

**Box 5-1****CONDITIONS THAT AFFECT MULTIPLE SYSTEMS**

- Autoimmune disorders
- Burns
- Cancer
- Cystic fibrosis
- Congestive heart failure (CHF)
- Connective tissue diseases:
  - Rheumatoid arthritis
  - Progressive systemic sclerosis (scleroderma)
  - Polymyositis
  - Sjögren's syndrome
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
- Endocrine disorders (e.g., diabetes, thyroid disorders)
- Environmental and occupational diseases
- Genetic diseases
- Infections (e.g., tuberculosis, human immunodeficiency virus [HIV])
- Malnutrition or other nutritional imbalance
- Metabolic disorders
- Multiple organ dysfunction syndrome (MODS)
- Renal failure (chronic)
- Sarcoidosis
- Shock
- Trauma
- Vasculitis

The associated fibrosis may cause progressive tissue damage and loss of function. Systemic effects of chronic inflammation may include low-grade fever, malaise, weight loss, anemia, fatigue, leukocytosis, and lymphocytosis (caused by viral infection).<sup>31</sup> Inflammation is reflected by an increased erythrocyte sedimentation rate (ESR). In general, as the disease improves, the ESR decreases.

### Systemic Factors Influencing Healing

In addition to local factors that affect healing (e.g., infection, blood supply, extent of necrosis, presence of foreign bodies, protection from further trauma or movement), a variety of systemic factors influence healing as well (see Box 6-4). Systemic factors may include general nutritional status, especially protein and vitamin C; psychologic well-being; presence of cardiovascular disease, cancer, hematologic disorders (e.g., neutropenia), systemic infections, and diabetes mellitus; and whether the person is undergoing corticosteroid or immunosuppressive therapy.<sup>99</sup>

Healing in specific organs varies according to the underlying cause and site of the injury. For example, myocardial infarctions heal by scarring, and the heart may be weakened. A cerebrovascular accident (CVA), or stroke, may cause permanent disability, and healing occurs by the formation of glial tissue (e.g., astrocytes, oligodendrocytes, and microglia) rather than by collagenous scar formation; this process is called *gliosis*.

In other organs, effective tissue regeneration depends primarily on the site of injury. Necrosis of only parenchy-

mal (functional visceral) cells with retention of the existing stroma (framework or structural tissue) may permit regeneration and restoration of normal anatomy, whereas necrosis that involves the mesenchymal framework (connective tissue, including blood and blood vessels) usually results in scar formation (e.g., as in hepatic cirrhosis). For further discussion, see Chapter 6.

### Consequences of Immunodeficiency

Immunodeficiency diseases are caused by congenital (primary) or acquired (secondary) failure of one or more functions of the immune system, predisposing the affected individual to infections that a noncompromised immune system could resist. The therapist is more likely to encounter individuals with acquired (rather than congenital) immunodeficiency from nonspecific causes, such as those that occur with viral and other infections; malnutrition; alcoholism; aging; autoimmune diseases; diabetes mellitus; cancer, particularly myeloma, lymphoma, and leukemia; chronic diseases; steroid therapy; cancer chemotherapy; and radiation therapy.<sup>52</sup>

Predisposition to opportunistic infections, resulting in clinical manifestations of those infections, is the primary consequence of immunodeficiency. Selective B-cell deficiencies predispose an individual to bacterial infections. T-cell deficiencies predispose to viral and fungal infections. Combined deficiencies, including acquired immunodeficiency syndrome (AIDS), are particularly severe because they predispose to many kinds of viral, bacterial, and fungal infections.

### Systemic Effects of Neoplasm

Malignant tumors, by their destructive nature of uncontrolled cell proliferation and spread, produce many local and systemic effects. Locally, the rapid growth of the tumor encroaches on healthy tissue, causing destruction, necrosis, ulceration, compression, obstruction, and hemorrhage.

Pain may or may not occur, depending on how close tumor cells, swelling, or hemorrhage occur to the nerve cells. This process also occurs locally at metastatic sites. Pain may occur as a late symptom as a result of infiltration, compression, or destruction of nerve tissue. Secondary infections often occur as a result of the host's decreased immunity and can lead to death.<sup>187</sup>

The person with a malignant neoplasm often presents with systemic symptoms such as gradual or rapid weight loss, muscular weakness, anorexia, anemia, and coagulation disorders (granulocyte and platelet abnormalities). Continued spread of the cancer may lead to bone erosion or liver, gastrointestinal (GI), pulmonary, or vascular obstruction. Other vital organs may be affected; increased intracranial pressure in the brain by tumor cells can cause partial paralysis and eventual coma. Hemorrhage caused by direct invasion or necrosis in any body part leads to further anemia or even death if the necrosis is severe.

Advanced cancers produce cachexia (wasting) as a result of tissue destruction and the body's nutrients being used by the malignant cells for further growth. Multiple mechanisms may be involved in this process, including

release of cytokines such as tumor necrosis factor (also called *cachectin*).

Paraneoplastic syndromes (see Chapter 9) are produced by hormonal mechanisms rather than by direct tumor invasion. For example, hypercalcemia can be caused in cases of lung cancer by the secretion of a peptide with parathyroid hormone, and polycythemia can be caused by the secretion of erythropoietin by renal cell carcinoma. Neuromuscular disorders, such as Eaton-Lambert syndrome, polymyositis/dermatomyositis, and hypertrophic pulmonary osteoarthropathy, are other examples of paraneoplastic syndromes that can occur as a systemic effect of neoplasm (see Tables 9-4 and 9-5).

### SPECIAL IMPLICATIONS FOR THE THERAPIST 5-1

#### **Systemic Effects of Pathology<sup>36,37</sup>**

Medical advances, the aging of America, the increasing number of people with multisystem problems, and the expanding scope of the therapist's practice require that the therapist anticipate, assess, and manage the manifestations of disease and pathology. Physical and occupational therapists are primary health care professionals who focus on maximizing functional capacity and physical independence by optimizing healthy active lifestyles and community-based living.

Interventions to maximize oxygen transport (e.g., mobilization, positioning, breathing control, and exercise) should be an important focus even in people who are acutely and critically ill. Enhancing oxygen transport centrally and peripherally improves the body's ability to respond to stress. At the same time, many therapy interventions elicit an exercise stimulus that stresses an already strained oxygen transport system. Exercise is now recognized as a prescriptive intervention in pathology that has indications, contraindications, and side effects. These factors necessitate careful and close monitoring of cardiopulmonary status, especially in the person with multisystem involvement.

Hematologic abnormalities require that the results of the client's blood analysis and clotting factors be monitored so that therapy intervention can be modified to minimize risks. Individualized treatment programs are developed for each person addressing the special needs of that client and the family, responding to physical, psychologic, emotional, and spiritual needs. The reader is encouraged to review an excellent article<sup>36</sup> for an additional in-depth discussion of specific implications for physical therapy management in systemic disease.

## **ADVERSE DRUG REACTIONS**

Drugs were once developed through a hit or miss process in which researchers would identify a compound and test it in cells and animals to determine its effect on disease. When a compound appeared to be successful, it was often tested in humans with little knowledge of how it worked

or what side effects it might have. Today, biochemists know much more about disease processes and work at the molecular level designing drugs to interact with specific molecules. Disease-modifying antirheumatic drugs (DMARDs), selective estrogen receptor modulators (SERMs), and cyclooxygenase enzyme 2 (COX-2) inhibitors are examples of such "designer drugs."

Drugs in the future will have greater molecular specificity, possibly with the ability to accommodate for gender, age, and genetic differences between individuals. Despite these advances, adverse drug reactions still remain a significant problem in the health care industry today.

#### **Definition and Overview**

*Adverse drug reactions* (ADRs) are defined as unwanted and potentially harmful effect(s) produced by medications or prescription drugs. The term usually excludes nontherapeutic overdosage such as accidental exposure or attempted suicide. *Side effects* are usually defined as predictable pharmacologic effects that occur within therapeutic dose ranges and are undesirable in the given therapeutic situation. Overdosage toxicity is the predictable toxic effect that occurs with dosages in excess of the therapeutic range for a particular person.<sup>59</sup>

ADRs are classified as *mild* (no antidote, therapy, or prolongation of hospitalization necessary), *moderate* (change in drug therapy required, although not necessarily a cessation of therapy; may prolong hospitalization or require special treatment), *severe* (potentially life-threatening, requires discontinuation of the drug and specific treatment of the adverse reaction), and *lethal* (directly or indirectly leads to the death of the person).

#### **Incidence**

Although it is recognized that ADRs are not uncommon, the exact incidence among ambulatory or outpatient clients remains undetermined. According to one study of primary care (outpatients) ADRs were common (25%) and often preventable.<sup>71</sup> The Centers for Disease Control and Prevention (CDC) report inappropriate medications are prescribed to older adults in about 1 out of every 12 visits (8%).<sup>76</sup>

Specific studies have been conducted to determine the rate of ADR-related admissions to hospitals, medication-dispensing errors in hospital pharmacies<sup>28</sup> and outpatient chemotherapy clinics,<sup>70</sup> and the rate of ADRs associated with immunizations.<sup>90</sup> Medication changes are also common during transfer between hospital and nursing home and are a cause of adverse drug events. Most changes are discontinuations, dose changes, and class substitutions.<sup>20</sup>

The Institute of Medicine reports that at least 7000 ADR deaths occur annually in the United States and account for 2% to 3% of hospitalizations. This most likely underestimates the actual number, and efforts are being made throughout the medical system to improve reporting and monitoring complications from drug reactions.

#### **Etiologic and Risk Factors**

Definite risk factors for experiencing a serious ADR can include age (over age 75, younger for some pharmaceu-

ticals), gender, ethnicity (occurring most often in older adult white women), concomitant alcohol consumption, new drugs, number of drugs, dosages, concomitant use of herbal compounds,<sup>34</sup> duration of treatment, non-compliance (e.g., unintentional repeated dosage), small stature, and presence of underlying conditions (e.g., hepatic or renal insufficiency).<sup>26,29,130</sup>

Of all the risk factors, age has the most prevalent effect in the aging American population. A number of factors that affect the distribution of drugs are altered by age. A decrease in lean body mass and an increase in the proportion of body fat result in a decrease in body water. As a result, water-soluble drugs (e.g., morphine) have a lower volume of distribution that speeds up onset of action and raises peak concentration. High peak concentrations are associated with increased toxicity.

On the other hand, lipid-soluble drugs are distributed more widely, have a delayed onset of action, and accumulate with repeated dosing. Aging adults are also at risk for drug accumulation because of changes in both metabolism and elimination. With advanced age, functional liver tissue diminishes and hepatic blood flow decreases. Consequently, the capacity of the liver to break down and convert drugs and their metabolites declines. This may be exacerbated by other changes such as age-related reduction in renal mass and blood flow, the accompanying decline in glomerular filtration and tubular reabsorption rates, and other conditions such as dehydration, cancer, heart failure, and cirrhosis.

Additionally, drugs commonly prescribed for older clients, such as the calcium-channel blockers verapamil and diltiazem and the antigout drug allopurinol, further slow drug metabolism, potentially contributing to toxicity and adverse drug reactions. The drugs most commonly associated with ADRs in the aging are listed in Box 5-2. Halothane (anesthesia)-induced hepatic necrosis and anaphylactic reaction to penicillin are among the most common fatal reactions. The risk of fatal reaction is increased in older adults taking multiple drugs.

ADRs may be dose-related (predictable drug injury) or non-dose-related (unpredictable or idiosyncratic drug injury). Dose-related effects may include drug toxicity from overdose, variations in pharmaceutical preparations, preexisting liver disease, presence of comorbidities such as renal or heart failure, or drug interactions. Non-dose-related effects may occur as a result of hypersensitivity, resulting in acute anaphylaxis or delayed hypersensitivity or other nonimmunologic idiosyncratic reactions, according to individual susceptibility.

Cardiac or pulmonary toxicity may occur as a result of irradiation and immunosuppressive drugs given to prepare recipients for organ transplantation or for treatment of cancer. Some of the more common specific target organs and effects are listed in Box 5-3.

### Clinical Manifestations

Rashes, fever, and jaundice are common signs of drug toxicity. Adverse skin (cutaneous) reactions include erythema, discoloration, itching, burning, urticaria, eczema, acne, alopecia, blisters, or purpura (Fig. 5-1). Onset may be within minutes to hours to days. Other signs and symptoms range from altered taste, anxiety, dizziness,

### Box 5-2

#### DRUGS THAT MOST COMMONLY CAUSE ADVERSE DRUG REACTIONS IN THE AGING

- Corticosteroids
- Digoxin
- Aminoglycoside antibiotic
- Anticoagulants (heparin and warfarin)
- Insulin overdose
- Aspirin
- Tranquilizers (phenothiazines)
- Sedative-hypnotics
- Antacids
- Oral hypoglycemics



**Figure 5-1**

Purpura. Hemorrhaging into the tissues, particularly beneath the skin or mucous membranes, producing raised or flat ecchymoses or petechiae. Seen most often in a physical therapy practice as a result of thrombocytopenia (e.g., drug-reaction or medication-induced, especially NSAIDs, methotrexate, Coumadin or warfarin; radiation- or chemotherapy-induced); also occurs in older adults as blood leaks from capillaries in response to minor trauma. (From Hurwitz S: *Clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 2, Philadelphia, 1993, Saunders.)

headache, nasal congestion, shakiness, and brief vomiting (mild reaction) to abdominal cramps, dyspnea, hypertension or hypotension, palpitations, tachycardia, and persistent vomiting (moderate reaction) to arrhythmia, seizures, laryngeal edema, profound hypotension, pulmonary edema, and cardiopulmonary arrest (severe reaction). Arthralgias and myalgias can be part of the mild or moderate reactions.

Older adults may develop ADRs that are clearly different from those seen in younger persons (Box 5-4).<sup>138</sup> The therapist may observe motor tics called *tardive dyskinesia*,

**Box 5-3****TARGET ORGANS AND EFFECTS OF ADVERSE DRUG REACTIONS****Heart**

- Arrhythmia
- Cardiomyopathy
  - Adriamycin
- Myocardial infarction
  - Oral contraceptives
- Orthostatic hypotension

**Lung**

- Alveolitis and interstitial fibrosis
  - Nitrofurantoin
  - Busulfan
  - Bleomycin
- Asthma
  - Aspirin
  - Propranolol
- Pneumonia
  - Corticosteroids
  - Immunosuppressants (see Table 5-3)

**Gastrointestinal Tract**

- Gingival hyperplasia
  - Phenytoin (Dilantin)
- Gastritis and peptic ulcer
  - Steroids
  - Aspirin
  - Other NSAIDs
- Pseudomembranous colitis
  - Broad-spectrum antibiotics

**Liver**

- Fatty change
  - Corticosteroids
  - Tetracycline
  - Aspirin (pediatrics: Reye's syndrome)
- Cholestatic jaundice
  - Phenothiazines
  - Anabolic-androgenic steroids
- Hepatitis
  - Halothane
  - Isoniazid
- Massive necrosis
  - Halothane
  - Acetaminophen (overdose)
- Adenoma
  - Oral contraceptives

**Fetal Injury**

- Phocomelia
  - Thalidomide
- Vaginal carcinoma
  - Diethylstilbestrol
- Discoloration of teeth
  - Tetracycline
- Multiple congenital anomalies
  - Antineoplastic agents
  - Phenytoin
  - Sodium warfarin

**Kidneys**

- Acute interstitial nephritis
  - Methicillin

- Other antibiotics
- Contrast dye for imaging studies
- Acute tubular necrosis
  - Gentamicin
  - Amphotericin B
- Chronic interstitial nephritis and papillary necrosis
  - Phenacetin
  - Acetaminophen
  - Aspirin, other NSAIDs

**Endocrine System**

- Adrenocortical atrophy
  - Corticosteroids

**Skeletal System**

- Osteoporosis, avascular necrosis
  - Corticosteroids

**Nervous System**

- Central
  - Intracranial hemorrhage
  - Warfarin; heparin; Lovenox (enoxaparin)
  - Cerebral infarction
  - Oral contraceptives
- Pseudodementia
  - Benzodiazepines
  - Narcotics

**Peripheral**

- Neuropathy
  - Vinblastine, vincristine (antineoplastic agents)

**Blood and Bone Marrow**

- Anemias
  - Penicillins
  - Cephalosporins
  - Methyldopa
  - Antimalarial drugs
  - Sulfonamides
  - Nitrofurantoin
  - Methotrexate
  - Phenytoin
  - Antineoplastic agents
- Thrombocytopenia (see Box 14-8)
- Deep vein thrombosis
  - Tamoxifen
  - Raloxifene
  - Estrogen
  - Megace

**Skin**

- Urticaria
  - Penicillins
  - Contrast dye for imaging studies
- Erythema nodosum
  - Sulfonamides
  - Oral contraceptives

**Ears, Nose, and Throat (ENT)**

- Deafness
  - Aminoglycosides (gentamicin)

**Eyes**

- Asthma induced by  $\beta$ -blockers used for glaucoma

NSAIDs, Nonsteroidal antiinflammatory drugs.

**Box 5-4****COMMON SIGNS AND SYMPTOMS OF ADVERSE DRUG REACTIONS IN THE AGING**

- Dry mouth (xerostomia)
- Restlessness
- Orthostatic hypotension (dizziness, weakness, decreased blood pressure, falls)
- Depression
- Confusion, delirium
- Impaired memory or concentration
- Nausea
- Constipation
- Incontinence
- Extrapyramidal syndromes (e.g., parkinsonism, tardive dyskinesia)
- Fatigue

which is a neurologic syndrome caused by the long-term use of neuroleptic drugs. Neuroleptic drugs are usually prescribed for psychiatric disorders but may be used for some GI and neurologic disorders. Tardive dyskinesia is characterized by repetitive, involuntary, purposeless movements. The client may demonstrate repetitive grimacing, tongue protrusion, lip smacking, puckering and pursing, and rapid eye blinking. Rapid movements of the arms, legs, and trunk may also occur. Involuntary movements of the fingers may give the person the appearance of playing an invisible guitar or piano.

Early symptoms of salicylate intoxication include tinnitus, disequilibrium, drowsiness, and a moderate delirium.<sup>130</sup> Digitalis toxicity is a life-threatening condition that may present with systemic (nausea, vomiting) or cardiac manifestations (see Table 12-5 and the section on Chemotherapy in this chapter).

### MEDICAL MANAGEMENT

Differentiating an ADR from underlying disease requires a thorough history, especially when a symptom appears 1 to 2 months after a medication regimen has been started. Monitoring blood cell counts, liver enzymes, electrolytes, blood urea nitrogen (BUN), and creatinine is indicated for certain drugs. Digoxin and other cardio-tropic drugs cause arrhythmias that require electrocardiogram (ECG) monitoring. With dose-related ADRs, dose modification is usually all that is required, whereas with non-dose-related ADRs, the drug therapy is usually stopped and reexposure avoided.

### SPECIAL IMPLICATIONS FOR THE THERAPIST

#### 5-2

##### **Adverse Drug Reactions**

Many people treated by physical therapists today have a pharmacologic profile. It is not unusual to find out during the client interview that the person is taking many different prescription or over-the-counter (OTC) medications. Often there is an equally long list of nutritional aids, supplements, herbs, or vitamins, sometimes referred to as nutraceuticals. Older adults

(aged 65 years or older) commonly have complicated medication regimens that may result in adverse drug events. Age-related physiologic changes result in altered pharmacokinetic and pharmacodynamic response to medications that contribute to adverse responses.<sup>68</sup>

Knowing when a person is having an ADR to medication or supplements versus experiencing symptoms of disease or illness is not always easily distinguished. Knowing about potential drug effects and using a drug guide to look up potential side effects is a good place to start.

Client/patient education is important. The therapist can remind his or her clients to take their medication as prescribed and to report any unusual signs and symptoms to their doctor, physician's assistant, or nurse practitioner. Encourage your clients to keep follow-up appointments with the health care professional who prescribed the drug and to make sure that person knows all drugs and supplements currently being taken.

If the therapist suspects drug- or nutraceutical-related signs or symptoms, several observations can be made and reported to the physician such as correlation between the time medication is taken and length of time before signs and symptoms appear (or increase). Additionally, family members can be asked to observe whether the signs or symptoms increase after each dosage. Documentation of observed or reported behavior or signs and symptoms and the date first observed is important. Make note of the client's clinical condition and your interventions. Follow your facility's policies for notification of suspected ADR.

Interpretation of drug-related or disease-induced signs and symptoms is beyond the scope of a therapist's practice, but the therapist can identify when these clinical manifestations are interfering with rehabilitation and make the necessary referral for evaluation. Any time a client has reached a plateau or has demonstrated poor potential for improvement, the therapist should consider that these responses may be a result of an ADR.

Any signs of tardive dyskinesia should be reported to the physician. There is no standard treatment for tardive dyskinesia. The first step is generally to stop or minimize the use of the neuroleptic drug. This may not be possible for anyone with a severe underlying condition. Replacing the neuroleptic drug with substitute drugs may help some people. Other drugs, such as benzodiazepines, adrenergic antagonists, and dopamine agonists, may also be beneficial.

Symptoms of tardive dyskinesia may continue even after the person has stopped taking the drugs (usually neuroleptics). Some symptoms may improve and/or disappear over time with proper medical management.

##### Exercise and Drugs

Exercise can produce dramatic changes in the way drugs are absorbed, distributed, localized, metabolized, and excreted in the body (pharmacokinetics). The magnitude of these changes is dependent on the

*Continued.*

characteristics of each drug (e.g., route of administration, chemical properties) and exercise-related factors (e.g., exercise intensity, mode, and duration).

A single exercise session can cause sudden changes in pharmacokinetics that may have an immediate impact on people who exercise during therapy. Exercise training can also produce changes in pharmacokinetics, but these tend to occur over a longer period and cause a slower and fairly predictable change in a person's response to certain medications. A detailed description of the effects of exercise, physical agents, and manual techniques on drug bioavailability is available.<sup>27,142</sup>

Drugs that are administered locally by transdermal techniques or by subcutaneous or intramuscular injection may have altered or increased absorption in the presence of exercise, local heat, or massage of the administration site.

In addition, allergic and potentially fatal anaphylactic drug reactions are mediated by exercise. The therapist should always consider the possibility that anyone in therapy taking drugs may have an altered response to those drugs as a result of interventions used in therapy.<sup>155</sup>

## SPECIFIC DRUG CATEGORIES

### Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are a heterogeneous group of drugs that reduce inflammation, provide pain relief, and reduce fever. NSAIDs are commonly used postoperatively for discomfort; for painful musculoskeletal conditions, especially among the older adult population; and in the treatment of inflammatory rheumatic diseases.

These medications may consist of OTC preparations, such as acetylsalicylic acid (ASA) or aspirin; other salicylates; ibuprofen (e.g., Advil, Motrin, Nuprin, Medipren, Rufen), naproxen (Aleve); or prescription drugs (Table 5-1). Because of their extensive clinical uses, NSAIDs are taken by over 13 million Americans.<sup>185</sup>

Although the incidence of serious side effects from using NSAIDs is rather low, the widespread use of readily available OTC NSAIDs results in a substantial number of people being adversely affected. Risk factors associated with increased toxicities include age, higher doses, volume depletion, concurrent use of corticosteroids or anticoagulants, previous history of GI bleed or ulcer, or serious comorbidities.<sup>24,185</sup> The use of NSAIDs is associated with a wide spectrum of potential clinical toxicities (Table 5-2), but serious side effects are most often seen with the GI tract, kidneys, and cardiovascular system.

