷ Well-managed prescriptive exercise regimens improve sleep and result in a decrease in pain and fatigue.⁵²

Only general concepts are included in this text; other texts are available for specific exercise regimens.^{15,112} Comprehensive reviews of evidence for effectiveness of exercise programs for individuals with fibromyalgia have been recently published.^{95, 96, 139}

Combining self-care and management strategies with an exercise program helps the individual reach the goals of optimal function and fitness while maintaining decreased pain and fatigue and increasing endurance for daily activities. A number of excellent self-care books are available for consumers.^{42, 57, 77, 242} Gentle stretching exercises performed routinely throughout the day may reduce fatigue. A cardiopulmonary fitness component should be included at whatever level the individual presents with at the time of assessment.

Sometimes the person's condition is so acute that exercise is not tolerated immediately. This is often the reason for using modalities in the early stage of therapy. Exercising too soon and committing to too much can set the person back considerably, but at the same time the therapist must keep in mind the long-term goal to increase strength and improve aerobic fitness.

Aquatic therapy is an ideal way to begin conditioning, especially for those individuals with FMS who have injuries, are overweight, or are sensitive to axial load. Aquatic therapy provides low-level progressive exercises, gradually increasing strength and endurance while improving overall cardiovascular fitness.^{8, 102} Ideal pool temperature is between 84° F and 90° F (compared with 82° F to 84° F for the general population and 90° F to 94° F for people with arthritic conditions).¹⁴²

As with all exercise programs with this population (whether aquatic or other therapy), people with fibromyalgia fatigue quickly and may have a low tolerance for exertion. The key is to avoid activating the peripheral sensory mechanisms in order to avoid increasing pain postexercise.

The person with FMS will respond to stimuli that would not ordinarily be perceived as painful (referred to as *allodynia*). This requires short exercise sessions, according to individual tolerance using the rate of perceived exertion (see Chapter 12), that are possibly even only 3 to 5 minutes at first.

The client is encouraged to increase exercise duration in small daily increments, sometimes only by seconds or minutes. Reaching a goal of 30 minutes of daily exercise may take weeks to months; some individuals are only able to tolerate one to three daily exercise cycles, each lasting only 5 to 10 minutes, but this will produce beneficial effects.

The individual with FMS must be taught to set aside the philosophy of “no pain, no gain” and to avoid “pushing through the pain.” In the normal individual, growth hormone is increased with exercise, but this does not happen in the person with FMS.

Rather, as a result of ANS dysfunction, reduced microcirculation (capillary flow and other small vessels that supply muscles) causes microtrauma in muscles with vigorous, strenuous, or excessive exercise. The resulting postexertional muscle pain or discomfort aggravates the abnormal pain filter experienced by this population. All causes of increased pain should be minimized, reduced, or eliminated.¹⁶

Poor compliance is common when the use of muscle relaxants, sedatives, or other medications reduce desire or drive to exercise. Symptoms of pain and fatigue increase during exercise, resulting in limited compliance and limited long-term benefits. The therapist can explain that

pain may result in part from muscle spasm and reduced blood flow to muscles, both of which can be aided by persistence in managing exercise.

Using training intensity as a measure of improvement may be helpful. Before performing the physical activity or exercise, compute the maximum heart rate ($MHR = 220 - \text{age}$). During the activity/exercise, take the pulse and record this for later calculations.

Once the activity/exercise is completed, compute the intensity of work: $I_w = \text{Pulse}/MHR$. Multiply I_w by the number of minutes exercised to determine the Training Index (TI) [$TI = I_w \times \text{number of minutes}$]. Keep track of the TI for each activity/exercise session and total them up for 1 week. Track this value over time to assess improved outcomes.⁵¹

People with fibromyalgia are also more vulnerable to overuse syndromes than people with normal muscle histology, requiring a slower, longer rehabilitation process. This may not be activity-induced as once thought, but rather may occur as a result of sarcolemmal abnormality.¹²² At present, until more is known and understood about this phenomenon, whenever possible, an aerobic exercise routine should become a part of the client's life before individual muscle group strengthening is started.

Additionally, TrPs, a separate entity from tender points, must be detected and eliminated before initiating exercise using those muscles. Specific assessment and intervention for TrP therapy is available,^{43,105,235} but it should be noted that TrPs are treatment resistant in some individuals with inadequate thyroid hormone at the cellular level. For these individuals, treatment of the underlying hypothyroidism and/or thyroid resistance is essential first.¹⁵⁶

Other resources include the Fibromyalgia Network Newsletter; P.O. Box 31750; Tucson, AZ 85751 (<http://www.fmnetnews.com>) and the American Fibromyalgia Syndrome Association; P.O. Box 9699; Bakersfield, CA 93389 (<http://www.afsafund.org>).

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