NSAIDs may cause GI symptoms ranging from mild dyspepsia to more serious complications such as GI bleeding, ulceration, and perforation. These serious side effects may occur without previous symptoms (e.g., dyspepsia) and are particularly more likely to occur in persons taking higher doses, in older adults, and with chronic use.

**Table 5-1 Nonsteroidal Antiinflammatory Drugs\***

Generic Name	Brand Name
<b>Prescription</b>	
celecoxib	Celebrex
diclofenac sodium	Voltaren
diflunisal	Dolobid
etodolac	Lodine
fenoprofen calcium	Nalfon
flurbiprofen	Ansaid
ibuprofen	Motrin (prescription strength)
indomethacin	Indocin
ketoprofen	Orudis, Oruvail
ketorolac tromethamine	Toradol (short-term use only)
meclomenate sodium	Meclomen
mefenamic acid	Ponstel
nabumetone	Relafen
naproxen	Naprosyn, Anaprox, Anaprox DS, EC
oxaprozin	Daypro
phenylbutazone	Butazolidin
piroxicam	Feldene
sulindac	Clinoril
tolmetin sodium	Tolectin
<b>Over-the-Counter (OTC)</b>	
aspirin	Anacin, Ascriptin†, Bayer†, Bufferin†, Ecotrin†, Excedrin†
ibuprofen	Advil, Motrin, Nuprin, Ibuprofen, various generic store brands
ketoprofen	Actron, Orudis KT
naproxen sodium	Aleve, various generic store brands

Modified from Goodman CC, Snyder TE: *Differential diagnosis in physical therapy*, ed 3, Philadelphia, 2000, WB Saunders.

\*The listing of these drugs does not imply endorsement.

†These all have "extras" in them beside aspirin but are known as aspirin products.

GI toxicity from NSAIDs is a serious problem in the United States, with over 100,000 people hospitalized because of serious complications and over 16,500 deaths each year.<sup>185,156</sup> Medications may be used prophylactically for clients requiring NSAID treatment (e.g., osteoarthritis or rheumatoid arthritis [RA]), such as proton pump inhibitors and misoprostol, which have been shown to reduce the development of symptomatic ulcers. Misoprostol may also reduce the risk for other serious GI complications.<sup>84</sup>

NSAIDs have multiple mechanisms of action, which affect the body both locally and systemically. One of these mechanisms is to inhibit the enzymes COX-1 and -2. COX-1 is involved in synthesizing prostaglandins from arachidonic acid and felt to be a "housekeeping" enzyme. When COX-1 is inhibited, there is a reduction in prostaglandins, resulting in a decrease of the protective mucosal barrier of the GI tract.

COX-2 is thought to be produced during states of inflammation. For this reason, NSAIDs were created that selectively inhibit COX-2 but not COX-1 (Vioxx, Celebrex, and Bextra), with the hope of reducing GI side effects. Yet further scrutiny and clinical trials<sup>19,21</sup> noted

**Table 5-2** Possible Systemic Effects of Nonsteroidal Antiinflammatory Drugs

<b>Site</b>	<b>Sign/Symptom</b>
Gastrointestinal	Indigestion, abdominal pain Gastroesophageal reflux Peptic ulcers GI hemorrhage and perforation Nausea, vomiting, diarrhea, constipation
Hepatic	Jaundice Transaminase elevation
Renal	Edema (exacerbation of CHF) Hypertension (particularly in clients with hypertension) Hyperkalemia Renal insufficiency <ul style="list-style-type: none"> <li>• Papillary necrosis</li> <li>• Nephrotic syndrome</li> <li>• Interstitial nephritis</li> </ul>
Hematologic	Renal dysgenesis (infants of mothers given NSAIDs during third trimester) Thrombocytopenia—ASA-related anemia
Cardiovascular	Prolonged bleeding time Blunt action of cardiovascular drugs (e.g., diuretics, ACE inhibitors, $\beta$ -blockers) Increase in blood pressure CHF (for those on diuretics or otherwise volume depleted)
Musculoskeletal	Suppression of cartilage repair and synthesis
Cutaneous	Skin reactions and rashes Pruritus Urticaria (hives), angioedema Sweating
Respiratory	Bronchospasm—ASA-sensitive asthma Rhinitis
Central nervous system	Headache Dizziness, lightheadedness Drowsiness Aseptic meningitis—rarely seen with ibuprofen therapy Tinnitus
Ophthalmologic	Confusion (elderly treated with ASA, indomethacin, ibuprofen) Blurred vision, decreased acuity Scotomata
Other	Anaphylaxis

GI, Gastrointestinal; CHF, congestive heart failure; NSAIDs, nonsteroidal antiinflammatory drugs; ASA, aspirin; ACE, angiotensin-converting enzyme.

that users of Vioxx exhibited an increase in myocardial infarctions and stroke.

In September 2004, Vioxx and subsequently Bextra were removed from the market. Celebrex remains on the market with a black-box warning, although questions continue as to whether this increase in cardiovascular events is a class-wide problem.<sup>107,157</sup> Although COX-2 inhibitors were initially designed to reduce GI bleeding, studies did not show this in people taking Celebrex long-term<sup>113</sup> and GI bleeding was significantly reduced but remained present with Vioxx.<sup>15</sup> COX-2 inhibitors may effectively reduce inflammation, yet they do not inhibit thromboxane, a prothrombotic enzyme, leading to continued platelet aggregation and serious cardiovascular complications.

In the kidney, COX-dependent prostaglandins are also involved with renin release, sodium excretion, and maintenance of renal blood flow, especially during times of volume contraction. To varying degrees, all NSAIDs can cause sodium retention and edema in susceptible people.

Inhibition of COX enzymes leads to hyperkalemia, because of the suppression of the renin-aldosterone system; sodium retention, with resulting edema; and decreased glomerular filtration rate (GFR), resulting in edema, hypertension, and rarely acute renal insufficiency.<sup>23,24</sup>

NSAIDs are also known to interact with hypertension medications, particularly angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -blockers, thereby modestly increasing blood pressure in persons with hypertension.<sup>135</sup> Papillary necrosis, nephritic syndrome, and interstitial nephritis infrequently occur as a result of NSAID treatment. Nephrotoxicity occurs especially in older clients with volume depletion, congestive heart failure (CHF), or underlying renal disorders. Careful monitoring is required of older adults taking NSAIDs in both the short- and long-term.<sup>126</sup>

NSAIDs are reversible platelet inhibitors resulting in antiplatelet activity. Aspirin is the most powerful agent because it irreversibly binds to platelets. A single dose of aspirin impairs clot formation for 5 to 7 days, and two

aspirin can double bleeding time. These characteristics of ASA also make it an important drug in the treatment of coronary artery disease, myocardial infarctions, and stroke.

### SPECIAL IMPLICATIONS FOR THE THERAPIST 5-3

#### **Nonsteroidal Antiinflammatory Drugs**

The therapist is advised to observe for any side effects or adverse reactions to NSAIDs especially among older adults; those taking high doses of NSAIDs for long periods (e.g., for RA); those with peptic ulcers, renal or hepatic disease, CHF, or hypertension; and those treated with anticoagulants. NSAIDs have antiplatelet effects that can be synergistic with the anticoagulant effects of drugs such as warfarin (Coumadin). Easy bruising and bleeding under the skin may be early signs of hemorrhage.

Ulcer presentation without pain occurs more often in older adults and in those taking NSAIDs. Often, people who take prescription NSAIDs also take Advil or aspirin. Combining these medications or combining these medications with drinking alcohol increases the risk for development of peptic ulcer disease.<sup>130</sup> Any client with GI symptoms should report these to the physician.

Musculoskeletal symptoms may recur after discontinuing NSAIDs because of the pain-relieving effects of antiinflammatory agents and the fact that they do not prevent tissue injury or affect the underlying disease process.<sup>110</sup>

Depending on the therapy intervention planned, the therapist may schedule the client according to the timing of the medication dosage. For example, with a chronic condition such as adhesive capsulitis, the goal may be to increase joint accessory motion, which requires more vigorous joint mobilization techniques. Relieving local painful symptoms may help the client remain relaxed during mobilization procedures.

When pain can be predicted (i.e., pain is brought on by treatment intervention), the drug's peak effect should be timed to coincide with the painful event. For nonopioids, such as NSAIDs, the peak effect occurs approximately 2 hours after oral administration. However, in a condition such as shoulder impingement syndrome, teaching the client proper positioning and functional movement to avoid painful impingement may require treatment without the maximal benefit of medication. The therapy session could be scheduled for a time just before the next scheduled dosage.

NSAIDs produce modest increases in blood pressure, averaging 5 mm Hg, and should be avoided in people with borderline blood pressures or who are hypertensive.<sup>135</sup> All NSAIDs are renal vasoconstrictors with the potential of increasing blood pressure, resulting in increased fluid retention, especially lower-extremity edema. NSAIDs also reduce the anti-hypertensive effects of  $\beta$ -blockers and ACE inhibitors and should generally be avoided in people receiving

these cardiac medications. Interaction between most NSAIDs and loop and thiazide diuretics reduces the effects of the diuretic and may lead to a worsening of CHF in a person predisposed to this condition.

It is important to check blood pressure the first few weeks of therapy and to periodically check thereafter to identify any adverse blood pressure response to the combination of NSAIDs, antihypertensive agents, and increased activity. In addition, NSAIDs may increase serum potassium and lithium levels. Indomethacin may increase the plasma concentration of digoxin, requiring close monitoring of digoxin levels.

#### **Immunosuppressive Agents**

Immunosuppressive agents are used traditionally and most frequently in organ and bone marrow transplantation. These medications have also been found to be helpful in treating a few other diseases, but because of their significant toxicities are only indicated for serious, debilitating, and nonresponding disease (e.g., RA and psoriasis) that have not responded to any other medication).

Immunosuppressive agents fall into five classes and have various mechanisms of action. The five main types of immunosuppressives include drugs that bind to small molecules (DNA or proteins in the cells), glucocorticoids, protein drugs, fusion proteins, and intravenous (IV) immune globulins.<sup>80</sup>

Cyclosporin (CSA), tacrolimus, and azathioprine are examples of small-molecule drugs. CSA and tacrolimus inhibit calcineurin, thereby inhibiting T-cell activation. Azathioprine interferes with deoxyribonucleic acid (DNA) synthesis. Newer small-molecule drugs include mycophenolate mofetil (MMF) and sirolimus (and everolimus, which is a derivative of sirolimus), which inhibit T- and B-cell proliferation and interfere with cytokine-driven T-cell proliferation, respectively.

Polyclonal antithymocyte globulin (Thymoglobulin) and muromonab-CD3 (Orthoclone OKT3) are targeted antibodies (protein drugs), which deplete or profoundly reduce lymphocytes ("depleting antibodies"). Basiliximab (Simulect) and daclizumab (Zenapax) are non-depleting antibodies, which inhibit T-cell activation. Corticosteroids are discussed in the next section.

IV immune globulins (IVIGs) have many uses; one use is for graft-versus-host disease.<sup>13</sup> These medications are often used at different times of transplantation, depending on the medical situation such as induction or aggressive immunosuppression during the first few days after transplant, maintenance, or acute rejection.

Drugs are administered at the lowest possible doses while still maintaining adequate immunosuppression. Individual medical factors often determine the choice of immunosuppressive agent. For example, clients who have hypertension or hyperlipidemia may be given tacrolimus instead of CSA. Usually, intensive immunosuppression is required only during the first few weeks after organ transplantation or during rejection crises. Subsequently, the

**Table 5-3** Major Immunosuppressive Agents and Adverse Effects\*

Agent	Indications for Use	Adverse Effects
Antithymocyte globulin (Thymoglobulin)	Renal transplant	Cytokine release syndrome (fever, chills, and hypotension), serum sickness, leukopenia, thrombocytopenia.
Azathioprine (Imuran, Azasan)	Renal transplant Bone marrow transplant Severe RA	Leukopenia, bone marrow depression, nausea, vomiting, liver toxicity (uncommon).
Basiliximab (Simulect)†	Renal transplant	Hypersensitivity reactions (uncommon) (administered with other agents, including CSA and corticosteroids—did not appear to add to side effects seen with these agents).
Corticosteroids (see Box 5-5)	Various inflammatory conditions Neoplasms Bone marrow, tissue, and organ transplant Autoimmune diseases Renal, cardiac, hepatic transplant Severe RA Severe psoriasis	Hypertension, osteoporosis, elevated glucose, nervousness, impaired wound healing, muscle weakness, cataracts, weight gain, cushingoid state, fluid and electrolyte disturbances, glaucoma.
CSA (Neoral, Sandimmune)		Hepatotoxicity, nephrotoxicity, tremor, hirsutism, hypertension, gum hyperplasia, syndrome similar to hemolytic-uremic syndrome, skin changes, hyperlipidemia, posttransplantation diabetes mellitus.
Daclizumab (Zenapax)‡ Muromonab-CD3 (Orthoclone OKT3)	Renal transplant Renal transplant Cardiac and hepatic transplant (in steroid-resistant acute rejection)	Hypersensitivity reactions. Cytokine-release syndrome (can be life threatening), pulmonary edema, cardiac arrest, seizures, cerebral edema (and other CNS events), acute renal failure.
IVIG	Immunodeficiency Immune thrombocytopenic purpura Inflammatory diseases	Nephrotoxicity, hemolysis, transfusion-associated lung injury, aseptic meningitis syndrome.
MMF (CellCept, Myfortic)	Renal, cardiac, and hepatic transplant	Diarrhea (and other GI disturbances), neutropenia, anemia.
Sirolimus (Rapamune, rapamycin)	Renal transplant	Hyperlipidemia, increases toxicity of CSA and tacrolimus, thrombocytopenia, delayed wound healing, delayed graft function, mouth ulcers, hypertension, interstitial pneumonitis, skin changes.
Tacrolimus (Prograf, FK506)	Hepatic and renal transplant	Hypertension (lower than CSA), hyperlipidemia, skin changes, hirsutism, gum hyperplasia, posttransplantation diabetes mellitus and neurotoxicity (more so than CSA), GI disturbances.

Data from Halloran PF: Immunosuppressive drugs for kidney transplantation. *N Engl J Med* 351 (26):2715-2729, 2004; manufacturer's inserts for health care professionals [Physicians' Desk Reference, 2006].

\*All immunosuppressive agents (except basiliximab and daclizumab) increase the incidence of infection and may increase the potential for malignancies (posttransplant lymphoproliferative disease, skin malignancies).

†Basiliximab and daclizumab are used with CSA (or equivalent) and corticosteroids.

‡RA, Rheumatoid arthritis; CSA, cyclosporine; IVIG, intravenous immune globulins; MMF, mycophenolate mofetil; CNS, central nervous system; GI, gastrointestinal.

immune system accommodates the graft and can be maintained with relatively small doses of immunosuppressive drugs with fewer adverse effects.

Complications of immunosuppressive medications are many and can be serious. Most agents exhibit three effects: the desired immunosuppressive effect, nonimmune toxicities, and adverse effects related to immunosuppression.<sup>30</sup> Nonimmune toxicities vary depending on the drug. Table 5-3 provides a summary of drug-related adverse effects of immunosuppressive agents.

Serious adverse reactions include anaphylactic reactions, renal failure, hepatotoxicity, cytokine-release syn-

drome, and neurotoxicities.<sup>134</sup> Careful drug monitoring is required for CSA and tacrolimus, since toxicities are often dosage dependent. Complete blood counts are needed with azathioprine therapy and lipid monitoring is required for the drug sirolimus.

Adverse effects related to immunosuppression are often the most serious consequences of transplantation. All immunosuppressive agents, except basiliximab and daclizumab, render transplant recipients prone to infection, particularly cytomegalovirus. There is also an increased risk of developing fungal (especially *Candida* species) and bacterial infections. Viruses, such as herpes

simplex virus and varicella zoster, may disseminate or reactivate.

An increase in certain kinds of malignancy occurs with long-term use of immunosuppressants, including lymphoma and other lymphoproliferative malignancies and nonmelanoma skin cancers.<sup>131</sup> Host and graft survival are improving, making infection and cancer more relevant complications. Newer protocols are being developed to reduce the risk for infection and cancer.<sup>80</sup>

CSA and azathioprine may be used in the management of severe, debilitating, active RA. The dosage used to treat RA is much lower than that used to treat transplant clients. Likewise, the side effects are fewer than those associated with doses for transplantation.

## SPECIAL IMPLICATIONS FOR THE THERAPIST 5-4

### **Immunosuppressants**

Careful handwashing is essential before contact with any client who is immunosuppressed. If the therapist has a known infectious or contagious condition, he or she should *not* work with the immunosuppressed client (see Table 8-5). Both client and therapist can wear a mask in the presence of an upper respiratory infection.

Peripheral neuropathies and subsequent functional impairment can be addressed by the therapist while the client waits for resolution of these side effects. Upper extremity splinting (e.g., cock-up splint for the hand) may be appropriate, or an ankle-foot orthosis to prevent falls and assist in continued and safe ambulation may be provided.<sup>22</sup> (See the section on Cancer and Exercise in Chapter 9.)

### Box 5-5

#### COMMONLY PRESCRIBED CORTICOSTEROIDS

- Betamethasone (Celestone; Diprolene [topical])
- Cortisone
- Desoximetasone (Topicort)
- Dexamethasone (Decadron)
- Fludrocortisone (Florinef acetate)
- Fluticasone (Flonase nasal spray)
- Hydrocortisone (Solu-Cortef; Cortef)
- Methylprednisolone (Medrol)
- Prednisolone (Pediapred; Orapred; Prelone)
- Prednisone (Deltasone)
- Triamcinolone (Aristocort [oral and topical]; Azmacort [inhaler])

### **Corticosteroids**

Corticosteroids are naturally occurring hormones produced by the adrenal cortex and gonadal tissue. These hormones are steroid-based with similar chemical structures but quite different physiologic effects. Generally, they are divided into *glucocorticoids* (Cortisol), which mainly affect carbohydrate and protein metabolism; *mineralocorticoids* (aldosterone), which regulate electrolyte and water metabolism; and *androgens* (testosterone), which cause masculinization. Many steroid hormones can be synthesized for clinical use. Box 5-5 contains a list of commonly prescribed synthetic corticosteroids.

Glucocorticoids are used to decrease inflammation in a broad range of local or systemic conditions (Box 5-6), for immunosuppression (see previous section on Immunosuppressive Agents), and as an essential replacement steroid for adrenal insufficiency.

Therapists most often see people who have received prolonged, systemic glucocorticoid therapy in the treatment of cancer, transplantation, autoimmune disorders (e.g., systemic lupus erythematosus), and respiratory diseases (e.g., asthma). Mineralocorticoids are given

for adrenal insufficiency or type IV renal tubular acidosis (RTA), while androgens are given for deficiency states.

Generally, glucocorticoids cause fluid imbalances, and mineralocorticoids cause electrolyte imbalances. However, mineral corticosteroids are used minimally (e.g., for adrenal insufficiency or adrenogenital syndrome). Most adverse effects seen by the clinical therapist will be related to glucocorticosteroids. Adverse effects of anabolic steroids primarily occur in an athletic or sports-training setting.

### **Adverse Effects of Glucocorticoids**

Glucocorticoids are effective antiinflammatory agents. They reduce inflammation by interacting with cell membrane receptors and activating antiinflammatory proteins (not requiring interaction with DNA). They also turn off genes involved with producing inflammatory agents (transrepression), such as cytokines, chemokines, adhesion molecules, and inflammatory enzymes, while turning on genes that produce antiinflammatory proteins (transactivation).<sup>165</sup> But long-term use to sustain the benefits of these drugs is accompanied by an increased risk of side effects and adrenal suppression.<sup>183</sup>

Most illnesses that require glucocorticoids for treatment are used for a limited time along with disease-modifying medications, while long-term use is only necessary for adrenal insufficiency and a few other diseases (e.g., RA and inhaled steroids for asthma).

Glucocorticoids affect many functions of the body, especially in persons taking long-term steroids. Therapists should be familiar with common adverse effects such as change in sleep and mood, GI irritation, hyperglycemia, and fluid retention (Table 5-4); side effects are related to dose and duration of treatment. The most serious side effect of steroid use is increased susceptibility to infection and the masking of inflammatory symptoms from infection or intra-abdominal complications.

Most clients taking glucocorticoids notice a change in mood, behavior, or sleep. Individuals often describe a nervous or "jittery" feeling. Symptoms may range from mild anxiety to confusion or psychosis. Changes are typically noted 5 to 14 days after glucocorticoid therapy

**Box 5-6****THERAPEUTIC USE OF GLUCOCORTICOIDS****Allergy/Immunology**

- Allergy
- Immunosuppression

**Dermatologic**

- Discoid lupus
- Eczema
- Lichen simplex chronicus
- Lichen planus
- Pemphigus

**Endocrine**

- Adrenal insufficiency

**Gastrointestinal**

- Alcoholic hepatitis (controversial)
- Inflammatory bowel disease
  - Crohn's disease
  - Ulcerative colitis

**Nephrology**

- Nephrotic syndrome

**Oncologic**

- Autoimmune anemia/thrombocytopenia in chronic lymphocytic leukemia
- Bowel obstruction (in nonsurgical situations)
- Chemotherapy-induced nausea/vomiting
- Hemolytic anemia
- Immune thrombocytopenic purpura
- Metastatic multiple myeloma
- Spinal cord compression
- Reduce intracranial pressure from brain metastasis

**Pulmonary**

- Acute respiratory distress syndrome
- Asthma
- COPD (exacerbation or severe disease)
- Interstitial lung disease
- Sarcoidosis

**Rheumatologic**

- Ankylosing spondylitis
- Giant cell arteritis
- Henoch-Schönlein purpura
- Inflammatory arthritis
  - Crystal-induced
  - Osteoarthritis
  - Psoriatic
  - Rheumatoid
- Inflammatory myopathies
- Polymyalgia rheumatica
- Steroid-induced myopathy
- Systemic lupus erythematosus

COPD, Chronic obstructive pulmonary disease.

begins; improvement is seen with withdrawal of the medication.

**Effects on Skin and Connective Tissue.** Effects on the skin and connective tissue include thinning of the subcutaneous tissue accompanied by splitting of elastic

**Table 5-4** Possible Adverse Effects of Prolonged Systemic Corticosteroids

System	Symptom
Metabolic	Increased glucose/protein metabolism Stimulates appetite, weight gain Fluid retention/edema Potassium loss (hypokalemia)
Endocrine	Delayed puberty Glucose intolerance; insulin resistance Hirsutism (hair growth) Cushing's syndrome (hypercortisolism) See Figs. 11-6 and 11-7
Cardiovascular	Dyslipidemia Increased blood pressure
Immune	Increased risk of opportunistic infections Activation of latent viruses Masking infection
Musculoskeletal	Increases muscle catabolism (degenerative myopathy, muscle wasting) Retardation of bone growth Tendon rupture Other musculoskeletal injuries Osteoporosis Osteonecrosis, avascular necrosis of femoral head Bone fractures
Gastrointestinal	Peptic ulcer disease Gastrointestinal bleeding, nausea, increased appetite
Nervous	Central nervous system: Change in behavior (insomnia, euphoria, nervousness) Psychosis, depression Changes in cognition, mood, and memory Cerebral atrophy Pseudotumor cerebri Autonomic nervous system: Dysfunction Peripheral nervous system: Peripheral neuropathy
Ophthalmologic	Cataracts, glaucoma
Integument	Acne Striae (stretch marks) Bruising, petechiae Skin atrophy, delayed wound healing Hirsutism

fibers with resultant red or purple striae (stretch marks). Ecchymoses (bruising) and petechiae are caused by decreased vascular strength.<sup>17</sup>

Glucocorticoids alter the response of connective tissue to injury by inhibiting collagen synthesis,<sup>143</sup> which is why these agents are used to suppress manifestations of collagen diseases. Clients who are taking steroids experience delayed wound healing with decreased wound strength, inhibited tissue contraction for wound closure, and impeded epithelialization.

**Steroid-Induced Myopathy.** In high doses, glucocorticoids can cause muscle weakness and atrophy called *steroid-induced myopathy*. Enzymes of gluconeogenesis are activated, leading to the breakdown of muscle protein,

**Table 5-5**

## Functional Classifications of Corticosteroid-Induced Myopathy

Level	Function
Advanced	Person has difficulty climbing stairs.
High	Person cannot rise from a chair.
Intermediate	Person cannot walk without assistance.
Low	Person cannot elevate extremities or move in bed.

Modified from Askari A, Vignos PJ, Moskowitz RVV: Steroid myopathy in connective tissue disease, *Am J Med* 61:485-492, 1976.

resulting in muscle wasting and atrophy severe enough to interfere with daily function and activities. Histologically, there is an increased variation in size and atrophy of muscles fibers, particularly type IIb.<sup>35</sup>

Steroid-induced myopathy is often insidious, appearing as painless weakness weeks to months after the initiation of treatment. There is no special or definitive test to make the diagnosis of myopathy. EMGs are often normal and muscle biopsies are nonspecific.

Clients present with bilateral atrophy and weakness of proximal muscles; the pelvis, hips, and thighs are typically affected first.<sup>98</sup> Upper limb muscles can be affected; occasionally distal limb muscles are involved. The diaphragm may also be involved, which results in difficulty breathing, especially in people with underlying pulmonary disease.

Recovery from chronic myopathy (with cessation of drug) is possible with reduction or discontinuation of the drug but may take from 1 to 4 months up to 1 to 2 years. Prognosis depends on the underlying diagnosis before treatment with corticosteroids (e.g., organ transplantation requiring long-term administration of glucocorticoids). Four functional classifications of muscle weakness can occur in people with steroid-induced myopathy (Table 5-5).

**Effect of Steroids on Growth.** Long-term use of glucocorticoids in children causes apoptosis of the chondrocytes at the epiphyseal plate, leading to growth retardation. Although there is an increase in bone synthesis once the drug is discontinued, full height may not be achieved.<sup>173</sup> In adults, prolonged use of glucocorticoids inhibits bone mineralization, induces apoptosis of osteoblasts, and encourages osteoclastic activity. There is also decreased GI calcium absorption and increased calcium excretion by the kidneys. These combined changes result in osteoporosis.<sup>143</sup> Strategies should be in place before extended therapy of glucocorticoids (greater than 3 months) to avoid bone loss.

Long-term exposure to corticosteroids increases the risk of avascular necrosis, which often requires orthopedic intervention (e.g., total hip replacement). Glucocorticoids are also associated with a fourfold to fivefold increase in the prevalence of vertebral fracture compared with individuals who are not treated with corticosteroids.<sup>145</sup>

These medications promote gluconeogenesis in the liver and lipolysis resulting in hyperglycemia. Individuals

already requiring oral diabetic agents or insulin frequently need an increase in their dosage. Persons at risk for diabetes (e.g., glucose intolerance) may require a diabetic agent. Glucose monitoring is essential.

For clients with asthma, long-term treatment with inhaled glucocorticoids is common. Glucocorticoids decrease inflammation and aid in counteracting the vaso-dilatation caused by  $\beta_2$  agonists. Researchers initially hoped that the inhaled delivery of the glucocorticoids would eliminate or significantly reduce the side effects of the glucocorticoids; but bone loss and other adverse effects remain problematic in people with asthma using inhaled steroids.<sup>91</sup>

Animal studies suggest that glucocorticoids may play a role in the development of diaphragm dysfunction in anyone with pulmonary impairment. Consistent with the previous discussion of glucocorticoids causing muscle weakness and atrophy, these drugs can cause a decrease in the force generation of the diaphragm. Physical therapy intervention may be helpful in counteracting this glucocorticoid-induced muscle dysfunction.<sup>53</sup>

The GI effects of steroids are fewer than NSAIDS, yet they are known to cause gastritis, esophageal irritation, GI bleeding, and less commonly, peptic ulcers. Many clients take both glucocorticoids and NSAIDS, increasing their risk for adverse GI events (e.g., ulcer with perforation). For these individuals, a GI protective agent (e.g., proton pump inhibitor or misoprostol) may be beneficial.

Glucocorticoids are also known to cause cataracts, both cortical and posterior subcapsular. Cataract formation is dependent on dose and duration of use. They typically develop bilaterally but slowly. Clients with a history of glaucoma and taking glucocorticoids long-term may have an increase in pressure while taking glucocorticoids, making pressure checks advisable.

Because glucocorticoids cause adrenal suppression, withdrawal must be slow and tapered to allow for endogenous hormones to be produced by the adrenal cortex. Severe adrenal insufficiency may follow sudden withdrawal of the medication, particularly in the presence of infection or other stress. The person may experience vomiting, orthostatic hypotension, hypoglycemia, restlessness, arthralgia, anorexia, malaise, and fatigue. These symptoms should be reported to the physician.

### Designer Glucocorticoids

As discussed previously, classic glucocorticoids bring about their antiinflammatory function by modulating gene transcription and inhibiting the production of proinflammatory factors (transrepression). Their adverse metabolic, cardiovascular, and behavioral effects, however, are believed to be related to the activation of genes and enzymes (transactivation).

New glucocorticoids are in development that would selectively enhance the antiinflammatory aspects of the drug while selectively activating transcription to decrease or avoid the adverse side effects, although there are many overlapping factors. These glucocorticoids are referred to as selective glucocorticoid receptor agonists (SEGRAs).<sup>17,150</sup> Studies and further trials will ultimately verify the use of these new agents.

### Anabolic-Androgenic Steroids

Anabolic-androgenic steroids (AASs), anabolic steroids, or "roids" are synthetic derivatives of the hormone testosterone. They are most commonly used in a nonmedical setting to develop secondary male characteristics (androgenic function) and to build muscle tissue (anabolic function).<sup>14-16</sup> The use of anabolic steroids to enhance physical performance by athletes has been declared illegal by all national and international athletic committees. Even so, an estimated one million individuals in the United States alone are current or past non-medical users of AASs. Administration of these compounds can be orally, intramuscularly, or by injection.

Recently 500 AAS users who frequented AAS internet sites were questioned about their habits. Ninety-nine percent stated they most frequently injected the steroids and 13% used unsafe needle practices.<sup>128</sup> One survey reports the average age at first-time use is 14 years with a significant number of children (15%) taking an AAS before the age of 10.<sup>160</sup>

Studies indicate that adolescent AAS users are significantly more likely to be males and to use other illicit drugs, alcohol, and tobacco.<sup>8</sup> Previously, more athletes were found to use AASs than nonathletes to enhance their sport.<sup>10</sup> However, questions are being raised as to the percentage who now use AASs for cosmetic reasons alone.<sup>128</sup> The goal is to advance to a more mature body build and enhance the masculine appearance.

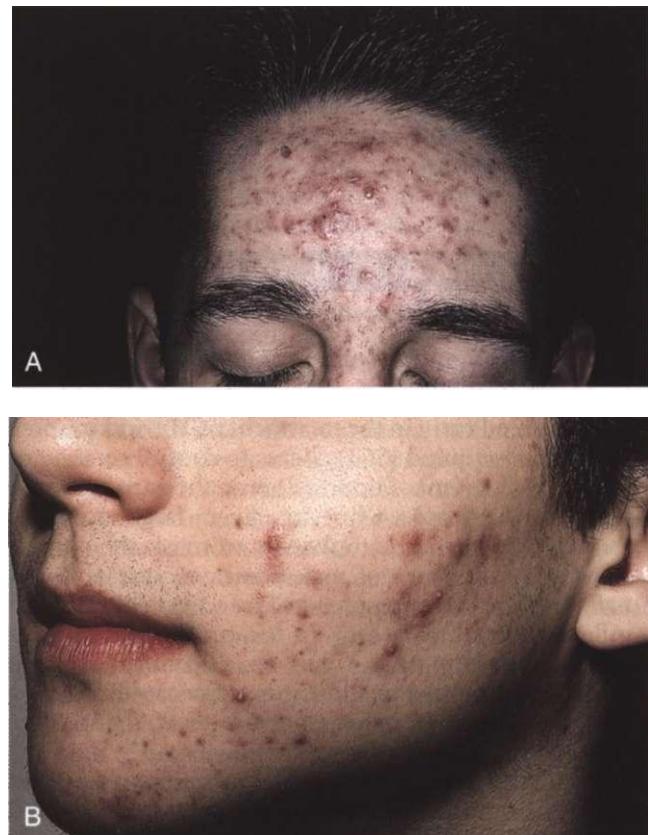
The use of this type of steroid is illegal and potentially unsafe, unless given under the direction of a licensed physician; most of these drugs cannot even be prescribed legally but are still obtained from other athletes, physicians, and coaches.<sup>160</sup>

Athletes tend to take doses that are 10, 100, or even 1000 times larger than the doses prescribed for medical purposes. They cycle the drugs before competition, a technique known as *stacking*, alternately tapering the dosage upward and downward before a competitive event. Human growth hormone has been used alone and in combination with anabolic steroids to further enhance athletic performance.

Nearly all users of AASs report side effects. The most common include an increase in sexual drive, acne vulgaris (Fig. 5-2), increased body hair, and an increase in aggressive behavior. Individuals may also exhibit an increase in low-density lipoproteins and a decrease in high-density lipoproteins, complicating atherosclerosis and coronary artery disease.<sup>81</sup>

Misuse of supraphysiologic doses of AASs for non-medical reasons has been linked with serious side effects such as hypertension, left ventricular hypertrophy, myocardial ischemia, peliosis hepatitis (liver tissue is replaced by hemorrhagic cysts), and sudden and premature death.<sup>148,163</sup>

Users of anabolic steroids may experience an increased susceptibility to tendon strains and injuries, especially biceps and patellar tendons, because muscle size and strength increase at a rate far greater than tendon and connective tissue strength. Adolescent steroid use may lead to accelerated maturation and premature epiphyseal closure.<sup>162</sup>



**Figure 5-2**

**Acne vulgaris on the forehead and lower face associated with the use of anabolic steroids.** It is considered an abnormal response to normal levels of the male hormone testosterone. The face, chest, back, shoulders, and upper arms are especially affected. There are many other causes of this form of acne; its presence does not necessarily mean the individual is using anabolic steroids. (From Callen JP: *Color atlas of dermatology*, ed 2, Philadelphia, 2000, WB Saunders.)

Homicides, suicides, poisonings, and other accidental deaths associated with AAS use have been attributed to impulsive, disinhibited behavior characterized by violent rages, mood swings, and/or uncontrolled drug intake.<sup>133,167</sup> Shared use of multidose vials, dividing drugs using syringes, and increased sexual risk-taking behavior are risk factors associated with AAS use and are potential routes for HIV and hepatitis infection.<sup>106</sup>

There are, however, legitimate medical uses for anabolic steroids that have come about as a result of physiologic evidence that anabolic steroids prevent loss of lean body mass. Oxandrolone, a synthetically derived testosterone, is approved as an adjuvant therapy to promote weight gain after weight loss secondary to chronic infections (HIV wasting), severe trauma (severe burns), and extensive surgery and to relieve bone pain associated with osteoporosis.<sup>42,44,60</sup>

Another anabolic steroid with a practical use is Anadrol. It is indicated for the adjuvant treatment of anemia secondary to a lack of red blood cell (RBC) production such as occurs in acquired and congenital aplastic anemia and myelofibrosis. Because of the side effects and drug interactions, these agents should be used with caution.

Other areas of testosterone use include in premenopausal women with a loss of libido and in aging men to prevent loss in muscle mass and strength.<sup>16,61,75</sup> The adverse effects of these steroids, however, make long-term use inadvisable, particularly in the doses often required for efficacy.

## SPECIAL IMPLICATIONS FOR THE THERAPIST 5-5

### Corticosteroids

#### Inflammation and Infection

In the rehabilitation setting, large doses of steroids are administered early in the treatment of TBI and in some spinal cord-injured (SCI) clients to control cerebral or spinal cord edema. Suppression of the inflammatory reaction in people who are given large doses of steroids may be so complete as to mask the clinical signs and symptoms of major diseases, intraabdominal complications, or spread of infection (blocking of inflammatory mediators). In the orthopedic population, local symptoms of pain or discomfort are also masked, so the therapist must exercise caution during evaluation or treatment to avoid exacerbating the underlying inflammatory process.

Increased susceptibility to the infections associated with impaired cellular immunity and the decreased rate of recovery from infection associated with corticosteroid use requires careful infection control. Special care should be taken to avoid exposing immunosuppressed clients to infection, and everyone in contact with that person should follow strict handwashing policies (see Special Implications for the Therapist: Control of Transmission, in Chapter 8).

Some facilities recommend that people with a white blood cell (WBC) count of less than 1000 mm<sup>3</sup> or a neutrophil count of less than 500 mm<sup>3</sup> wear a protective mask. Therapists should ensure that anyone who is immunosuppressed is provided with equipment that has been disinfected according to standard precautions (see Appendix A).

If back pain occurs in a person who is receiving corticosteroids, diagnostic measures should be undertaken to rule out osteoporosis or compression fracture.

#### Intensive Care Setting

Although clients in the intensive care unit (ICU) are often treated with steroids for various serious illnesses, the use of these medications may increase the risk for complications, such as infection, impaired wound healing, ICU-acquired paresis (ICUAP) or muscle weakness,<sup>40</sup> or death. Individuals who develop ICUAP have been found to require mechanical ventilation for a longer period of time compared to those without ICUAP, supporting clinical observations that clients treated with glucocorticoids often experience difficulty weaning from the ventilator or clearing lung secretions.

Glucocorticoids (methylprednisolone) do not improve persistent acute respiratory distress syndrome

(ARDS), and if begun 2 weeks after the initial episode, may increase the risk for death.<sup>54</sup> Glucocorticoids, however, may be of benefit to clients with chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation.<sup>121</sup> Studies are ongoing to determine the most efficacious use of glucocorticoids in this fragile population.

#### Intraarticular Injections

Occasionally, intraarticular injections of corticosteroids are necessary to control acute pain in a joint that is not responding to oral analgesics, particularly if an effusion is present. Such injections can provide short-term relief and improve the client's mobility and function.<sup>95</sup> The rationale for use in the joint is to suppress the synovitis because no evidence currently indicates that intraarticular injections retard the progression of erosive disease. Intraarticular injections must be carefully selected, and no single joint should have more than three or four injections before other procedures are pursued.<sup>120</sup>

Most steroid injections are accompanied by an anesthetizing agent, such as lidocaine or bupivacaine, which usually provides immediate pain relief, although the antiinflammatory effect may require 2 to 3 days. During this time, the client should be advised to continue using proper supportive positioning and avoid movements that would otherwise aggravate the previous symptoms.

Some controversy remains as to whether the person can bear weight on the joint for several days after the injection; a less conservative approach permits nonstrenuous activity. Vigorous exercise may speed resorption of the steroid from the joint and reduce the intended effect. Intraarticular injection of corticosteroids may also result in pigment changes that are most noticeable among dark-skinned people.

#### Exercise and Steroids

The harmful side effects of glucocorticoids can be delayed or reduced in their severity by physical activity, regular exercise (aerobic or fitness), strength training, and proper nutrition. Unfortunately, these clients are often too sick to engage in exercise at all, much less at a level of intensity that would reverse myopathy. When possible, the therapist can help emphasize the importance of exercise, especially activities that produce significant stress on the weight-bearing joints (e.g., walking; jogging is not usually recommended), to decrease the calcium loss from long bones that is attributable to prolonged steroid use. It is essential to consult with the client's physician before initiating aerobic exercise.

Glucocorticoid-induced changes in body composition in heart transplant recipients occur early after transplantation. However, 6 months of specific exercise training restores fat-free mass to levels greater than before transplantation and dramatically increases skeletal muscle strength. Resistance exercise, as a part of a strategy to prevent steroid-induced myopathy, should be initiated early after transplantation (see Chapter 21).<sup>203</sup>

Strength training or stair exercise is one way to maintain the large muscle groups of the legs, which are most affected by the muscle-wasting properties of corticosteroids. The treatment plan should also include closed-chained exercises to prevent shearing forces across joint lines and to allow for normal joint loading, prevention of vertebral compression fractures, and education about proper body mechanics during functional activities.<sup>164</sup>

Client education on the importance of proper footwear and choice of exercise surfaces is important for the individual receiving long-term corticosteroid therapy. For the person at risk for avascular necrosis of the femoral head, exercising the surrounding joint musculature in a non-weight-bearing position may be required.

### Monitoring Vital Signs

Long-term use of corticosteroids may result in electrolyte imbalances (e.g., hypokalemia, hypocalcemia, metabolic alkalosis, sodium and fluid retention, edema, and hypertension), which necessitates monitoring of vital signs during aerobic activity because of the demand placed on the cardiovascular system in conjunction with these adverse effects. (See the section on Guidelines for Activity and Exercise in Appendix B.)

Many glucocorticoids have mineralocorticoid activity as well. This causes sodium and fluid retention and enhanced angiotensin II activity, leading to hypertension. Careful monitoring of blood pressure should be performed in clients with previously existing high blood pressure, since glucocorticoid administration may require an increase in the dosage of antihypertensives.

Increased fluid retention may also lead to an exacerbation of CHF in susceptible people; monitoring for signs and symptoms of heart failure is important. Clients may develop hypokalemia secondary to potassium loss from the kidneys; individuals with a history of hypokalemia or taking diuretics benefit from monitoring of blood chemistries.

### Steroids, Nutrition, and Stress

People taking steroids may be advised to increase their dietary intake of calcium and vitamin D to counteract the loss of calcium in the urine.<sup>129</sup> Clients may also require a medication to decrease the loss of bone such as a bisphosphonate.<sup>141</sup> Protein intake is recommended for muscle growth to offset steroid-induced catabolism. Individuals may also require potassium supplementation because of increased potassium loss in the urine.

Corticosteroids stimulate gluconeogenesis and interfere with the action of insulin in peripheral cells, which may result in glucose intolerance or diabetes mellitus or may aggravate existing conditions in diabetes. Regular blood glucose monitoring is recommended to detect steroid-induced diabetes mellitus.

Some facilities establish exercise protocols based on blood glucose levels. Exercise is not recommended for people with blood glucose levels greater than

300 mg/dl without ketosis or greater than 250 mg/dl with ketosis.<sup>5</sup>

Clients taking glucocorticoids long-term for Addison's disease or RA may need to increase the required dosage during medically stressful situations, particularly with infections or surgery. Temporary mineralocorticoid dosage increases may also be indicated if the client receiving replacement mineralocorticoid experiences profuse diaphoresis for any reason (strenuous physical exertion, heat spells, or fever).<sup>65</sup> Either of these situations requires physician evaluation.

### Psychologic Considerations

Corticosteroid use can result in a range of mood changes from irritability, euphoria, and nervousness to more serious depression and psychosis. Insomnia is often also a reported problem during corticosteroid therapy. The intensity of changes in mood may depend on the dosage administered, the sensitivity of the individual, and the underlying personality. When intense changes are observed, the physician should be notified so that an adjustment in dosage can be made.

Chronic corticosteroid use may alter a person's body image because of changes in adipose tissue distribution, thinning of skin, and development of stretch marks. The classic characteristics of a cushingoid appearance may develop, including a moon-shaped face; enlargement of the supraclavicular and cervicodorsal fat pads (buffalo hump); and truncal obesity (see Figs. 11-6 to 11-8).

Some people may be extremely self-conscious about these cosmetic changes, and others may be emotionally devastated by them; caution is required in discussing assessment findings with the client. These cosmetic changes do reverse when the drug is discontinued slowly.

The therapist needs to be aware of the affected individual's coping abilities. Treatment intervention can include educating the individual about traditional stress-management techniques. Therapists can facilitate psychosocial support by contacting social work and clinical nurse specialists to integrate programs such as survivorship support groups and image consultants.

### Anabolic Steroids

Therapists working with athletes, especially adolescent athletes, may observe signs and symptoms of (non-medical, illegal) anabolic steroid use, including rapid weight gain (10 to 15 lbs in 3 weeks); elevated blood pressure and associated peripheral edema; acne on the face, upper back, and chest; alterations in body composition, with marked muscular hypertrophy; and disproportionate development of the upper torso along with stretch marks around the back and chest. After prolonged anabolic steroid use, jaundice may develop.

Therapists working with adolescents may see cases of recurrent tendon or muscle strain. Soft tissues working under the strain of added muscle bulk and body mass take longer than expected for physiologic

*Continued.*

healing to occur. Reinjury is not uncommon under these conditions.

Other signs of steroid use include needle marks in the large muscle groups, development of male pattern baldness, and gynecomastia (breast enlargement). Abscesses from injection use may also develop. Among females, secondary male characteristics may develop such as a deeper voice, breast atrophy, and abnormal facial and body hair. Irreversible sterility can occur (females being affected more than males), and menstrual irregularities may develop in women.

Changes in personality may occur; the user may become more aggressive or experience mood swings and psychologic delusions (e.g., believe he or she is indestructible). "Roid rages," sometimes referred to as *steroid psychosis* and characterized by sudden outbursts of uncontrolled emotion, may be observed. Severe depression is one of the signs of withdrawal from steroids. Withdrawal from AASs is a risk factor for suicide.

Despite the side effects of AAS use, steroid users are not readily apparent. The therapist who suspects an athlete may be using anabolic steroids should report findings to the physician and consider approaching that person to discuss the situation. The U.S. Olympic Committee (USOC) provides a toll-free hotline ([800] 233-0393) for questions on steroids, medications, and prohibited substances. The U.S. Antidoping Agency (USADA) also offers an on-line drug reference at <http://www.usantidoping.org>.

Testing for elevated blood pressure may provide an opportunity for evaluation of anabolic steroid use. Information as to the long-term adverse effects of anabolic steroids should be provided as part of the education process for all athletes. The therapist or trainer can provide healthy and safe strength training, stressing the importance of nutrition and proper weight-training techniques.

## RADIATION INJURIES

### Definition and Overview

Radiation therapy, or radiotherapy, is the treatment of disease (usually cancer) by delivery of radiation to a particular area of the body. Radiation therapy is one of the major treatment modalities for cancer used in approximately 60% of all cases of cancer (see Chapter 9). Radiotherapy is used in the local control phase of treatment but has both direct and indirect toxicities associated with its use. Radiation reactions and injuries are the harmful effects (acute, delayed, or chronic) to body tissues of exposure to ionizing radiation.

Today, a pencil-thin beam of radiation can be targeted to deliver extremely high doses of radiation to within a millimeter of a cancer site. Advanced computer technology creates a three-dimensional model of the tumor to allow target mapping. Careful preplanning and delivery of targeted, modulated radiation doses have contributed to a reduced number of radiation side effects.

### Etiologic and Risk Factors

Risk factors for developing radiation toxicities arising from therapeutic radiation are often multifactorial, depending on the organ radiated, individual variations and tolerance, tumor type, volume radiated, and fraction size (Table 5-6).

People may also be exposed to radiation found in the environment, such as radon in their homes, or when rare nuclear events release large amounts of radioactivity, exposing people to total body irradiation (TBI). Bone marrow transplant clients may receive TBI as a preparative regimen.

According to the seventh report on the Biological Effects of Ionizing Radiation (BEIR VII) issued by the National Academy of Science, exposure to even low-dose imaging radiology (including computed tomography [CT] scans) can result in the development of malignancy. Exposure to

**Table 5-6** Factors Contributing to Radiation Toxicity

ENTEROCOLITIS				
Neurotoxicity	Dermatitis	Acute	Chronic	Pulmonary
High total dose	Total dose/volume irradiated	Large volume irradiated	Older age	Older age
High fractionation dose	Fractionation dose	High total dose	Received postoperative radiation	Lower performance status
Large field size	Surface area exposed	High fractionation dose	Presence of collagen vascular disease	Lower baseline pulmonary function
Increased edema		Receiving concurrent chemotherapy	Received concurrent chemotherapy	Large volume treated
Age less than 12 and greater than 60 years			Poor radiation technique	
Concurrent chemotherapy				
Presence of underlying diseases that affect the vasculature (diabetes, hypertension)				
Stereotactic surgery and interstitial brachytherapy				

Data from Cross NE, Glantz MJ: Neurologic complications of radiation therapy, *Neurol Clin* 21 (1):249-277, 2003; Hymes SR, Strom EA, Fife C: Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006, *J Am Acad Dermatol* 54 (1):28-46, 2006; Nguyen NP, Antoine JE: Radiation enteritis. In Feldman M, Friedman LA, Sleisenger MH, editors: *Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management*, ed 7, Philadelphia, 2002, WB Saunders; Machtay M: Pulmonary complications of anticancer treatment. In Abeloff MD, Armitage JO, Niederhuber JE, et al, editors: *Clinical oncology*, ed 3, New York, 2004, Churchill-Livingstone.

medical x-rays is linked with leukemia, thyroid cancer, and breast cancer. There is a 1 in 1000 chance of developing cancer from a single CT scan of the chest, abdomen, or pelvis. The latency period for leukemias is 2 to 5 years and 10 to 30 years for solid tumors.<sup>114</sup>

### Pathogenesis

Radiation therapy uses high-energy ionizing radiation to kill cancer cells. Irradiation is an effective treatment for cancer because it directly destroys hydrogen bonds between DNA strands within cancer cells. This prevents ongoing cellular replication. Although cells in all phases of the cell cycle can be damaged by radiation, cells in G<sub>2</sub> and M phases (see Fig. 9-3) have the greatest sensitivity to radiation, making rapidly dividing cells most likely to be damaged.

Ionizing radiation interacts with nuclear DNA directly or indirectly to inhibit replicating capacity, resulting in apoptosis (programmed cellular death) or cellular necrosis. The radiation causes the breakage of one or both strands of the DNA molecule inside the cells, thereby preventing their ability to grow and divide.

Ionizing radiation also causes the production of free radicals (see discussion of free radicals Chapter 6), which leads to membrane damage and breakdown of structural and enzymatic proteins, resulting in cell death. Often arterioles supplying oxygenated blood are damaged, resulting in inadequate nutritional supply, leading to ischemia and death of the irradiated tissues. The damage to nucleic acids may result in gene mutations, possibly leading to neoplasia years later (see the section on Mechanisms of Cell Injury in Chapter 6).

### Clinical Manifestations and Medical Management

The clinical manifestations of radiation, similar to risk factors associated with radiation therapy, depend on individual variations, location and type of tumor, radiation volume and fraction dose, and organ system involved. Although newer techniques allow for organ shielding and lower volumes and fraction doses, radiation therapy continues to cause symptoms and injuries.

Each organ has its own tolerance to radiation, therefore injuries vary between organ systems. Yet there are some general principles that encompass radiation therapy injuries. Most organ systems exhibit both acute injuries that occur within 30 days of irradiation and delayed injuries that occur more than 30 days later (Table 5-7). Acute injuries are frequently self-limiting, whereas delayed effects are often irreversible and difficult to treat. Acute symptoms may delay further radiation treatments because of damage to GI mucosa, bone marrow, and other vital tissues.

Management of acute injuries is often treated symptomatically with RBCs and platelet transfusions, antibiotics, fluid and electrolyte maintenance, and other supportive medical measures as needed. With prognosis poor in many cases of delayed radiation complications, more effort is being placed on prevention. Clinicians have been attempting to optimize total dose, fractionation size, and total volume being radiated.<sup>55,102</sup>

Modifications are made when chemotherapy is used in conjunction with radiation and prophylactic medications are under investigation to prevent damage or

complications.<sup>86,1140,170,189</sup> Researchers are also developing more targeted therapy, which would increase tumor sensitivity while reducing damage to adjacent, normal tissue.<sup>4</sup>

Because there are unique or specific injuries to different organ systems, the following section specifies clinical manifestations, treatment, and research pertaining to different organ systems.

**Radiation Esophagitis and Enterocolitis.** The esophagus is a centrally located organ in the mediastinum and is often involved in the radiation fields under treatment for lung cancer. An acute reaction may occur within 2 to 3 weeks after the initiation of radiation therapy manifested by abnormal peristalsis activity,odynophagia (pain with swallowing), and dysphagia (difficulty swallowing).

Although uncommon with radiation alone (1.3% for lung cancer), clients are more likely to develop severe esophagitis after the use of a chemosensitizer (14% to 49%),<sup>180</sup> requiring hospitalization for tube feeding, pain control, and hydration. The medication amifostine, presumed to be a free radical scavenger, may be helpful in reducing the frequency and/or severity of esophagitis.<sup>181</sup> Resolution of symptoms typically occurs 1 to 3 weeks after completion of radiotherapy. Late esophagitis is a result of inflammation and fibrosis of tissue, causing stricture and fistula formation. Dilation and surgical repair may be necessary.<sup>182</sup>

As in other organs receiving radiation, the intestines exhibit both acute and chronic symptoms of radiation treatment. Acutely, the rapidly dividing stem cells located in the crypts of Lieberkühn are induced into apoptosis, or programmed cellular death. This increased rate of stem cell loss contributes to acute radiation enteritis, reducing the surface area required for nutrient absorption and leading to dehydration and malnutrition.

Intestinal motility also changes, causing diarrhea, abdominal cramping, and nausea. If the terminal ileum is included in the radiation field, there may be a reduction in the absorption of B12 and bile acids leading to B12 deficiency and steatorrhea, respectively.<sup>118</sup> Abnormal intestinal motility can occur after the first treatment, but symptoms become most pronounced around the third week of treatment.

Dehydration may require hospitalization and a break in the radiation schedule but is usually not life-threatening. Concurrent chemotherapy causes an increase in cellular damage when compared to radiation alone, with resulting neutropenia leading to serious infections and sepsis.

The incidence of chronic radiation enteritis is unknown and probably underreported but may occur in up to 15% of cases involving the intestines. Symptoms are insidious, occurring 6 months to 25 years after treatment.<sup>118</sup> Unlike acute radiation symptoms, chronic symptoms often require treatment or surgery with more serious outcomes.

Radiation frequently causes fibrosis of tissues that may lead to strictures in the intestines, bowel obstruction, fistulas with abscess formation, ulceration with bleeding, and malabsorption. Intracavitary implants can also cause rectal damage.

**Table 5-7** Immediate and Delayed Effects of Ionizing Radiation\*

System Affected	Immediate	Delayed Effect
Musculoskeletal		Soft tissue (collagen) fibrosis, contracture, atrophy Orthopedic deformity
Neuromuscular	Fatigue Decreased appetite Subtle changes in behavior and cognition Short-term memory loss Ataxia (subacute)	Myelopathy (spinal cord dysfunction) Cerebral injury, neurocognitive deficits Radionecrosis (headache, changes in personality, seizures) Plexopathy (brachial, lumbosacral, or pelvic plexus) Gait abnormalities
Cardiovascular/pulmonary	Fatigue, decreased endurance Radiation pneumonitis	Radiation fibrosis (lung) Cardiotoxicity <ul style="list-style-type: none"> <li>• Coronary artery disease</li> <li>• Myocardial ischemia/infarction</li> <li>• Pericarditis</li> </ul> Lymphedema
Integumentary	Erythema Edema Dryness, itching Epilation or hair loss (alopecia) Destruction of nails Epidermolysis (loose skin) Delayed wound healing	Skin scarring, delayed wound healing, contracture Telangiectasia (vascular lesion) Malignancy (basal cell, squamous cell, melanoma)
Other	Gastrointestinal: Anorexia, nausea, dysphagia; vomiting, diarrhea, xerostomia (dry mouth); stomatitis (inflammation of mouth mucosa); esophagitis; intestinal stenosis Renal/urologic: Urinary dysfunction	Bone marrow suppression (anemia, infection, bleeding) Cataracts Endocrine dysfunction (cranial radiation) including amenorrhea, menopause, infertility, decreased libido Hepatitis Nephritis, renal insufficiency Malignancy <ul style="list-style-type: none"> <li>• Skin cancer</li> <li>• Leukemia</li> <li>• Lung cancer</li> <li>• Thyroid cancer</li> <li>• Breast cancer</li> </ul>

\*Some of the delayed effects of radiation (e.g., cerebral injury, pericarditis, pulmonary fibrosis, hepatitis, nephritis, gastrointestinal disturbances) may be signs of recurring cancer. The physician should be notified of any new symptoms, change in symptoms, or increase in symptoms.

Preventive strategies under investigation include free radical scavengers, antioxidants, and use of cytoprotective agents.

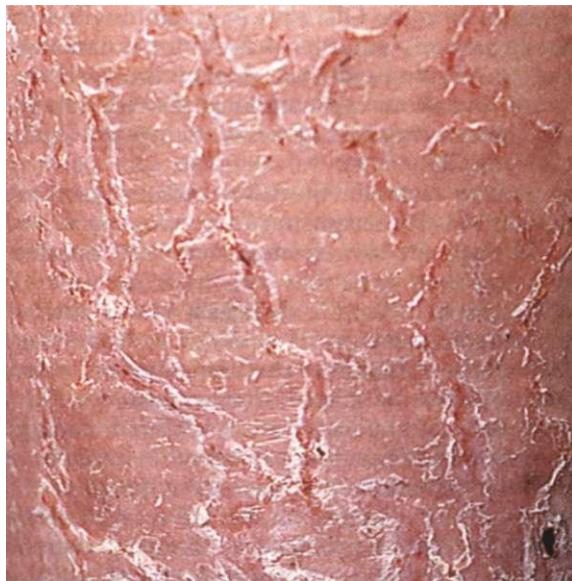
**Radiation Heart Disease.** Radiation to the chest can cause pericarditis, coronary heart disease, and myocardial disease. People at greatest risk for radiation-induced heart disease include those who received mediastinal radiotherapy for breast cancer, testicular cancer, or Hodgkin's disease before associated risks were known and radiation regimens were changed. Radiation-induced aortic valve disease has been reported in people who had radiation of the mediastinum for Hodgkin's disease 20 to 30 years ago.<sup>82,88</sup> Studies from survivors of atomic bombings suggest that the risk of mortality from radiation-induced heart disease is greatest when the dose is between 0 and 4 Gy and usually occurs at least a decade after irradiation.<sup>166,172</sup>

**Radiation Lung Disease.** The lung is a radiosensitive organ that can be affected by external beam radiation therapy. Pulmonary toxicity is fairly uncommon and determined by the volume of lung radiated, the dose and

fraction rate of therapy, concurrent chemotherapy, older age, lower baseline pulmonary function, and lower performance status.<sup>103</sup>

The two syndromes of pulmonary response to radiation are an acute phase (radiation pneumonitis) and a chronic phase (radiation fibrosis). *Radiation pneumonitis* is caused by significant interstitial inflammation creating a reduction of gas exchange. The hallmark of this toxicity is symptoms out of proportion to other findings, including appearance on radiographs. It usually occurs 2 to 3 months (range, 1 to 6 months) after completion of radiotherapy and typically resolves within 6 to 12 months.

Symptoms range from a dry cough with dyspnea on exertion to severe cough and dyspnea at rest.<sup>103</sup> Rarely, clients may develop acute respiratory distress requiring intubation and ventilation. The National Cancer Institute has developed a grading system called Common Terminology Criteria for Adverse Events (CTCAE), version 3 (Grades 0 to 5), which does not recognize acute versus chronic symptoms but rather grades events such as

**Figure 5-3**

Dry desquamation with scaling associated with radiation. (From Habif TP: *Clinical dermatology*, ed 4, Edinburgh, 2004, Mosby.)

aspiration or dyspnea. (This grading system is available on-line at <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.)

Diagnosis of radiation pneumonitis can prove difficult if underlying disease, such as COPD, is present. Clients with grade 1 or 2 radiation pneumonitis respond well to corticosteroids, although their use can increase the risk for serious infection. Grades 3 and 4 radiation pneumonitis typically have a poor outcome.

*Pulmonary radiation fibrosis* may occur months after radiation therapy. Radiation fibrosis is progressive and symptoms may develop slowly. Only supportive therapy is available, such as oxygen supplementation, bronchodilators, and treating infection. Corticosteroids have no value, but studies are ongoing to find preventive measures.<sup>7,109,145</sup>

Other radiation-induced pulmonary problems include formation of bronchopleural fistulas, pneumothorax, hemoptysis, and bronchial stenosis.

**Radiation Dermatitis.** Damage to the skin is one of the more common side effects of radiation since it is involved in most therapies, despite tumor location. While most injury to the skin is reversible, severe reactions can cause delay in therapy or a change in dosing. The cutaneous affects of radiation can be separated into acute, consequential-late, and chronic.

The National Cancer Institute has provided guidelines for grading acute cutaneous damage to the skin after radiation. Grade 1 reactions resemble sunburn and are accompanied by hair loss, dry desquamation, pruritus, dyspigmentation, and scaling (Fig. 5-3). These changes are secondary to damage of the hair follicles and sebaceous glands. The term *desquamation* is preferred to "radiation burn"; the latter term is unacceptable and no longer used in clinical practice.

Grade 2 reactions produce persistent erythema or patchy moist desquamation in the folds and creases of the skin, often associated with pain and edema. Bullae

**Figure 5-4**

Radiation dermatitis. Acute or chronic inflammation of the skin caused by exposure to ionizing radiation (radiation therapy for cancer). Symptoms may include redness, blistering, and sloughing of the skin. The condition can progress to scarring, fibrosis, and atrophy as shown here. (From Callen JP: *Color atlas of dermatology*, ed 2, Philadelphia, 2000, WB Saunders.)

may form, rupture, and become superinfected. These changes present 4 to 5 weeks into therapy and peak 1 to 2 weeks after treatment completion. Complete healing requires 1 to 3 months.<sup>89</sup>

Confluent, moist desquamation of the skin with pitting edema characterizes grade 3 reactions. Compared to grade 2 reactions, the edematous erythema of grade 3 is not confined to the skin folds. Grade 4 reactions (rare) are severe with skin necrosis or ulceration of full-dermis thickness associated with bleeding. Infrequently, grade 4 reactions do not heal and progress into consequential late effects, eliciting fibrosis with breakdown of necrotic tissue, ulceration, and exposure of underlying structures such as bone.<sup>51</sup> These injuries are difficult to heal, since much of the tissue is avascular secondary to radiation.

While consequential late effects are persistent acute changes, chronic radiation-induced effects develop months to years after treatment. Repeated doses of radiation without sufficient time between doses to repair can lead to significant cutaneous injury. This injury is often manifested by atrophic skin, telangiectasia, hyperpigmentation, and hypopigmentation.

Sebaceous glands, hair follicles, and nails may be permanently affected. Fibrosis of the dermis accompanied by absorption of collagen creates contracted, atrophic skin, which is susceptible to tearing and ulceration (Fig. 5-4). An abnormal proliferation of arteriole cells may occur, causing thrombosis of the vessels, which combined with fibrosis, inhibits healing and predisposes



**Figure 5-5**

**Radiation recall.** This person had small cell cancer of the lung treated with radiation. Cytoxan treatment some months later elicited erythema and desquamation within the portal of radiation. This lesion is in the healing phase. (From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Churchill Livingstone.)

ulcers to infection. These complex ulcers are painful and difficult to heal.

Treatment of acute cutaneous injury is typically symptomatic. For grade 1 and 2 reactions, washing with water or a gentle, low pH agent is sufficient to keep the skin clean and reduce bacterial load. Antiperspirants and talcum powders should be avoided in the radiation field. Ointments and creams can often benefit irritated and dry skin after radiotherapy.

Treatment of ulcers and erosions from radiation does not require specific therapy, but the same general principles of wound care apply (such as providing a moist environment, pain control, removing necrotic tissue, and protection against infection).<sup>99</sup> Various dressings may be utilized, depending on the wound type (e.g., burn pads or foam dressings can be used for exudative wounds).

Other modalities that have been used include biosynthetic, artificial, and bioengineered skin; lasers<sup>151</sup>; and recombinant platelet-derived growth factor (PDGF).<sup>186</sup> Diligence is required to keep fibrotic tissue intact. Active and passive range-of-motion exercises are important to retain mobility and reduce contractures.

The drug pentoxifylline<sup>41</sup> and hyperbaric oxygen therapy (HBOT)<sup>58</sup> have been used to enhance healing, and studies exploring prophylactic uses are ongoing. HBOT administers 100% oxygen under higher-than-atmospheric pressure, helping the body recognize damaged tissue and restoring up to 80% of the preinjury vascular density. High levels of oxygen in the tissues support healing by facilitating angiogenesis.

Another type of radiation-induced reaction is *radiation recall*. Radiation recall reactions (Fig. 5-5) are inflammatory reactions that occur in a previously irradiated site after the administration of certain chemotherapeutic drugs (e.g., dactinomycin, doxorubicin, bleomycin, methotrexate, gemcitabine, and paclitaxel) or antibiotics.<sup>96</sup>

Exposure to ultraviolet rays (e.g., tanning booths or outdoor exposure) is also a risk factor for radiation recall. Anyone undergoing radiation therapy is advised to use sunscreen and avoid exposure to ultraviolet A or B rays (which enhance the effect of radiation therapy) to prevent radiation recall.

Recall may occur in the skin, mucous membranes, lungs, central nervous system (CNS), esophagus, and GI tract, although the skin is most frequently involved.<sup>146</sup> Months and even years may pass from the time of the initial radiation therapy to the onset of this reaction. A more immediate reaction (within 2 to 3 days) often occurs after the initiation of chemotherapy and is usually characterized by a mild, sunburned appearance. The skin may itch or burn; the reaction can last hours to days.

More significant reactions exhibit moist desquamation with blister formation and may even progress to full dermis necrosis and ulceration. Radiation recall involving other organs can be problematic but may respond to supportive measures, corticosteroids, or antiinflammatory medications.<sup>92</sup>

**Effects of Radiation on Connective Tissue.** Radiation therapy, especially teletherapy, is well known to cause significant long-term or chronic effects on the connective tissue. Acute irradiation toxicity is less likely because connective tissue has a slower turnover or reproductive rate and striated muscle tolerates relatively high doses of radiation.

Late changes, such as fibrosis, atrophy, and contraction of tissue, can occur to any area irradiated but especially to collagen tissue. In growing bones and limbs, irradiation can cause profound and irreversible changes resulting in limb-length discrepancies and scoliosis requiring orthopedic surgical correction. Weakness of the bone may lead to pathologic fractures.

Fibrosis of connective tissue can result in edema, decreased range of motion, and functional impairment. Radiation of the pelvic cavity often causes dense pelvic adhesions that may cause painful motion restrictions and more rarely, plexopathy. Subsequently, these effects lead to soft tissue fibrosis, resulting in decreased range of motion, pain, and in some cases, lymphedema.

The fibrotic effect of radiation on the circulatory and lymphatic system is typically seen in a loss of elasticity and contractility of the irradiated vessels that are required to transport the blood, lymph, and waste products from the area of the body being exposed.<sup>9</sup>

Although lymphatic vessels maintain their structural integrity after being irradiated, fibrosis occurs in the surrounding tissue. This effect can inhibit normal growth of lymphatic vessels into healing tissues and delay lymphatic proliferation in response to inflammation.<sup>105a</sup> These types of effects can be minimized by sparing lymphatics from the radiation portal, but presently, up to 30% of breast cancer survivors in the United States develop lymphedema sometime in their lifetime.

It is important to remember that lymphedema may not be a side effect of radiation but rather a sign of advanced progressive metastases associated with cancer recurrence. Lymphedema can develop when lymphatic overload contributes to systemic congestion; a medical differential diagnosis is required.

Currently, physical therapy and supportive measures are the mainstay of therapy, although newer modalities and medications are under investigation.<sup>124</sup>

**Effects of Radiation on the Nervous System.** As radiation therapy is used more frequently and aggressively in treating malignancies, toxicities to the nervous system increase. The incidence of nervous system toxicity related to radiation increases as the volume of nervous tissue being irradiated increases and the total dose and fraction size increase.<sup>32</sup>

Despite knowing risk factors for nervous system damage, toxicities continue to occur because individual reactions vary, safe thresholds are not known in all cases, and excessive doses may be used in an attempt to cure a malignancy. Studies determining the incidence of long-term effects of radiation are lacking but high total dose, high fractionation dose, and concomitant chemotherapy probably increase the risk.

Clinical manifestations of nervous system radiation toxicity can be separated into three categories: acute, subacute, and delayed. Neurologic symptoms relating to acute and subacute complications are most often self-limiting, requiring only supportive measures. The chronic or delayed complications are more often severe and progressive. Therapies for these complications are often palliative at best, although hyperbaric oxygen and anti-coagulation have demonstrated questionable improvement.<sup>74,100,139,190</sup>

**Acute Symptoms.** Acute symptoms generally occur during the period of treatment. The most common symptom is progressive and sometimes debilitating fatigue. Other clinical manifestations of cranial irradiation may include lethargy, short-term memory difficulties, and subtle changes in behavior and cognition. General symptoms that may occur during brain irradiation include decreased appetite, dry skin, hearing loss, hair loss, and decreased salivation.

Cranial radiation can often cause changes in short-term memory, cognition, and personality, ultimately leading to radiation-related encephalopathy or frank dementia.<sup>33</sup> Clients infrequently demonstrate hydrocephalus accompanied by ataxia and incontinence.<sup>38,168</sup>

Acute radiation encephalopathy, probably related to edema, is an uncommon reaction secondary to brain irradiation, causing headache, nausea and vomiting, lethargy, seizures, new focal deficits, and mental status changes. Because of careful planning and use of the drug dexamethasone, the incidence has significantly decreased, although it can be life-threatening in clients that do develop this complication.

**Subacute Symptoms.** Subacute symptoms (early delayed), noted 1 to 4 months after the completion of therapy, are fairly uncommon. If treatment included the cervical spine (and to a lesser degree the thoracic), clients may experience subacute myelopathy, a tingling, shock-like sensation passing down the arm or trunk when the neck is flexed (Lhermitte's sign). This sign occurs in up to 15% of clients receiving mantle radiation therapy for Hodgkin's disease.

Symptoms are usually self-limiting and peak 4 to 6 months after treatment. Irradiation of the brainstem may cause ataxia, nystagmus and dysarthria. Occasionally, a

transient brachial plexopathy occurs, causing paresthesias and muscle weakness, which improves over time.

**Delayed Complications.** While many of the acute and subacute complications of radiation are self-limiting or mild, late or delayed complications (late delayed) can be more serious and do not appear for months to years after therapy. For example, when exposed to radiation, cerebral vasculature, as well as other arteries, such as the carotid and coronary arteries, may be damaged, leading to coronary artery disease, transient ischemic attacks, stroke, or myocardial infarction.<sup>37</sup> Other late effects are described as follows and in Table 5-7.

**RADIONECROSIS.** One of the best-described complications of whole-brain radiotherapy is delayed cerebral radionecrosis. Symptoms occur in approximately 5% of persons who receive over 5000 cGy of cranial radiation and include headache, changes in cognition and personality, focal neurologic deficits, and seizures. Another serious long-term complication of radiotherapy of the brain is the development of tumors, including meningiomas, gliomas, lymphomas, fibrosarcomas, and malignant schwannomas. These tumors are often aggressive and difficult to cure.

Radiation of the brain may affect the hypothalamic system. Abnormalities in growth hormone, gonadotropins, thyrotropin, and corticotropin may be seen. Hyperprolactinemia commonly occurs and can resolve spontaneously.<sup>32</sup> Hyperprolactinemia is a condition of elevated serum prolactin, which is an amino acid protein produced in the anterior pituitary gland. Its primary function is to enhance breast development during pregnancy and to induce lactation. Women present with changes in menstruation and infertility; men present with visual disturbances or headache.

**MYELOPATHY.** Radiotherapy of the spinal cord may cause a radiation-induced myelopathy. This can present as the Brown-Séquard syndrome or as a motor neuron syndrome. The Brown-Séquard syndrome displays muscle weakness that ultimately leads to paraparesis or quadriplegia. Motor neuron syndrome is uncommonly seen after pelvic radiation (testicular cancer). Clients develop muscle weakness with atrophy of muscles, fasciculations, and areflexia. Sensory examination remains unchanged. This syndrome can progress over years before reaching a plateau.

**PLEXOPATHY.** The brachial and lumbar plexuses may also be damaged after treatment. Clinical manifestations of radiation-induced brachial plexopathy include paresthesias with progressive motor deficits, lymphedema, and pain. Many clients lose hand function or develop arm paralysis.<sup>11,57</sup>

The incidence of brachial plexopathy after radiation therapy has been reduced significantly with improved treatment, but women who were given large daily fractions of postoperative telecobalt therapy to the axillary, supraclavicular, and parasternal lymph node regions years ago have shown a progression of both prevalence and severity of the late effects many years later, including arm paralysis.<sup>93</sup>

Today, with improved irradiation techniques (e.g., matching fields, maintaining the client's position between fields, and avoiding overlapping fields that can cause hot

spots), the overall incidence is about 0.5% of all cases of irradiated breast cancer. Plexopathies can be caused by cancer recurrence or new cancer onset rather than the effects of irradiation and must be differentially diagnosed by a physician.

Lumbar plexopathy is also possible when the pelvic area is irradiated. Clinical manifestations of radiation-induced plexopathy appear to be a result of fibrosis around the nerve trunks and include paresthesias, hypoesthesia, progressive weakness, decreased reflexes, and pain.<sup>78</sup>

Currently, no curative treatment is available for either brachial or lumbar plexopathies, although therapeutic interventions can achieve significant pain control and improve strength and function in the affected limb.<sup>78</sup> Comprehensive strategies may be required in cases of lymphedema (see Chapter 13).

**Pregnancy.** The fetus is very sensitive to radiation. Pregnant women or those who suspect they may be pregnant must avoid all possible exposure to sources of radiation. Congenital anomalies that develop after intrauterine exposure, especially if it occurs during early pregnancy or 2 to 12 weeks after conception during organ development, may include microcephaly, growth and mental retardation, hydrocephalus, spina bifida, blindness, cleft palate, and clubfoot. Later development of cancer, especially leukemia and thyroid cancer, is most often reported when the fetus is exposed to a source of radiation.<sup>175</sup>

## SPECIAL IMPLICATIONS FOR THE THERAPIST

5-6

### Radiation

#### Radiation Hazard for Health Care Professionals

People who receive external radiation do not give off radiation to those who come in contact with them. Internal implants can present some hazards to others as long as the implant is in place. Pregnant staff members should avoid all contact with the internally radiated client.

When administering direct care, staff members should plan interventions so that each task can be accomplished as quickly as possible. Distance provides some protection; therefore it is advisable to use positions that place the staff person as far away from the radioactive implant as possible. For example, if the implant is in the pelvis, the caregiver might stand at the head or foot, not the side, of the bed.

The use of protective lead aprons or portable shields may be recommended according to the hospital protocol. Each staff member is encouraged to know and follow the recommended policies and procedures for the given institution. A film badge or ring badge worn on the outside of any protective devices or clothing of the caregiver records the cumulative dose of radiation received and is used to monitor exposure over a period. When removed, this badge should be stored in a location where no additional radiation exists.

Some sources of radiation (e.g., iodine 131, phosphorus 32) are excreted in body fluids (e.g., urine, sweat, tears, or saliva) for several days after administration to the client. These clients are placed in strict radioactive isolation during hospitalization and treatment. All articles used by the client, such as urinals, toothpicks, tissues, and bed linens, are considered as a possible radiation hazard. Disposal of all such items should follow hospital protocol. Good quality examination gloves made of latex or a strong synthetic material (not vinyl) are adequate for general care, although the use of two sets of gloves is recommended when in direct contact with body fluids deemed radioactive.<sup>188</sup>

Careful removal and disposal of any personal protective equipment worn by the therapist must be done according to radiation safety instructions posted. Thorough handwashing after glove removal is essential.<sup>188</sup>

### Postradiation Therapy

For the client who is in the process of receiving external radiation therapy, handwashing before treating the client is essential to protect him or her from infection. Skin care precautions include the following:

- Avoid topical use of alcohol or other drying agents, lotions, gels, oils, or salves; creams and gels on the skin can potentiate the received skin dosage and lead to increased adverse effects; do not wash away markings for the target area.
- Avoid positions in which the client is lying on the target area.
- Avoid exposure to direct sunlight, heat lamps, or other sources of heat, including thermal modalities.

Delayed wound healing associated with radiotherapy requires assessment early on of other factors that impair wound healing such as smoking or tobacco use, poor nutrition, weight loss before the start of treatment, and infection.<sup>136</sup>

Radiation to the low back may cause nausea, vomiting, or diarrhea because the lower digestive tract is exposed to the radiation.<sup>115</sup> Radiation of the pelvic cavity often causes dense pelvic adhesions that can cause painful motion restrictions. The therapist's role in the postradiation treatment of these clients is to increase range of motion and provide stretching exercises. Early, aggressive intervention by the therapist is essential to prevent or minimize restrictive scarring.

Some effects of radiation on the nervous system can develop years after treatment, although radiation plexopathy can develop many years after exposure to the radiation doses used 20 or 30 years ago. The therapist should be aware of anyone at risk for seizures, observe for any signs of seizure activity, and take appropriate actions to ensure client safety.

Anyone with neurologic signs or symptoms of unknown cause must be questioned about past medical history (cancer, heart disease) and the possibility of prior radiation treatment, keeping in mind that progressive disease or a vascular event can also cause an acute or subacute neurologic event. The physician must rule out cancer recurrence in anyone with a

previous history of cancer and evaluate for the presence of some other cause of new onset neurologic signs and symptoms.

### Postradiation Infection

Signs and symptoms of infection are often absent because the immunosuppressed person cannot mount an adequate inflammatory response. Fever may be the first and only sign of infection. Swelling, redness, and pus may be absent in infected tissue. The therapist must observe very carefully for any sign of infection, anemia, or bleeding and other signs of thrombocytopenia (see Chapter 14).

### Radiation Therapy and Exercise

Radiation and chemotherapy can cause permanent scar formation in the lungs and heart tissues, whereas drug-induced cardiomyopathies can contribute to limitations in cardiovascular function (see the section on Chemotherapy and Exercise in this chapter, the section on Cancer and Exercise in Chapter 9, and Box 9-6 and Tables 40-8 and 40-9).

Both of these variables require monitoring of vital signs when working with people who are recovering or in remission from cancer treatments. Clients should be taught to monitor their own vital signs including pulse rate, respiratory rate, perceived exertion rate (PER), which is not to exceed 15 to 17 for moderate intensity training or submaximal testing, and observe for early signs of cardiopulmonary complications of cancer treatments such as dyspnea, pallor, excessive perspiration, or fatigue during exercise.

Low- to moderate-intensity aerobic exercise (e.g., self-paced walking) during the weeks of radiation treatment can help manage treatment-related symptoms by improving physical function and lowering reported levels of fatigue, anxiety, depression, and sleep disturbance.<sup>108,153</sup>

A successful aerobic training protocol for a client with cancer should include client education, an exercise evaluation, and an individualized exercise prescription. Ideally, these components of cancer treatment should begin when the person receives the diagnosis. Current guidelines recommend that clients should be advised not to exercise within 2 hours of chemotherapy or radiation therapy because increases in circulation may increase the effects of the treatments.<sup>72</sup> Guidelines for choosing an exercise test and prescribing an exercise prescription are available.<sup>152</sup>

Additionally, it is very important that the client carry out careful, daily stretching during and after radiation treatment. Postradiated tissue can tear when stretching. Therapist and client must observe for blanching of the skin and avoid stretching beyond that point. Stretching must be continued for 18 to 24 months postradiation as the fibrotic process continues for that amount of time.

## CHEMOTHERAPY<sup>111</sup>

Systemic chemotherapy plays a major role in the management of the 60% of malignancies that are not curable by regional modalities. As with radiation therapy, chemotherapy acts by interfering with cellular function and division. Chemotherapy may be used to cure cancer, to palliate or stabilize disease as preliminary therapy before bone marrow transplantation, or as adjuvant therapy.

In contrast to most cells in the body, tumor cells undergo frequent cell division, leading to an accumulation of cells that are cytologically and histologically defective. Cellular processes needed to support this increased cell division, such as DNA synthesis, DNA repair, DNA replication, and RNA transcription, are themselves accelerated. The principal goal of chemotherapy is to destroy malignant cells with the least harm to normal cells or the host. However, most chemotherapeutic agents are nonspecific and therefore affect both malignant and normal cells.<sup>144</sup>

Researchers first used these unique characteristics of tumor cells as targets for antitumor drugs in the mid 1940s. Goodman and Gillman successfully reduced tumor size in adults with non-Hodgkin's lymphoma with mustine, a drug that disrupts the normal structure of DNA.<sup>94</sup> This discovery led to the development of many new drugs, commonly referred to as *chemotherapeutic drugs*, which specifically target those processes needed to support mitotic activity and cell division. Although such drugs have been successful in treating a wide variety of cancers, they are unable to distinguish cancerous from noncancerous cells (i.e., they lack specificity) often attacking normal, as well as cancerous, cells.

### Characteristics and Categories of Chemotherapeutic Drugs

Chemotherapeutic drugs are *systemic drugs*, meaning that they travel throughout the body rather than remain confined to a specific area. They are able to reach cells in the primary tumor and cancerous cells that may have escaped from the primary tumor. Many chemotherapeutic agents are systemic and nonspecific, which means they can reach and exert their toxic effects on noncancerous cells as well.

Normal cells most at risk for damage by chemotherapeutic agents are those that normally have high mitotic rates such as hepatic cells, cells that make up epithelial layers, bone marrow cells, and hair cells. However, virtually every organ in the body can be affected by these drugs; for this reason, chemotherapy is often accompanied by multisystem problems and disease.

Four broad categories of systemic chemotherapeutic agents are generally recognized, each of which interferes in some manner with compounds or processes that contribute to cell growth (Table 5-8). Specifically, alkylating agents insert themselves into DNA strands, disrupting the normal structure of the strand, preventing the successful replication of an exact copy of that DNA strand, creating a break in the DNA strand. These compounds are mutagenic and potentially carcinogenic.

**Table 5-8** Major Toxicities Commonly Associated with Cancer Chemotherapeutic Agents

Cytotoxic (Chemotherapy) Agents	Major Toxicities
<b>Alkylating Agents</b>	
Busulfan (Myleran)	Myelosuppression*
Carmustine	Pulmonary toxicity
Chlorambucil (Leukeran)	Myelosuppression
Cisplatin (Platinol)	Neurotoxicity (peripheral neuropathy), renal toxicity, ototoxicity
Cyclophosphamide (Cytoxan)	Hemorrhagic cystitis
Dacarbazine	Myelosuppression, liver toxicity
<b>Antimetabolites</b>	
Methotrexate	Mucositis
Mercaptopurine (6-MP)	Mucositis, headache, fatigue, anorexia, myalgia
Fluorouracil (5-FU)	Mucositis
Cytarabine	Myelosuppression, liver inflammation, neurotoxicity
Etoposide	Myelosuppression
<b>Antibiotics</b>	
Doxorubicin (Adriamycin)	Cardiomyopathy: CHF
Daunorubicin (DaunoXome)	Myelosuppression, cardiomyopathy
Mitomycin (Mutamycin)	Reversible and nonreversible pulmonary fibrosis
Bleomycin (Blenoxane)	Myelosuppression
<b>Plant Alkaloids</b>	
Vinblastine	Neurotoxicity
Vincristine	Neurotoxicity, neuromyopathy
Paclitaxel (Taxol)	Myelosuppression, neuromyopathy

\*Myelosuppression: bone marrow suppression resulting in anemia, leukopenia leading to infection, and thrombocytopenia.

Drugs known as *antimetabolites* are structurally similar to the purine and pyrimidine bases that form the backbone of each DNA strand. These drugs act either by being incorporated into the DNA strand, leading to the synthesis of a defective DNA strand, or by inhibiting enzymes necessary for DNA and RNA replication, as well as protein synthesis.

Several chemotherapeutic agents are antibiotics. These compounds are incorporated into the DNA strand, preventing the synthesis of DNA and RNA. These compounds also lead to the formation of free radicals, which can damage DNA and cell membranes. Finally, a variety of *plant alkaloids* are effective in treating cancers, because they interfere with the formation of the mitotic spindle, subcellular structures that transfer genetic material from the mother cell to the two daughter cells.

Although systemic chemotherapy drugs remain the mainstay of chemotherapy, drugs targeting critical biochemical pathways unique to tumor cells have become available. These so-called targeted therapies include imatinib mesylate (Gleevec) and trastuzumab (Herceptin). Gleevec specifically attacks the Philadelphia chromosome, which is a chromosome translocation found in chronic myelogenous leukemia.

The anti-HER2 antibody trastuzumab (Herceptin) is used to treat some women with breast cancer. About 30% of individuals with breast cancer have increased expression of the human epidermal growth factor receptor (HER2), resulting in aggressive tumors and poor prognosis. Herceptin specifically targets these receptors and in doing so, increases the likelihood of tumor regression in select individuals. These targeted therapies do not ran-

domly attack rapidly dividing cells, so they generally cause fewer and less severe side effects than do chemotherapy drugs.<sup>77</sup>

## Adverse Effects of Chemotherapy

Many chemotherapy agents have unique, dose-limiting toxicities. Chemotherapy drugs are used in combination for their specific actions on cells and care is taken not to use agents with significant overlapping toxicities. The short- and long-term toxicities of commonly used chemotherapy drugs are outlined in Table 5-8 (see also Table 9-7).

Most chemotherapeutic agents have the propensity to cause nausea and vomiting with the administration of the drug, and mucositis, diarrhea, myelosuppression, and alopecia often occur after treatment. Many cause sterility and are toxic to a fetus.<sup>132</sup>

Cognitive deficits referred to as chemotherapy related cognitive dysfunction (CRCD) can have a dramatic effect on a person's quality of life. These deficits can be subtle or dramatic, transient or permanent, or stable or progressive.<sup>69</sup>

## Alopecia

Alopecia (hair loss) is the most noticeable cutaneous side effect of chemotherapy and often the most distressing because it has a profound social and psychologic impact on the individual. Actively growing hair or anagen hair is the most rapidly proliferating cell population in the human body and therefore very susceptible to the effects of systemic chemotherapeutic agents. Chemotherapy also

renders the hair shaft more fragile and thus prone to significant damage with minimal trauma. As a result, hair breaks, falls out, and is not replaced.

Alopecia is more likely to occur when high-dose chemotherapy is used to treat the cancer (not all chemotherapy regimens have this effect) and typically occurs within 2 to 3 weeks after the onset of chemotherapy. Hair loss is not restricted to the scalp, but because this area has the greatest amount of anagen hair, the greatest losses occur here. Hair loss is temporary, with regrowth typically occurring 4 to 6 weeks after termination of treatment. Full hair restoration may require 1 to 2 years to complete and may be accompanied by changes in hair color, texture, and type.<sup>83</sup>

### Gastrointestinal Toxicity

Over 75% of clients receiving combination chemotherapy experience nausea and vomiting, which typically occurs 1 to 2 hours after the administration of the agent, with the effects peaking at 4 to 10 hours after administration and lasting approximately 12 to 24 hours. Potential medical complications of chemotherapy-induced emesis include dehydration, electrolyte and acid-base disturbances, and anorexia with accompanying weight loss.<sup>12</sup> A variety of antiemetic drugs are currently available, and often these drugs are given in combination.<sup>117</sup> However, these drugs are not without their own side effects.

Other agents, such as high-dose cisplatin, are known to cause delayed nausea and vomiting, with symptoms occurring 1 to 5 days after drug administration. Some people suffer nausea and vomiting before drug administration apparently in anticipation of becoming sick. Acute nausea and vomiting is usually the most severe, whereas the course of delayed nausea and vomiting can be prolonged, leading to dehydration and poor nutrition.

The mechanisms responsible for nausea and vomiting are varied and not completely understood, and different drugs may cause nausea by utilizing different pathways. One mechanism, which has been described in animals for high-dose cisplatin, proposes that the drug causes the release of serotonin in the small intestine (perhaps because of mucosal damage), which then triggers afferent vagal nerves to the vomiting center of the brain.<sup>56</sup> Research in this area has led to the development of antiemetics that block specific receptors. These agents may alleviate delayed nausea and vomiting.

Chemotherapy drugs cause the most damage to rapidly dividing cells. Although this is the means by which eradication of tumor cells occurs, these cytotoxins also affect cells that normally divide quickly, such as cells of the oral cavity and GI tract. Damage to the cells lining the GI tract result in the diarrhea so often seen after treatment. The cytotoxic effects of many chemotherapy drugs cause an inflammation of the mucosal epithelium in the GI tract. The resulting mucositis occurs when these injured cells are unable to replace themselves. This effect can occur anywhere in the GI tract and presents differently depending on where the damage occurs.<sup>73</sup> Like nausea and vomiting, mucositis and diarrhea lead to dehydration and malnutrition.

### Myelosuppression

Because many chemotherapeutic agents are not specific for cancer cells, they adversely affect normal cells, causing a number of serious side effects. Myelosuppression (inhibition of bone marrow production of blood cells and platelets resulting in anemia, leukopenia, and thrombocytopenia) is the most common and dose-limiting adverse effect of chemotherapy and can be the most lethal.<sup>101</sup>

Chemotherapeutic agents destroy the proliferating progenitor cells found in bone marrow that are destined to develop into mature blood cells. In doing so, these drugs limit the ability of the body to replace blood cells as they die or lose their effectiveness. Individuals receiving chemotherapy agents often develop some form of cytopenia, including anemia, leukocytopenia, and thrombocytopenia, 10 to 14 days after starting a course of chemotherapy. Withdrawal of the drug usually allows the progenitor cell populations to rebound and levels of blood cells to increase. High-dose chemotherapy may prolong the time needed to repopulate the bone marrow, leaving the person cytopenic for extended periods of time.

Prolonged or severe myelosuppression frequently delays scheduled treatments and increases the risk of serious infections, bleeding, or reduced endurance. With increased dosages or more frequent administration of drugs, more profound and prolonged myelosuppression may occur. However, the use of prophylactic antibiotics and colony-stimulating factors (granulocyte colony-stimulating factor [G-CSF] and/or granulocyte-macrophage colony-stimulating factor [GM-CSF]) has helped dramatically in the prevention of infection and control of myelosuppression.

Erythropoietin is often administered to increase RBC synthesis and reduce anemia; interleukin II is administered to reduce thrombocytopenia. Administration of blood products can also help alleviate adverse effects. Infection is the most serious adverse effect of myelosuppression (neutropenia) and is associated with significant morbidity and mortality.<sup>147</sup> Individuals who develop neutropenic infections are treated with antibiotics and various colony-stimulating factors to stimulate the proliferation and differentiation of hematopoietic progenitor cells, ultimately increasing the numbers of mature WBCs.

### Fatigue

It has been estimated that between 70% and 100% of all individuals with cancer will experience cancer-related fatigue (CRF).<sup>66</sup> Symptoms of CRF include persistent sense of tiredness that is not relieved by rest, shortness of breath, decreased ability to focus or concentrate, and decreased ability to perform daily tasks.<sup>125</sup> Although most people will experience fatigue during treatment (chemotherapy, postsurgery, or postradiation), upwards of 35% still experience fatigue 24 months after completing therapy.<sup>116</sup>

Fatigue often peaks within a few days for individuals receiving cyclic chemotherapy then declines until the next treatment cycle. Fatigue significantly reduces quality of life. It is generally agreed that fatigue has multiple

cancer-related or treatment-induced causes that can be described as being either physiologic or psychologic. Physiologic causes of fatigue include underlying disease; cancer treatment; anemia; infection; accompanying pulmonary, hepatic, cardiac, and renal disorders; sleep disorders; poorly controlled pain; and malnutrition. Psychologic causes of fatigue include anxiety disorders, depressive disorders, and cognitive losses that include decreased attention span and concentration.<sup>137</sup>

Because CRF is multifactorial, multidimensional interventions involving both physical and psychologic components are required to successfully treat it. Such an approach has proved to be successful.<sup>174</sup>

### **Cardiotoxicity**

All categories of chemotherapeutic agents can cause cardiac disease, but the anthracyclines are the most damaging to the heart. The anthracycline class of drugs, particularly doxorubicin (Adriamycin) and daunorubicin (DaunoXome), is well known for its increase risk of cardiomyopathy leading to irreversible CHF.<sup>191</sup>

Trastuzumab has been associated with a 2% risk of developing significant cardiac dysfunction, which increases to approximately 16% when this drug is used in combination with anthracyclines or cyclophosphamide (Cytoxan).<sup>154</sup>

Chemotherapy drugs known as antimetabolites (see Table 5-8), including the widely used agent 5-fluorouracil (5-FU), can produce ischemia and sequelae (e.g., heart attack) if not treated. Other nonchemotherapy agents used to treat cancer such as interleukin-2 or Gleevec are also linked to cardiotoxicity.

High-dose regimens and the total dose per course increase the likelihood of developing cardiac disease. Cessation of the drug will often decrease symptoms.<sup>191</sup> Target therapies are also known to cause cardiotoxicity.

CHF and left ventricular failure with decreased endurance and other associated symptoms can occur early (within 6 to 12 months after initial treatment) or as late as 5 to 20 years after treatment. The risk for developing a cardiomyopathy increases as cumulative doses exceed 550 mg/m<sup>2</sup>. This factor often limits the amount of these drugs that can be given even if the tumor is responding to the drug. Currently, this can be at least partially avoided by adjusting the dose, using liposomal-based agents, or using a cardioprotective drug such as dexrazoxane.

Alkylating agents and antimetabolites are known to cause heart failure months to years after treatment, especially if the person taking these drugs also received radiation or an anthracycline. Acute cardiotoxicity is a greater adverse effect of these drugs, causing ischemic syndrome ranging from angina pectoris to myocardial infarctions.

The earliest signs of drug-induced cardiomyopathy include tachycardia and inability to return to baseline heart rate after exertion.<sup>158</sup> There has also been a relationship noted between the use of 5-FU and the development of myocardial ischemia.<sup>171</sup>

Chemotherapeutic agents have proved very effective in reducing the mortality and morbidity from many forms

of cancer. With chemotherapy increasing life expectancy, many people who have a history of cancer are just as much at risk for cardiac disease as they are from recurrent cancer.<sup>152</sup>

### **Pulmonary Toxicity**

Pulmonary toxicity from chemotherapy is relatively uncommon but potentially fatal. Bleomycin, BCNU (carmustine), and mitomycin have the highest incidences of pulmonary toxicity, compared with other agents, causing a diffuse pneumonitis. For those clients with previous unrelated pulmonary disease, the development of pulmonary pneumonitis or fibrosis may be life-threatening.

### **Renal Toxicity**

Many medications have renal toxicities, including cisplatin, methotrexate, and mitomycin. A careful evaluation of renal function must be performed before each course of chemotherapy. While the drugs themselves may be renal toxic, these agents also contribute to the occurrence of tumor lysis syndrome.

Tumor lysis syndrome occurs when cytotoxic drugs destroy malignant cells, releasing large amounts of metabolites and ions into the bloodstream. The kidneys are unable to tolerate the sudden load, leading to hyperkalemia, hyperuricemia, hypocalcemia, and uremia. This can be life-threatening, leading to cardiac dysrhythmias and renal failure. Clients who have renal insufficiency before treatment, large tumors, or rapidly dividing tumors that are sensitive to chemotherapy are at highest risk for this syndrome.

Hemorrhagic cystitis can occur in clients receiving cyclophosphamide or ifosfamide. The metabolite created from these agents (acrolein) irritates the bladder, causing bleeding. Mesna (2-mercaptoethanesulfonate) can be administered with the drug to detoxify this metabolite and reduce the risk of hemorrhagic cystitis.

### **Hepatic Toxicity**

Acute or chronic hepatotoxicity is possible because many of the chemotherapeutic agents are metabolized in the liver. Drugs requiring dose modification for hepatitis include daunorubicin, doxorubicin, methotrexate, VP-16, vincristine, and vinblastine. Venoocclusive disease of the liver is seen in half of the bone marrow transplant clients, secondary to preconditioning chemotherapy, causing significant mortality.<sup>45</sup>

### **Neuropathies**

Many chemotherapeutic agents adversely affect the nervous system either peripherally or systemically. The vinca-alkaloids, cisplatin, and the taxanes are particularly damaging to the peripheral nervous system, damaging the peripheral neurons and leading to a variety of defects (e.g., myalgia, distal symmetric sensory loss, motor weakness, foot drop, numbness, tingling, and muscle atrophy).

Symptoms can develop within hours after an infusion or may not appear for several weeks to months after

treatment has stopped. Peripheral neuropathies tend to be directly related to the cumulative dose administered and the dose intensity. The appearance of a peripheral neuropathy often limits the total dose given and forces the discontinuation of a specific drug.

Signs and symptoms of a peripheral neuropathy tend to resolve with removal of the drug. Other factors that may influence the development of neuropathies include patient age, type, dose and frequency of chemotherapy, preexisting nerve condition, and nutritional status. Pre-existing neuropathies and previous chemotherapy treatment are thought to make individuals more vulnerable to peripheral neuropathies.<sup>176</sup>

Central nervous neuropathies have also been described for chemotherapeutic agents capable of crossing the blood-brain barrier such as cisplatin, methotrexate, and cytarabine.<sup>176</sup> Symptoms can appear quickly after receiving drugs and may include headaches, strokes, seizures, and aseptic encephalopathy.

Affected individuals may complain of noticeable short-term memory loss or difficulty concentrating classified as a mild cognitive impairment (MCI) but often referred to as "chemo brain" or "brain fog." Chemotherapy-induced MCI occurs in up to 40% of patients.<sup>159,179</sup> Many people using computers on the job report delays in their work output as they have to relearn and retrain themselves to do tasks that were automatic before cancer treatment.<sup>67</sup>

Symptoms are transient but may take several years to disappear.<sup>104</sup> Of increasing concern is the observation that chemotherapy-induced CNS defects may take many months to years to develop. For example, 26% of long-term survivors of methotrexate treatment presented with neurologic complications, including both motor and cognitive deficits 68 months after treatment.<sup>18</sup>

## Adverse Effects of Stem-Cell Transplantation

The use of high-dose chemotherapy with stem-cell transplantation (SCT) has increased as a treatment for malignant diseases such as leukemia and lymphomas. The individual may receive reinfusion of his or her own stem cells (autologous or autoSCT) or infusion of stem cells from a healthy donor (alloSCT).

SCT is preceded by an intensive course of high-dose chemotherapy and/or total body irradiation to destroy any residual malignant cells in the body. The process is called the *conditioning regimen*. The risk of infection is great during this phase before the "rescue" when tumor-free stem cells are introduced into the body.

Diminished functional capacity, poorer quality of life, and increased symptoms are typical immediately after the ablative regimen. Side effects of this treatment are those typical of transplantation, chemotherapy, and/or radiotherapy and include nausea, vomiting, anorexia (appetite and weight loss), mucositis, hemorrhagic cystitis, fluid and electrolyte imbalances, dermatologic reactions, renal failure, venoocclusive disease, and graft-versus-host disease.

## SPECIAL IMPLICATIONS FOR THE THERAPIST

5-7

### **Chemotherapy**

The period during chemotherapy administration is critical for each client who may be susceptible to spontaneous hemorrhage and infection. Anyone receiving chemotherapeutic drugs is at increased risk of acquiring an infection because these drugs often reduce WBC numbers.

Because neutropenia can occur with a normal WBC count, the number of absolute neutrophil count (ANC) is often used as a measure of neutropenia. An ANC count of less than 1500 cells per mm<sup>3</sup> defines neutropenia.

The usual precautions for infection control must be strictly adhered to, including proper hand hygiene and the usual precautions for thrombocytopenia (see Chapter 14). The importance of strict handwashing technique with an antiseptic solution cannot be overemphasized.

The therapist should be alert to any sign of infection and report any potential site of infection such as mucosal ulceration or skin abrasion or tear. Check skin for petechiae, ecchymoses, cellulitis, and secondary infection.

Myelosuppression or bone marrow suppression is the most frequent side effect of many chemotherapeutic drugs. These drugs can cause the circulating numbers of one or more of the mature RBCs to fall to dangerous levels. Significantly decreased hemoglobin, hematocrit, and RBC numbers can compromise an individual's ability to engage in physical activity.

Drug-induced mood changes ranging from feelings of well-being and euphoria to depression and irritability may occur; depression and irritability may also be associated with the cancer. Knowing these and other potential side effects of medications used in the treatment of cancer can help the therapist better understand client reactions during rehabilitation or therapy intervention.

Collectively, the therapist should do the following:

- Be aware of the possibility of myelosuppression in the person on chemotherapy drugs.
- Monitor the hematology values in these individuals.
- Be aware of the signs and symptoms of the major side effects of myelosuppression (e.g., anemia, infection, and bleeding).
- Treat clients appropriately within the context of the limitations and risks represented by myelosuppression.

As part of the cancer care team, the therapist should keep abreast of reliable up-to-date information about treatment. The American Cancer Society (ACS) publishes many patient education materials such as *Understanding Chemotherapy: A Guide for Patients and Families*. These types of introductory materials may help the therapist come to a better understanding of the patient's own early experiences and questions.

*Continued.*

Patient education materials are usually provided free. Contact the local ACS office; if there is no local or district office, then contact the national organization ([www.cancer.org](http://www.cancer.org) or (800) ACS-2345).

### Late Effects of Chemotherapy

It is important for the therapist to realize that the adverse effects of many chemotherapeutic agents may not appear for many years after treatment has been completed. For example, bleomycin can cause significant pulmonary fibrosis resulting in decreased pulmonary function; Adriamycin can cause significant cardiac damage 5 to 20 years after treatment; and growth hormone deficiency is the most common endocrinopathy after cranial radiation for brain tumor.

Survivors face an increased risk of morbidity, mortality, and diminished quality of life associated with cancer treatment. Risk is further modified by the survivor's genetics, lifestyle habits, and comorbid health conditions. Oeffinger and Hudson provide an in-depth review of the potential long-term complications and excellent tool for clinicians to use when providing care for a survivor.<sup>122</sup>

Because a therapist is less likely to see individuals receiving these drugs acutely, the greater concern is for the cardiac and other organ damage, which manifests itself months to years after the cancer treatment has ended. Survivors of childhood and adolescent cancer are one of the higher risk populations seen. The curative therapy administered for the cancer also affects growing and developing tissues.<sup>122</sup>

Careful history taking is important in gaining this information. The therapist must be aware of this because it may explain the symptoms the therapist is evaluating or create comorbid conditions that impact the plan of care. See Chapter 12 for more information regarding the cardiotoxicity of chemotherapeutic agents.

### Neuropathy

Neuropathy can occur as a result of the neurotoxic effects of chemotherapy (e.g., cisplatin, vincristine, or vinblastine), causing sensory, motor, and/or autonomic deficits. The therapist should pay attention to any reports of pain, burning pain, numbness, and/or the sensation of pins and needles in the hands and/or feet, as well as motor deficits in lower extremity muscles.

Sensory or motor loss in the lower extremities can lead to gait abnormalities, loss of balance, and increased risk for falls. Careful attention should be paid to lower extremity peripheral sensation and manual muscle testing during the history and physical examination of anyone currently on these drugs or for those who have recently discontinued their use.

For the immobile client, prevention of pressure ulcers through client and family education and positioning with appropriate protection (e.g., footboard to prevent foot drop and protective coverings such as sheepskin and eggshell foam) are also important. For the mobile client, safety standards must be followed

during ambulation because of weakness and numbness of the extremities.

### Chemotherapy and Exercise<sup>46</sup>

Fatigue is a common and severe problem for many individuals undergoing chemotherapy or chemoradiotherapy to the extent that some people are unable to carry out usual daily activities (see the section on Radiation Therapy and Exercise in this chapter), both during treatment and for months afterward. The therapist can identify CRF as a potential problem by asking individuals undergoing cancer treatment to quantify their fatigue level from zero (no fatigue) to 10 (extreme fatigue) using the visual analogue scale (VAS).

Before beginning or advancing an exercise program, the therapist should screen for possible energy draining conditions such as dehydration (especially for anyone with vomiting and/or diarrhea), malnutrition, anorexia, and sleep disturbances.

Additionally, other effects of treatment, such as anemia and cardiotoxicity, can severely affect a person's functional ability. Although erythropoietin (e.g., EpoGen/Procrit) is available to reverse anemia from chemotherapy for specific cancers, exercise is an important adjunct in client treatment.

Research has shown that people recovering from high-dose chemotherapy should not be instructed to rest but should increase physical activity to reduce fatigue and improve physical performance.<sup>52</sup> Prolonged rest and decreased activity coupled with sleep disturbances or too much sleep can contribute to CRF. An optimal balance of rest and physical exercise is essential to the successful treatment of these symptoms.<sup>2,3,46,48,184</sup>

Results indicate that 6 weeks of endurance training consisting of low-to-moderate levels of aerobic exercise (walking for 30 minutes daily on a treadmill after an interval-training program) yielded a significant improvement of physical performance and a reduction of fatigue, along with an improved mood and reduced mental stress while undergoing chemotherapy.<sup>47</sup> Additionally, no reported increases in chemotherapy-related complications were associated with an endurance-training program.

Clearly, low-to-moderate physical levels of aerobic activity yield a reduction in fatigue and an improvement in quality of life,<sup>46,49,125</sup> so the challenge to the therapist is to keep the client active in the context of the fatigue. The therapist can monitor the presence and extent of fatigue in these individuals and schedule treatment times that coincide with periods when they have the most energy. Activities and activity demands need to be tailored to match the energy levels of the client. Teaching the use of energy conservation techniques can increase the energy available for activities of daily living (ADLs) and participation in therapy sessions.

Before any type of vigorous exercise or rehabilitative treatment is initiated, laboratory values should be evaluated (see Box 9-6). For those clients with symptomatic anemia, therapists should follow precautions as outlined (see the section on Anemia in Chapter

14). Bone marrow suppression is a common and serious side effect of many chemotherapeutic agents. It is extremely important to monitor the hematology values in clients receiving antineoplastic treatment.

Winningham suggests that exercise should be restricted when hemoglobin levels fall below 10 g/dl (see Box 9-6); however, clients can experience fatigue with values between 10 and 13 g/dl. Reference values may vary from person to person and especially among clients who are being treated using principles of bloodless medicine (see Chapter 14).

Chemotherapeutic drugs often cause thrombocytopenia or depress the number of platelets. Because platelets are essential for clot formation, symptoms of this condition include easy or excessive bruising, nose or gum bleeds, skin rashes, or petechiae. Platelet counts of less than 50,000/ml have been suggested as a contraindication to physical activity, but people with platelet counts of 10,000/ml have been successfully treated. See also Chapter 9 for further discussion of cancer, physical activity, and exercise training.



**Figure 5-6**

**Nodular vasculitis caused by inflammation of the medium blood vessels.**  
(From du Vivier A: *Atlas of clinical dermatology*, ed 2, London, 2002, Gower.)

## SPECIFIC DISORDERS AFFECTING MULTIPLE SYSTEMS

### Vasculitic Syndromes

*Vasculitis* is a term that applies to a diverse group of diseases characterized by inflammation in blood vessel walls. The primary forms of vasculitis encountered in a therapy practice include giant cell (temporal) arteritis, Takayasu's arteritis, Behcet's disease, polyarteritis nodosa, Wegener's granulomatosis, and Kawasaki disease. These are discussed in greater detail in Chapter 12. Because the pathogenesis of most forms of vasculitis remains poorly understood and cases of vasculitis show great variability, it may not be possible to apply a specific disease label to such cases. Such instances of vasculitis may be diagnosed as *systemic vasculitis*.

Blood vessels of different sizes in various parts of the body may be affected by vasculitis, causing a wide spectrum of clinical manifestations. The inflammation often causes narrowing or occlusion of the vessel lumen and produces ischemia of the tissues that are supplied by the involved vessels. The inflammation may weaken the vessel wall, resulting in aneurysm or rupture. Large vessel disease often produces limb claudication, aortic dilation, and bruits. Vasculitis of the medium vessels causes cutaneous nodules (Fig. 5-6), gangrene of the digits, mononeuritis multiplex, and microaneurysms. Palpable purpura, glomerulonephritis, and alveolar hemorrhage can be seen in affected small vessels.

Most clients with vasculitis will exhibit constitutional symptoms such as fever, arthralgias, arthritis, weight loss, and malaise.<sup>161</sup> Vasculitis may occur as a primary disease (as described previously); as a secondary manifestation of other illnesses such as RA, infection, malignancy, or serum sickness; or as a drug-induced illness.

### Rheumatoid Arthritis

RA is best known as a progressive, autoimmune disease affecting the synovial tissue and joints. Yet RA has many extraarticular manifestations involving bone, muscle, eyes, lung, heart, and the skin. The most frequent skin manifestation is the rheumatoid nodule. These are most commonly found subcutaneously on extensor surfaces, such as the forearm, but have been noted on the heart, lung, sacrum, larynx, and leptomeninges.

RA involvement of the lungs and heart is multiple and varied, depending on the portion of the organ affected. Other extraarticular conditions that can occur with RA include vasculitis, anemia, and osteopenia/osteoporosis. *Rheumatoid vasculitis* has become much less frequent over the last decade, probably because of disease-modifying agents, yet it remains the most feared complication of RA, with considerable morbidity and mortality. Vasculitis is more common in men and usually develops in persons with the most significant active disease (deforming arthritis and high rheumatoid factor titers). (See the section on Collagen Vascular Disease in Chapter 12.)

Clinical features of systemic rheumatoid vasculitis are diverse because any size blood vessel may be involved anywhere in the body. The most common findings are cutaneous lesions such as nail-edge infarctions (e.g., splinter hemorrhages; see Fig. 27-14), purpura (see Fig. 5-1), and skin ulcers (e.g., pyoderma gangrenosum). Skin ulcers usually develop suddenly as deep, punched-out lesions at sites that are unusual for venous

ulceration, such as the dorsum of the foot or the upper calf.

Neurologic manifestations of RA vasculitis present most commonly as either a mild distal sensory neuropathy (paresthesia or numbness) or as a severe sensorimotor neuropathy such as mononeuritis multiplex. These clients exhibit sensory symptoms with muscle weakness (e.g., foot drop). These may be the only extraarticular manifestations of RA.

Vasculitis may involve visceral organs such as the heart (causing a myocardial infarction) and lungs (leading to pulmonary hypertension). Infarction of the intestine may occur, requiring bowel resection.

Systemic manifestations of rheumatoid vasculitis may include unexplained weight loss, anorexia, and malaise. Malaise may be related to the release of cytokines (substances released by lymphocytes with various immunologic functions) and may be accompanied by fatigue, low-grade fever, and night sweats. Individuals with severe RA who experience any of these symptoms should be referred to the physician for further evaluation. Clients with multiple manifestations of vasculitis have a poor prognosis and require aggressive treatment.

Anemia secondary to RA is usually mild with normocytic/hypochromic features. Over three-fourths of people with RA and anemia have anemia of chronic disease, which is typically proportional to the disease severity and resolves as RA is brought under control. If iron deficiency is noted in an RA client, sources of bleeding must be explored such as GI bleeding from therapy with NSAIDs. Vitamin B12 and folate deficiency are also common in this population and should also be addressed. The therapist should follow special precautions related to anemia until the disease is under control (see Special Implications for the Therapist: Anemia in Chapter 14).

Osteopenia and osteoporosis may result from postmenopausal bone loss, treatment with glucocorticoids, or general immobility, but it may also be an inherent part of RA. Because most clients with RA may have all these risk factors for bone loss, they should be aggressively treated to reduce bone loss. With long-standing disease, osteoporosis may become generalized and can lead to fractures after minimal stress, particularly the fibula.

## Systemic Lupus Erythematosus

Lupus erythematosus is an autoimmune disease that appears in two forms: discoid lupus erythematosus (DLE), which affects only the skin, and systemic lupus erythematosus (SLE), which affects both multiple organ systems and the skin and can be fatal. SLE most commonly causes rashes of the skin, polyarthritis, and myalgias. The most serious complications affect the heart, kidneys, and CNS. Like RA, SLE is characterized by recurring remissions and exacerbations, although complete remission is rare.

SLE affects women eight times as often as men, increasing to 15 times as often during childbearing years. (For further discussion of DLE see Chapter 10; see Chapter 7 for discussion of SLE.)

## Systemic Sclerosis

Systemic sclerosis, also known as *progressive systemic sclerosis* (PSS) or scleroderma, is a generalized connective tissue disorder of unknown etiology characterized by thickening and fibrosis of the skin. It may also affect internal organs, namely the heart, lungs, GI tract, and kidneys.

Although there are many subgroups termed *scleroderma*, it is often categorized into two main subgroups: diffuse cutaneous scleroderma (skin involvement of the trunk, face, and proximal and distal extremities) and limited cutaneous scleroderma (involvement of the skin of the face and neck but distal to the elbow and knee). Limited cutaneous scleroderma was previously known as the CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia). These subgroups help clinically prognosticate since individuals with diffuse cutaneous scleroderma are more likely to develop organ involvement earlier in the progression of the disease.

There is significant variability of symptoms and organ involvement between clients. It affects women more than men, especially between ages 30 and 50 years. Scleroderma has no current significant disease-modifying treatments and the morbidity and mortality are high. Approximately 30% of people with PSS die within 5 years of onset. (See Chapter 10 for discussion of this condition.)

## Tuberculosis

Tuberculosis (TB) is an acute or chronic infection caused by *Mycobacterium tuberculosis*. Although the primary infection site is the lung, mycobacteria commonly exist in other parts of the body; this is referred to as *extrapulmonary tuberculosis*. The extrapulmonary sites may include the renal system, skeletal system (osteomyelitis; vertebral TB is known as *Pott's disease*), GI tract, meninges (tuberculous meningitis), and genitals. Extrapulmonary tuberculosis occurs with increased frequency in people with HIV infection (see Chapter 15 for more on pulmonary tuberculosis; see Chapter 25 for more on tuberculous spondylitis [*Pott's disease*]).

## Sarcoidosis

Sarcoidosis is a multisystem disorder characterized by the formation of noncaseating granulomas, which are inflammatory cells (e.g., mononuclear inflammatory cells or macrophages) usually surrounded by a rim of lymphocytes. These granulomas may develop in any organ but often are noted in multiple organs at once, including the lungs, lymph nodes, liver, bones, or eyes (see Box 15-10) and may be accompanied by skin lesions (see Fig. 15-21). Presenting symptoms of sarcoidosis can often be confused with other inflammatory or infectious processes, making the diagnosis difficult. In the United States, sarcoidosis occurs predominantly among blacks and affects twice as many women as men.

Sarcoidosis is often referred to as either acute or chronic. Acute sarcoidosis is abrupt in onset, frequently

involving the eyes and skin. Bell's palsy may also be seen. Acute sarcoidosis is transient, often with a good prognosis and complete resolution of symptoms. Chronic sarcoidosis is typically more insidious in onset and occurring in older individuals. Fibrosis formation is prevalent, involving the heart, lung, kidneys, and bone. There is significant morbidity and mortality associated with chronic sarcoidosis, with recurrence of the disease despite treatment (see Chapter 15 for a complete discussion of this condition).

## Multiple Organ Dysfunction Syndrome

### Overview

Care of critically ill people has progressed significantly during the last 50 years. Substantial advances have been made in the care of shock, acute renal failure, acute brain injury, and acute respiratory failure, with more people surviving these conditions.

However, despite these advances, progressive deterioration of organ function may occur in people who are critically ill or injured. People often die of complications of disease, rather than from the disease itself. Multiple organ dysfunction syndrome (MODS) is often the final complication of a critical illness; it is one of the most common causes of death in the ICU.<sup>63</sup>

### Definition and Etiologic and Risk Factors

MODS, also called *multiple organ failure syndrome* (MOFS), is the progressive failure (more than 24 hours) of two or more organ systems after a severe illness or injury. Although sepsis and septic shock are the most common causes,<sup>192</sup> infection is not required for its development. MODS also can be triggered by ARDS, severe inflammatory processes (e.g., pancreatitis), other types of shock, and traumatic injury (e.g., burns or surgery). MODS carries a high mortality rate that increases with each organ that fails.

Systemic inflammatory response syndrome (SIRS) characterizes the clinical manifestations of hypermetabolism (e.g., increased temperature, heart rate, and respirations) present in many clients with MODS. Because it is a response to tissue insult or injury, SIRS is present in many individuals admitted to an ICU.

After an initial insult or injury, other factors can increase the risk of developing MODS/SIRS, including inadequate or delayed resuscitation, age over 65 years, alcoholism, diabetes, surgical complications (e.g., infection, hematoma formation), bowel infarction, or the previous existence of organ dysfunction (e.g., renal insufficiency).

### Pathogenesis

Although MODS may be a final common pathway in critical illnesses, actual causes and cellular changes leading to MODS are not completely understood. Most likely multiple mechanisms and factors are responsible or contribute to the development of MODS. In response to illness or traumatic injury, the neuroendocrine system activates stress hormones (e.g., Cortisol, epinephrine, norepinephrine, or endorphins) to be released into the

circulation, whereas the sympathetic nervous system is stimulated to compensate for complications such as fluid loss and hypotension.

Because of the initial insult, proinflammatory cytokines (e.g., interferons and tumor necrosis factor) and enzymes are released with the overall effect of massive uncontrolled systemic immune and inflammatory responses. This hyperinflammation and hypercoagulation perpetuates edema formation, cardiovascular instability, endothelial damage, and clotting abnormalities.

At the same time, initial oxygen consumption demand increases because the oxygen requirements at the cellular level increase. Flow and oxygen consumption are mismatched because of a decrease in oxygen delivery to the cells caused by maldistribution of blood flow, myocardial depression, and a hypermetabolic state. The end result is abnormal cellular respiration and function (tissue hypoxia with cellular acidosis and death), resulting in the multiple organ dysfunction characteristic of MODS.<sup>127</sup>

### Clinical Manifestations

A clinical pattern in the development of MODS has been well established. After the precipitating event, low-grade fever, tachycardia, dyspnea, SIRS, and altered mental status develop. The lung is the first organ to fail, resulting in ARDS (see Chapter 15).

Between 7 and 10 days, the hypermetabolic state intensifies, GI bacteremia is common, and signs of liver and kidney failure develop. During days 14 to 21, renal and liver failures progress to a severe status and the GI and immune systems fail, with eventual cardiovascular collapse. Ischemia and inflammation are responsible for the CNS manifestations. Protein metabolism is also affected, and amino acids derived from skeletal muscle, connective tissue, and intestinal viscera become an important energy source. The result is a significant loss of lean body mass.

### MEDICAL MANAGEMENT

Prevention and early detection and supportive therapy are essential for MODS, as no specific medical treatment exists for this condition. A way to halt the process, once it has begun, has not yet been discovered. Pharmacologic treatment may include antibiotics to treat infection, inotropic agents (e.g., dopamine or dobutamine) to counteract myocardial depression, and supplemental oxygen and ventilation to keep oxygen saturation levels at or above 90%.

Fluid replacement and nutritional support are also provided. The recent development of monoclonal antibodies to modulate or inhibit the immune and inflammatory responses may lead to more specific pharmacologic treatment.<sup>97</sup>

MODS is the major cause of death (usually occurring between days 21 and 28) after septic, traumatic, and burn injuries. If the affected individual's condition has not improved by the end of the third week, survival is unlikely. The mortality rate of MODS is 60% to 90% and approaches 100% if three or more organs are involved, sepsis is present, and the individual is older than 65 years.

## SPECIAL IMPLICATIONS FOR THE THERAPIST

5-8

**Multiple Organ Dysfunction Syndrome**

Only the critical care or burn unit therapist will encounter the client with MODS/SIRS. The hypermetabolism associated with this condition is accompanied by protein catabolism, primarily of skeletal muscle and visceral organs. Lean body mass can be significantly depleted in 7 to 10 days, necessitating skin precautions and skin care.

the scope of this text. For a more in-depth study of these concepts, the reader is referred to the latest edition of Guyton AC, Hall JE: *Textbook of medical physiology*, Philadelphia, WB Saunders.

**Aging and Fluid and Electrolyte Balance**

The volume and distribution of body fluids composed of water, electrolytes, and nonelectrolytes vary with age, gender, body weight, and amount of adipose tissue. Throughout life, a slow decline occurs in lean body or fat-free mass with a corresponding decline in the volume of body fluids. Only 45% to 50% of the body weight of aging adults is water compared with 55% to 60% in younger adults. This decrease represents a net loss of muscle mass and a reduced ratio of lean body weight to total body weight and places older people at greater risk for water-deficit states.

There are also changes in the kidney that further potentiate the risk for fluid and electrolyte disturbances. With increasing age, there is a decrease in renal mass and glomerular filtration rate (GFR). This in turn may lead to the inability of the aging kidney to excrete free water in the face of fluid excess, causing hyponatremia.

Yet hypernatremia can also be problematic in the aging adult secondary to a defect in the ability of the kidney to concentrate urine combined with a decreased thirst despite dehydration, often seen with age. Although these changes are seen in normal aging, factors that depress the sensorium in the frail and sick elderly (stroke and medications) further complicate hypernatremia by suppressing the natural compensatory mechanism for fluid intake.

Infection, dementia, neurologic disorders, and other systemic illnesses can decrease the release of arginine vasopressin (AVP), further placing older adults at high risk for dehydration.<sup>25</sup> Renin and aldosterone decrease with age accompanied by a blunted response to aldosterone. These changes can lead to hyperkalemia, particularly if other factors are present such as the use of potassium-sparing diuretics.

**Fluid Imbalances****Overview**

Approximately 45% to 60% of the adult human body is composed of water, which contains the electrolytes that are essential to human life (see the section on Electrolytes in this chapter). This life-sustaining fluid is found within various body compartments, including the intracellular (within cells), interstitial (space between cells), intravascular (within blood vessels), and transcellular compartments.

Fluid in the transcellular compartment is present in the body but is separated from body tissues by a layer of epithelial cells. This fluid includes digestive juices, water, and solutes in the renal tubules and bladder, intraocular fluid, joint-space fluid, and cerebrospinal fluid. The fluid in the interstitial and intravascular compartments comprises approximately one-third the total body fluid, called the *extracellular fluid* (ECF). Fluid found inside the cells

**FLUID AND ELECTROLYTE IMBALANCES**

Observing clinical manifestations of fluid or electrolyte imbalances may be an important aspect of client care, especially in the acute care and home health care settings. Identifying clients at risk for such imbalances is the first step toward early detection.

The causes of fluid and electrolyte imbalance are many and varied and include disease processes, injury, medications, medical treatment, dietary restrictions, and imbalance of fluid intake with fluid output.<sup>169</sup> The most common causes of fluid and electrolyte imbalances in a therapy practice include burns, surgery, diabetes mellitus, malignancy, alcoholism, and the various factors affecting the aging adult population (Box 5-7).

This is a brief presentation of the normal homeostatic processes of fluid and electrolyte balance. The interactions of these systems and how they maintain fluid and electrolyte balance and acid-base regulation are beyond

**Box 5-7****FACTORS AFFECTING FLUID AND ELECTROLYTE BALANCE IN THE AGING**

- Acute illness (fever, diarrhea, vomiting)
- Bowel cleansing for GI diagnostic testing
- Change in mental status
- Constipation
- Decreased thirst mechanism
- Difficulty swallowing
- Excessive sodium intake:
  - Diet
  - Sodium bicarbonate antacids (e.g., Alka-Seltzer)
  - Water supply or water softener
  - Decreased taste sensation (increased salt intake)
- Excessive calcium intake:
  - Alkaline antacids
- Immobility
- Laxatives (habitual use for constipation)
- Medications:
  - Antiparkinsonian drugs
  - Diuretics
  - Propranolol
  - Tamoxifen (breast cancer therapy)
- Sodium-restricted diet
- Urinary incontinence (voluntary fluid restriction)

accounts for the remaining two-thirds of total body fluid, called the *intracellular fluid* (ICF).

The cell membrane is water permeable with equal concentrations of dissolved particles on each side of the membrane maintaining equal volumes of ECF and ICF and preventing passive shifts of water. Passive shifts occur only if an inequality occurs on either side of the membrane in the concentration of solutes that cannot permeate the membrane. For example, water will move from one compartment to another if there is a change in sodium ion concentration.

The following five types of fluid imbalances may occur:

1. ECF volume deficit (ECFVD)
2. ECF volume excess (ECFVE)
3. ECF volume shift
4. ICF volume excess (ICFVE)
5. ICF volume deficit (ICFVD)

A simpler approach to this subject is to view fluid shifts in terms of intravascular or extravascular movement. Movement from the vascular space to the extravascular areas and vice versa takes place easily and is the first mechanism of extracellular movement.

*Increased intravascular fluid* results in CHF and increased pulse and respiration. *Decreased intravascular fluid* results in decreased blood pressure and increased pulse and respirations. However, *increased extravascular fluid* may cause edema, ascites, or pleural effusion. *Decreased extravascular fluid* results in decreased skin turgor and fatigue. The material in this section is presented on the bases of three broad categories: fluid deficit, fluid excess, and fluid shift (see Chapter 13).

### Etiologic Factors and Pathogenesis

Maintaining constant internal conditions (homeostasis) requires the proper balance between the volume and distribution of ECF and ICF to provide nutrition to the cells, allow excretion of waste products, and promote production of energy and other cell functions. Maintenance of this balance depends on the differences in the concentrations of ICF and ECF fluids, the permeability of the membranes, and the effect of the electrolytes in the fluids.

A fluid imbalance occurs when either the ICF or ECF gains or loses body fluids or electrolytes, causing a fluid deficit or a fluid excess. Sodium is the major ion that influences water retention and water loss. A deficit of body fluids occurs with either an excessive loss of body water or an inadequate compensatory intake. The result is an insufficient fluid volume to meet the needs of the cells. It is manifested by dehydration (Box 5-8); hypovolemia, such as blood or plasma loss; or both. Severe fluid volume deficit can cause vascular collapse and shock.

An *excess* of water occurs when an overabundance of water is in the interstitial fluid spaces or body cavities (edema) or within the blood vessels (hypervolemia). A *fluid shift* occurs when vascular fluid moves to interstitial or intracellular spaces or interstitial or intracellular fluid moves to vascular fluid space.

Fluid that shifts into the interstitial space (i.e., fluid not in the vascular compartment) and remains there is referred to as *third-space fluid*. Third-space fluid is commonly seen in a therapy practice as a result of altered

### Box 5-8

#### CLINICAL MANIFESTATIONS OF DEHYDRATION

- Absent perspiration, tearing, and salivation
- Body temperature (subnormal or elevated)
- Confusion
- Disorientation; comatose; seizures
- Dizziness when standing
- Dry, brittle hair
- Dry mucous membranes, furrowed tongue
- Headache
- Incoordination
- Irritability
- Lethargy
- Postural hypotension
- Rapid pulse
- Rapid respirations
- Skin changes:
  - Color: gray
  - Temperature: cold
  - Turgor: poor
  - Feel: Warm, dry if mild; cool, clammy if severe
- Sunken eye
- Sunken fontanel (children)

capillary permeability secondary to tissue injury or inflammation, but the most common cause is liver disease. Decreased serum protein (albumin) associated with liver disease and/or states of malnutrition results in third-space fluid.

Other areas called *potential spaces* can fill with fluid in the presence of inflammation or fluid imbalances. Examples of potential spaces include the peritoneal cavity fluid (e.g., ascites) and the pleural cavity (e.g., pleural effusion).

### Clinical Manifestations

*Fluid volume deficit* (FVD) is most often accompanied by symptoms related to a decrease in cardiac output such as decreased blood pressure, increased pulse, and orthostatic hypotension. FVD can occur from loss of blood (whether obvious hemorrhage or occult GI bleeding), loss of plasma (burns or peritonitis), or loss of body fluids (diarrhea, vomiting, diaphoresis, or lack of fluid intake), resulting in dehydration.

Hypernatremia occurs if the body fluid loss is a loss of body water without solute components (e.g., diabetes insipidus). Most often, however, body fluid losses contain both body water and its solute components. The affected individual experiences symptoms of thirst, weakness, dizziness, decreased urine output, weight loss, and altered levels of consciousness (i.e., confusion). Significant decreases in systolic blood pressure (less than 70 mm Hg) result in symptoms of shock and require immediate medical treatment and possibly life-sustaining emergency management.

*Fluid volume excess* (FVE) is primarily characterized by weight gain and edema of the extremities. With intravascular FVE, other clinical manifestations include dyspnea, engorged neck veins, and a bounding pulse. In the early stages, if the fluid is in the third space (interstitial fluid

between cells), the person may not exhibit any of these symptoms.

*Fluid shift* from the vascular to the extravascular (interstitial) spaces (e.g., burns or peritonitis) is manifested by signs and symptoms similar to fluid volume deficit and shock, including skin pallor, cool extremities, weak and rapid pulse, hypotension, oliguria, and decreased levels of consciousness. When the fluid returns to the blood vessels, the clinical manifestations are similar to those of fluid overload such as bounding pulse and engorgement of peripheral and jugular veins.

## MEDICAL MANAGEMENT

The ECF is the only fluid compartment that can be readily monitored; clinically, the status of ICF is inferred from analysis of plasma and the condition of the person. A fluid balance record is kept on any individual who is susceptible or already experiencing a disturbance in the balance of body fluids. In addition, medical evaluation of clinical signs and laboratory tests are helpful in the assessment of a person's hydration status. Laboratory tests may include serum osmolality, sodium, hematocrit, and BUN measurements (see the section on Laboratory Values in Chapter 40).

Serum osmolality measures the concentration of particles in the plasma portion of the blood. Osmolality increases with dehydration and decreases with overhydration. Serum sodium is an index of water deficit or excess; an elevated level of sodium in the blood (hypernatremia) would indicate that the loss of water from the body has exceeded the loss of sodium such as occurs in the administration of osmotic diuretics, uncontrolled diabetes insipidus, and extensive burns. Hematocrit increases with dehydration and decreases with excess fluid. BUN serves as an index of kidney excretory function; BUN increases with dehydration and decreases with overhydration (see Table 40-2).

Treatment is directed to the underlying cause; in the case of FVD, the aim is to improve hydration status. This may be accomplished through replacement of fluids and/or electrolytes by oral, nasogastric, or IV means.

### SPECIAL IMPLICATIONS FOR THE THERAPIST

5-9

#### Fluid Imbalances

##### Monitoring Fluid Balance

Fluid balance is so critical to physical well-being and cardiopulmonary sufficiency that fluid input and output records are often maintained at bedside. The therapist may be involved in maintaining these records, which also include fluid volume lost in wound drainage, GI output, and fluids aspirated from any body cavity. Body weight may increase by several pounds before edema is apparent. The dependent areas manifest the first signs of fluid excess. Individuals on bed rest show sacral swelling; people who can sit on the edge of the bed or in a chair for prolonged periods tend to show swelling of the feet and hands.<sup>35</sup>

Water and fluids should be offered often to older adults and clients with debilitating diseases to prevent body fluid loss and hypernatremia. However, increas-

ing fluid intake in clients with CHF or severe renal disease is usually contraindicated.

Caffeinated fluids and alcohol can increase water loss, thereby increasing the serum sodium level; these beverages should be avoided to prevent fluid loss due to this diuretic effect. Water is the preferred fluid for hydration except in athletic or marathon race situations, which require replacement of electrolytes.<sup>64</sup>

Thirst is not always a reliable signal for fluid intake or even dehydration. A person may not feel "thirsty" until the body reaches a dangerous point of fluid loss. Therapists and clients should both be encouraged to keep water and clear fluids on hand and drink on a schedule rather than wait until they feel thirsty. Many people confuse thirst for hunger and eat instead of drinking when the thirst mechanism does kick in.

Urine is good gauge of adequate hydration. A low volume of dark or highly concentrated urine is a yellow flag. When accompanied by other signs of dehydration (e.g., dry mouth, irritability, constipation, fatigue, or muscle weakness), it becomes a red flag.

#### Dehydration

Healthy older adults can become at risk for dehydration for many physiologic and psychosocial reasons. Older individuals have an impaired thirst response to dehydration; abnormal circadian rhythm of AVP leads to nocturia and increased fluid loss. Other contributing medical factors include diabetes, urinary tract infections, renal failure, and medications such as diuretics.<sup>112</sup>

Psychosocial factors also play a key role in the development of dehydration in the older age group. Isolation, depression, and confusion are associated with reduced oral intake and impaired fluid status and can make dehydration worse.<sup>112</sup>

Dehydration (water deficit) degrades endurance exercise performance, and physical work capacity is diminished even at marginal levels of dehydration (defined clinically as a 1% loss of body weight through fluid loss). Alterations in  $V_{O_{2 \text{ max}}}$  occur with a 2% or more deficit in body water loss. Greater body water deficits are associated with progressively larger reductions in physical work capacity.

Dehydration results in larger reductions in physical work capacity in a hot environment (e.g., aquatic or outdoor setting) for individuals in any age group, as compared with a thermally neutral environment. Prolonged exercise that places large demands on aerobic metabolism is more likely to be adversely affected by dehydration than is short-term exercise.<sup>30</sup>

Core body temperature increases predictably as the percentage of dehydration increases. The heart rate increases about 6 beats/minute for each 1% increase in dehydration. This is not true for older adults, who may have limited rate changes with increased activity.

Older individuals are especially at risk for negative sequelae associated with dehydration. Hospitalization for dehydration is common and mortality is high. Almost 50% of Medicare patients who are

hospitalized with dehydration die within a year of admission.<sup>112,177,178</sup>

Anyone with hypovolemia cannot compensate as easily with an increased heart rate like younger people can, so shock is more difficult to treat. In addition, aging individuals are often being treated with cardiac medications, such as ( $\beta$ -blockers or digoxin, that block or inhibit a rapid heart rate and limit rate changes with increased activity. Heart transplant recipients also have a unique situation because the heart has been denervated (see Special Implications for the Therapist: Heart Transplantation in Chapter 21).

Individuals exercising in the heat, including aquatic exercise, should be encouraged to drink water in excess of normally desired amounts. When exercise is expected to cause an increase of more than 2% in dehydration, target heart rate modifications are necessary.<sup>105</sup>

Severe losses of water and solutes can lead to hypovolemic shock. It is important for the therapist to be aware of possible fluid losses or water shifts in any client who is already compromised by advanced age or by the presence of an ileostomy or tracheostomy that results in a continuous loss of fluid.

Dehydration may contribute to underlying disabilities caused by orthostatic hypotension and dizziness. It may result in symptoms, such as confusion and weakness, that can interfere with rehabilitation outcomes, especially after orthopedic surgery.<sup>112</sup>

Because the response to fluid loss is highly individual, it is important to recognize the early clinical symptoms of fluid loss (see Box 5-6) and to carefully monitor clients who are at risk (e.g., observe for symptoms and monitor vital signs). People at risk for profound and potentially fatal FVD, as in severe and extensive burns, should be assessed frequently and regularly for mental acuity and orientation to person, place, and time.

### Skin Care

Careful handling of edematous tissue is essential to maintaining the integrity of the skin, which is stretched beyond its normal limits and has a limited blood supply. Turning and repositioning the client must be done gently to avoid friction. A break in or abrasion of edematous skin can readily develop into a pressure ulcer.

Client education may be necessary in the proper application and use of antiembolism stockings, lower-extremity elevation, and the need for regular exercise. Clients should be cautioned to avoid crossing the legs, putting pillows under the knees, or otherwise creating pressure against the blood vessels.<sup>50,119</sup>

## Electrolyte Imbalances

### Overview

Electrolytes are chemical substances that separate into electrically charged particles, called *ions*, in solution. The electrolytes that consist of positively charged ions, or *cations*, are sodium ( $\text{Na}^+$ ), potassium ( $\text{K}^+$ ), calcium ( $\text{Ca}^{2+}$ ), and magnesium ( $\text{Mg}^{2+}$ ). Those that consist of negatively

charged ions, or *anions*, are chloride ( $\text{Cl}^-$ ); bicarbonate ( $\text{HCO}_3^-$ ); and phosphate ( $\text{PO}_4^{3-}$ ).

Concentration gradients of sodium and potassium across the cell membrane produce the membrane potential and provide the means by which electrochemical impulses are transmitted in nerve and muscle fibers. Sodium affects the osmolality of blood and therefore influences blood volume and pressure and the retention or loss of interstitial fluid. Sodium imbalance affects the osmolality of the ECF and is often associated with fluid volume imbalances.

Adequate potassium is necessary to maintain function of sodium-potassium membrane pumps, which are essential for the normal muscle contraction-relaxation sequence. Imbalances in potassium affect muscular activities, notably those of the heart, intestines, and respiratory tract, and neural stimulation of the skeletal muscles.

Calcium influences the permeability of cell membranes and thereby regulates neuromuscular activity. Calcium plays a role in the electrical excitation of cardiac cells and in the mechanical contraction of the myocardial and vascular smooth muscle cells. An imbalance in calcium concentrations affects skeletal muscle, bones, kidneys, and the GI tract. Conditions that can cause movement of calcium from the bones into the ECF (e.g., bone tumors, multiple fractures, or osteoporosis) can cause hypercalcemia. (Other causes of hypocalcemia or hypercalcemia are listed in Table 5-9).

Magnesium, an important intracellular enzyme activator, exerts physiologic effects on the nervous system that resemble the effects of calcium. Magnesium plays a role in maintaining the correct level of electrical excitability in the nerves and muscle cells by acting directly on the myoneural junction. Magnesium depresses acetylcholine release at synaptic junctions; when concentrations of  $\text{Mg}^{2+}$  in the plasma are altered, then associated changes also occur in the concentration of  $\text{Ca}^{2+}$ . Magnesium imbalances affect parathyroid hormone (PTH) function and if severe, can change or impair end-organ response to PTH.

Neuromuscular irritability results from hypomagnesemia (e.g., poor diet, chronic alcohol abuse, diuretic use, or prolonged diarrhea), and magnesium excess (rare but occurs with renal failure or the overuse of magnesium-containing antacids) causes neuromuscular depression affecting the musculoskeletal and cardiac systems.<sup>123</sup>

### Etiologic and Risk Factors

An electrolyte imbalance exists when the serum concentration of an electrolyte is either too high or too low. Stability of the electrolyte balance depends on adequate intake of water and the electrolytes and on homeostatic mechanisms within the body that regulate the absorption, distribution, and excretion of water and its dissolved particles.

Bodily fluid loss associated with weight loss, excessive perspiration, or chronic vomiting and diarrhea are the most common causes of electrolyte imbalance. Many other conditions can interfere with these processes and result in an imbalance (see Table 5-9).

Ischemia is accompanied by electrolyte disturbances, particularly the release of potassium, calcium, and

**Table 5-9** Causes of Electrolyte Imbalances

	Risk Factors for Imbalance
<b>Potassium</b>	
Hypokalemia	Dietary deficiency (rare) Intestinal or urinary losses as a result of diarrhea or vomiting (anorexia, dehydration), drainage from fistulas, overuse of gastric suction Trauma (injury, burns, surgery): damaged cells release potassium, are excreted in urine Medications such as potassium-wasting diuretics, steroids, insulin, penicillin derivatives, amphotericin B Metabolic alkalosis Cushing's syndrome, severe magnesium deficiency Hyperaldosteronism Integumentary loss (sweating) Type 2 renal tubular acidosis Diabetic ketoacidosis
Hyperkalemia	Conditions that alter kidney function or decrease its ability to excrete potassium (chronic renal disease or renal failure) Intestinal obstruction that prevents elimination of potassium in the feces Addison's disease Chronic heparin therapy, lead poisoning, insulin deficit, NSAIDs, ACE inhibitors, cyclosporine Trauma: crush injuries, burns Metabolic acidosis Rhabdomyolysis Tumor lysis syndrome Hyperglycemia Digitalis toxicity Hypoaldosteronism
<b>Sodium</b>	
Hyponatremia	Inadequate sodium intake (low-sodium diets) Excessive intake or retention of water (kidney failure and heart failure) Excessive water loss and electrolytes (vomiting, excessive perspiration, tap-water enemas, suctioning, use of diuretics, diarrhea) Loss of bile (high in sodium) as a result of fistulas, drainage, GI surgery, and suction Trauma (loss of sodium through burn wounds, wound drainage from surgery) IV fluids that do not contain electrolytes Adrenal gland insufficiency (Addison's disease) or hypoaldosteronism Cirrhosis of the liver with ascites SIADH: brain tumor, cerebrovascular accident, pulmonary disease, neoplasm with ADH production, medications, pain, nausea Hypothyroidism Nephrotic syndrome
Hypernatremia	Decreased water intake (comatose, mentally confused, or debilitated client) Water loss (excessive sweating, osmotic diarrhea), fever, heat exposure, burns Hyperglycemia Excess adrenocortical hormones (Cushing's syndrome) IV administration of high-protein, hyperosmotic tube feedings and diuretics Diabetes insipidus Central: loss of neurohypophysis from trauma, surgery, neoplasm, CVA, infection Nephrogenic: renal resistance to ADH drugs (lithium), hypercalcemia, papillary necrosis, pregnancy
<b>Calcium</b>	
Hypocalcemia	Inadequate dietary intake of calcium and inadequate exposure to sunlight (vitamin D) necessary for calcium use (especially older adults) Impaired absorption of calcium and vitamin D from intestinal tract (severe diarrhea, overuse of laxatives, and enemas containing phosphates; phosphorus tends to be more readily absorbed from the intestinal tract than calcium and suppresses calcium retention in the body) Hypoparathyroidism (injury, disease, surgery) Severe infections or burns Overcorrection of acidosis Pancreatic insufficiency Renal failure Hypomagnesemia (especially with alcoholism) Medications: anticonvulsive medications

**Table 5-9** Causes of Electrolyte Imbalances—cont'd

Risk Factors for Imbalance	
Hypercalcemia	Hyperparathyroidism, hyperthyroidism, adrenal insufficiency Multiple fractures Excess intake of calcium (excessive antacids), excess intake of vitamin D, milk alkali syndrome Osteoporosis, immobility, multiple myeloma Thiazide diuretics Sarcoidosis Tumors that secrete PTH (bone, lung, stomach, and kidney) MEN tumors (types I and II)
<b>Magnesium</b>	
Hypomagnesemia	Decreased magnesium intake or absorption (chronic malnutrition, chronic diarrhea, bowel resection with ileostomy or colostomy, chronic alcoholism, prolonged gastric suction, acute pancreatitis, biliary or intestinal fistula) Excessive loss of magnesium (diabetic ketoacidosis, severe dehydration, hyperaldosteronism and hypoparathyroidism) Vitamin D deficiency Impaired renal absorption ATN Medications: diuretics, cisplatin, fosfarnet, cyclosporine, amphotericin B Hyperthyroidism Metabolic acidosis SIADH Pregnancy
Hypermagnesemia	Chronic renal and adrenal insufficiency Overuse of antacids and laxatives containing magnesium Severe dehydration (resulting oliguria can cause magnesium retention) Overcorrection of hypomagnesemia Near-drowning (aspiration of sea water) Intestinal obstruction Trauma, burns Hypothyroidism Addison's disease Shock, sepsis

Modified from Home M, Bond E: Fluid, electrolyte, and acid-base imbalances. In Lewis S, Heitkemper M, Dirksen S, eds: *Medical-surgical nursing: assessment and management of clinical problems*, ed 5, St Louis, 2000, Mosby.

NSAIDs, Nonsteroidal antiinflammatory drugs; ACE, angiotensin-converting enzyme; GI, gastrointestinal; IV, intravenous; SIADH, syndrome of inappropriate antidiuretic hormone; ADH, antidiuretic hormone; CVA, cerebrovascular accident; PTH, parathyroid hormone; MEN, multiple endocrine neoplasia; ATN, acute tubular necrosis.

magnesium from cells when cellular death ensues (see the section on Cell Injury in Chapter 6). Myocardial cells deprived of necessary oxygen and nutrients lose contractility, thereby diminishing the pumping ability of the heart. Diuretics also can produce mild-to-severe electrolyte imbalance. These factors explain the careful observation of specific electrolyte levels in the cardiac client.

### Clinical Manifestations

In a therapy practice, paresthesias, muscle weakness, muscle wasting, muscle tetany, and bone pain are the most likely symptoms first observed with electrolyte imbalances (Table 5-10). (See the Clinical Manifestations section under Common Causes of Fluid and Electrolyte Imbalances in this chapter.)

### MEDICAL MANAGEMENT

Potassium, calcium, sodium, and chloride can be measured in plasma. Intracellular levels of electrolytes cannot be measured; therefore all values for electrolytes are expressed as serum values. Serum values for electrolytes are given as milliequivalents per liter (mEq/L) or milli-

grams per deciliter (mg/dL) (see Table 40-2). As with fluid imbalances, the underlying cause of electrolyte imbalances must be determined and corrected. Electrolyte supplementation, when needed, can be given orally or intravenously.

### SPECIAL IMPLICATIONS FOR THE THERAPIST 5-10

#### Electrolyte Imbalances

Encourage adherence to a sodium-restricted diet prescribed for clients. The use of OTC medications for people on a sodium-restricted diet should be approved by the physician. Encourage activity and alternate with rest periods. Monitor for worsening of the underlying cause of fluid or electrolyte imbalance and report significant findings to the nurse or physician.

If dyspnea and orthopnea are present, teach the client to use a semi-Fowler position (head elevated 18 to 20 inches from horizontal with knees flexed) to promote lung expansion. Frequent position changes

*Continued.*

**Table 5-10** Clinical Features of Various Electrolyte Imbalances

		<b>System Dysfunction</b>
<b>Potassium Imbalance</b>		
Cardiovascular	<b>Hypokalemia</b> Dizziness, hypotension, arrhythmias, ECG changes, cardiac arrest (with serum potassium levels $<2.5 \text{ mEq/L}$ )	<b>Hyperkalemia</b> Tachycardia and later bradycardia, ECG changes, cardiac arrest (with levels $>7.0 \text{ mEq/L}$ )
GI	Nausea and vomiting, anorexia, constipation, abdominal distention, paralytic ileus or decreased peristalsis	Nausea, diarrhea, abdominal cramps
Musculoskeletal	Muscle weakness and fatigue, leg cramps	Muscle weakness, flaccid paralysis
Genitourinary	Polyuria	Oliguria, anuria
Central nervous system (CNS)	Malaise, irritability, confusion, mental depression, speech changes, decreased reflexes, pulmonary hyperventilation	Areflexia progressing to weakness, numbness, tingling, and flaccid paralysis
Acid-base balance	Metabolic alkalosis	Metabolic acidosis
<b>Calcium Imbalance</b>		
CNS	<b>Hypocalcemia</b> Anxiety, irritability, twitching around mouth, laryngospasm, seizures, Chvostek's sign, apathy, irritability, confusion	<b>Hypercalcemia</b> Drowsiness, lethargy, headaches, depression, or Trousseau's sign
Musculoskeletal	Paresthesia (tingling and numbness of the fingers), tetany or painful tonic muscle spasms, facial spasms, abdominal cramps, muscle cramps, spasmodic contractions	Weakness, muscle flaccidity, bone pain, pathologic fractures
Cardiovascular	Arrhythmias, hypotension	Signs of heart block, cardiac arrest in systole, hypertension
Gastrointestinal (GI)	Increased GI motility, diarrhea from dehydration	Anorexia, nausea, vomiting, constipation, dehydration, polyuria, prerenal azotemia
<b>Sodium Imbalance</b>		
CNS	<b>Hyponatremia</b> Anxiety, headaches, muscle twitching and weakness, confusion, seizures	<b>Hypernatremia</b> Agitation, restlessness, seizures, ataxia, confusion
Cardiovascular	Hypotension; tachycardia; with severe deficit, vasomotor collapse, thready pulse	Hypertension, tachycardia, pitting edema, excessive weight gain
GI	Nausea, vomiting, abdominal cramps	Rough, dry tongue; intense thirst
Genitourinary	Oliguria or anuria	Oliguria
Respiratory	Cyanosis with severe deficiency	Dyspnea, respiratory arrest, and death (from dramatic rise in osmotic pressure)
Cutaneous	Cold clammy skin, decreased skin turgor	Flushed skin; dry, sticky mucous membranes
<b>Magnesium Imbalance</b>		
Neuromuscular	<b>Hypomagnesemia</b> Hyperirritability, tetany, leg and foot cramps, Chvostek's sign (facial muscle spasms induced by tapping the branches of the facial nerve)	<b>Hypermagnesemia</b> Diminished reflexes, muscle weakness, flaccid paralysis, respiratory muscle paralysis that may cause respiratory impairment
CNS	Confusion, delusions, hallucinations, seizures	Drowsiness, flushing, lethargy, confusion, diminished sensorium
Cardiovascular	Arrhythmias, vasomotor changes (vasodilation and hypotension), occasionally hypertension	Bradycardia, weak pulse, hypotension, heart block, cardiac arrest

are important in the presence of edema; edematous tissue is more prone to skin breakdown than normal tissue.

Older adults have frequent problems with hypokalemia most often associated with the use of diuretics. Assessment for signs and symptoms of electrolyte imbalance must be ongoing, and changes need to be reported immediately. Decreased potassium levels can result in fatigue, muscle cramping, and cardiac dysrhythmias, usually manifested by an irregular pulse rate or complaints of dizziness and/or palpitations.

Fatigue and muscle cramping increase the chance of musculoskeletal injury. Observing for accompanying signs and symptoms of fluid and electrolyte imbalances will help promote safe and effective exercise for anyone with the potential for these disorders.

With appropriate medical therapy, cardiac, muscular, and neurologic manifestations associated with electrolyte imbalances can be corrected. Delayed medical treatment may result in irreversible damage or death.

## Common Causes of Fluid and Electrolyte Imbalances

### Overview

The exact mechanisms of fluid and electrolyte imbalances are outside the scope of this text. A brief description of the common causes and overall clinical picture encountered in a therapy practice is included here. Burns, surgery, and trauma may result in a fluid volume shift from the vascular spaces to the interstitial spaces. Tissue injury causes the release of histamine and bradykinin, which increases capillary permeability, allowing fluid, protein, and other solutes to shift into the interstitial spaces.

In the case of burns, the fluid shifts out of the vessels into the injured tissue spaces, as well as into the normal (unburned) tissue. This causes severe swelling of these tissues and a significant loss of fluid volume from the vascular space, which results in hypovolemia. Severe hypovolemia can result in shock, vascular collapse, and death. In the case of major tissue damage, potassium is also released from the damaged tissue cells and can enter the vascular fluids, causing hyperkalemia.

In an attempt to treat shock, large quantities of fluid are administered intravenously to maintain blood pressure, cardiac output, and renal function. After 24 to 72 hours, capillary permeability is usually restored and fluid begins to leave the tissue spaces and shift back into the vascular space. If renal function is not adequate, the accumulation of fluid used for treatment and fluid returning from the tissue spaces into the vascular space can cause fluid volume overload. Fluid overload can then cause CHF or pulmonary edema.

*Diabetes mellitus* (type 1) may result in a condition called *diabetic ketoacidosis*, which is caused by an overproduction of ketones and the accompanying metabolic acidosis that occurs (see Chapter 11). As the pH of the blood decreases (acidosis), the accumulating hydrogen moves from the ECF to the ICF. Movement of hydrogen into the cells promotes the movement of potassium out of the cells and into the ECF. As the potassium enters the vascular space, the plasma potassium levels increase. However, since significant diuresis is also occurring, the accumulated potassium is quickly excreted in the urine. As a result, severe potassium losses occur (hypokalemia), which unless treated immediately, cause life-threatening cardiac dysrhythmias.

*Tumors* often produce peptides that can affect fluid and electrolyte balance. These peptides cause neurologic, hormonal, dermatologic, and hematologic symptoms or syndromes often referred to as paraneoplastic syndromes (see Chapter 9). The peptides released by tumors are not regulated by normal suppression feedback loops; consequently, the ectopic hormone continues to be released by the tumor, often causing serious electrolyte imbalances. An ectopic hormone arises at or is produced at an abnormal site or in a tissue where it is not normally found. One example of this phenomenon is the ectopic production of antidiuretic hormone (ADH) by lung carcinomas, resulting in hyponatremia.

A more local effect of malignancy occurs when metastases to the skeletal system produce hypercalcemia from the osteolysis of bone. The treatment of malignancies

also can create fluid and electrolyte imbalances such as occurs with hormonal treatment for breast cancer (e.g., tamoxifen can cause hypercalcemia). Hyponatremia and hypokalemia may also result from nausea and vomiting caused by chemotherapy. Certain chemotherapeutic drugs (e.g., vincristine and cyclophosphamide) are associated with the syndrome of inappropriate antidiuretic hormone (SIADH), causing hyponatremia.

Hyponatremia is also the most common electrolyte imbalance affecting hospitalized patients. Causes of hyponatremia in this population group include sodium loss from diuretics, vomiting, or wound draining and water gain if the person receives too much of a hypotonic IV fluid.

*Alcohol withdrawal* and *eating disorders* are also associated with physiologic changes that can include electrolyte imbalances. See discussion of each individual condition in Chapter 3.

### Clinical Manifestations

The effects of a fluid or electrolyte imbalance are not isolated to a particular organ or system (Box 5-9). Symptoms most commonly observed by the therapist may include skin changes, neuromuscular irritability (muscle fatigue, twitching, cramping, or tetany), CNS involvement, edema, and changes in vital signs, especially tachycardia and postural (orthostatic) hypotension (see Box 12-11).

*Skin changes* include changes in skin turgor and alterations in skin temperature. In a healthy individual, pinched skin will immediately fall back to its normal position when released, a measure of skin turgor. In a person with

#### Box 5-9

#### CLINICAL MANIFESTATIONS OF FLUID/ELECTROLYTE IMBALANCE\*

##### Skin Changes

- Poor skin turgor
- Changes in skin temperature

##### Neuromuscular Irritability

- Muscle fatigue
- Muscle twitching
- Muscle cramping
- Tetany

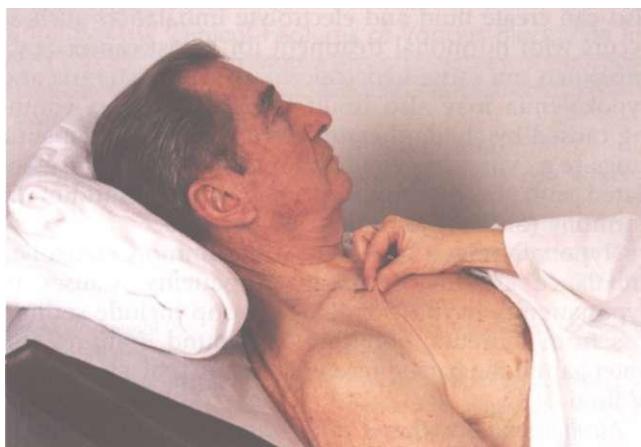
##### CNS Involvement

- Changes in deep tendon reflexes
- Seizures
- Depression
- Memory impairment
- Delusions
- Hallucinations

##### Edema

- Changes in vital signs:
  - Tachycardia
  - Postural hypotension
  - Altered respirations

\*Only signs and symptoms most likely to be seen in a therapy practice are included here.



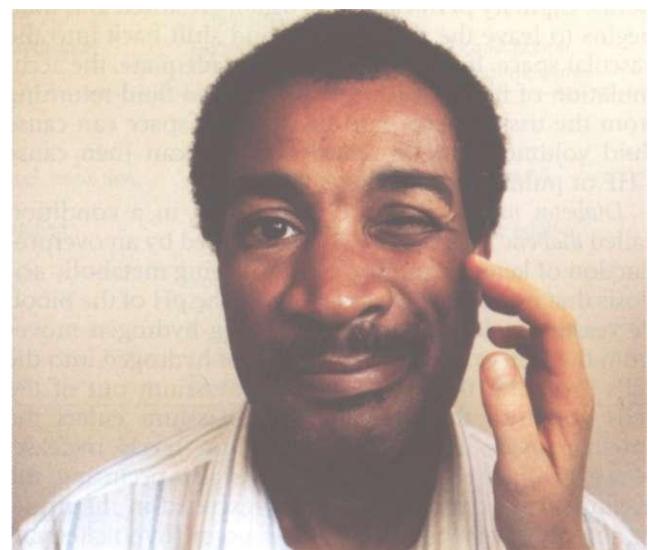
**Figure 5-7**

Testing skin turgor (normal resiliency of a pinched fold of skin). Turgor is measured by the time it takes for the skin and underlying tissue to return to its original contour after being pinched up. If the skin remains elevated (i.e., tented) for more than 3 seconds, turgor is decreased. Normal turgor is indicated by a return to baseline contour within 3 seconds when the skin is mobile and elastic. Turgor decreases with age as the skin loses elasticity; testing turgor of some older persons on the forearm (the standard site for testing) is less valid because of decreased skin elasticity in this area. (From Jarvis C: *Physical examination and health assessment*, ed 4, Philadelphia, 2004, WB Saunders.)



**Figure 5-8**

Carpopedal attitude of the hand, a form of latent tetany associated with hypocalcemia, is called *Trousseau's sign*. This can be tested for by inflating a blood pressure cuff on the upper arm to a level between diastolic and systolic blood pressure and maintaining this inflation for 3 minutes. A positive test results in the carpal spasm shown here. (From Ignatavicius DD, Workman ML: *Medical-surgical nursing: critical thinking for collaborative care*, ed 5, Philadelphia, 2006, WB Saunders.)



**Figure 5-9**

To check for *Chvostek's sign*, tap the facial nerve above the mandibular angle, adjacent to the ear lobe. A facial muscle spasm that causes the person's eye and upper lip to twitch, as shown, confirms tetany. (From Ignatavicius DD, Workman ML: *Medical-surgical nursing: critical thinking for collaborative care*, ed 5, Philadelphia, 2006, WB Saunders.)

FVD, such as dehydration, the skin flattens more slowly after the pinch is released and may even remain elevated for several seconds, referred to as *tenting* of tissue (Fig. 5-7). Tissue turgor can vary with age, nutritional state, race, and complexion and must be accompanied by other signs of FVD to be considered meaningful.

Skin turgor may be more difficult to assess in older adults because of reduced skin elasticity compared with that of younger clients. Skin temperature may become warm and flushed as a result of vasodilation (e.g., in metabolic acidosis) or pale and cool because of peripheral vasoconstriction compensating for hypovolemia.

*Neuromuscular irritability* can occur as a result of imbalances in calcium, magnesium, potassium, and sodium. (See Chapter 24 for discussion of osteoporosis associated with calcium loss.) Specific signs of neuromuscular involvement associated with these imbalances occur because of increased neural excitability, specifically increased acetylcholine action at the nerve ending, resulting in lowering of the threshold of the muscle membrane.

*Tetany* (continuous muscle spasm) is the most characteristic manifestation of hypocalcemia. The affected person may report a sensation of tingling around the mouth (circumoral paresthesia) and in the hands and feet, and spasms of the muscles of the extremities and face. Less overt signs (latent tetany) can be elicited through Trousseau's sign (Fig. 5-8); Chvostek's sign (Fig. 5-9); and changes in deep tendon reflexes (DTRs) (Table 5-11). Many other factors can produce abnormalities in DTRs requiring the therapist to evaluate altered DTRs in light of other clinical signs and client history.

*Nervous system* involvement may occur in the peripheral system (hyperkalemia) or the CNS (hypocalcemia,

hypercalcemia, hyponatremia, and hypernatremia). CNS manifestations of hypocalcemia may include seizures, irritability, depression, memory impairment, delusions, and hallucinations. In chronic hypocalcemia, the skin may be dry and scaling, the nails become brittle, and the hair is dry and falls out easily.

Signs and symptoms of hyponatremia occur when a drop in the serum sodium level pulls water into cells. When this happens, the client may experience headaches, confusion, lethargy, muscle weakness, and nausea. These

**Table 5-11** Changes in Deep Tendon Reflexes Associated With Fluid/Electrolyte Imbalance

Increased (Hyperactive)	Decreased (Hypoactive)
Hypocalcemia	Hypercalcemia
Hypomagnesemia	Hypermagnesemia
Hypernatremia	Hyponatremia
Hyperkalemia*	Hyperkalemia
Alkalosis	Acidosis

\*Generally hyperkalemia is accompanied by decreased or absent deep tendon reflexes (DTRs); some sources do report hyperactive DTRs with hyperkalemia. In the clinical situation, DTRs are never used to determine a potassium imbalance. They are a warning sign for the therapist to assess the client further and report all pertinent findings.

symptoms are easily mistaken for complications from anesthesia or analgesia.

*Hypokalemia* seen in a therapy practice can be associated with diuretic therapy; excessive sweating, vomiting, or diarrhea; diabetic acidosis; trauma; or burns. It is accompanied by muscular weakness that can progress to flaccid quadriplegia. The weakness is initially most prominent in the legs, especially the quadriceps; it extends to the arms, with involvement of the respiratory muscles soon after.<sup>123</sup> Severe hypokalemia can cause paralysis, respiratory failure, cardiac arrhythmias, and hypotension. Finally, a condition called *rhabdomyolysis* (disintegration of striated muscle fibers with excretion of myoglobin in the urine) can occur with potassium or phosphorus depletion.

*Edema*, defined as an excessive accumulation of interstitial fluid (fluid that bathes the cells), may be either localized or generalized. Generalized edema may be characterized by shortness of breath, ankle swelling, nocturia, and orthopnea. Other manifestations of generalized edema may include decreased urinary output; weight gain; labored, shallow, and increased respiratory rate; distended neck veins at 45-degree elevation of the head; changes in blood pressure; and abnormal laboratory findings (e.g., electrolytes, serum creatinine, BUN, and hemoglobin).

Pulmonary edema results from excessive shifting of fluid from the vascular space into the pulmonary interstitium and air spaces. When edema forms secondary to fluid retention, the clinical picture is usually one of pitting edema (Fig. 5-10).

*Vital sign changes*, including pulse, respirations, and blood pressure, may signal early development of fluid volume changes. Decreased blood pressure and tachycardia are usually the first signs of the decreased vascular volume associated with FVD as the heart pumps faster to compensate for the decreased plasma volume. Irregular pulse rates and dysrhythmias may also be associated with magnesium, potassium, or calcium imbalances.

Orthostatic hypotension is another sign of volume depletion (hypovolemia). Moving from a supine to standing position causes an abrupt drop in venous return, which is normally compensated for by sympathetically mediated cardiovascular adjustments. For example, in the healthy individual, increased peripheral resistance and



**Figure 5-10**

Severe, dependent, pitting edema occurs with some systemic diseases, such as congestive heart failure and hepatic cirrhosis. Note the finger-shaped depressions that do not refill after pressure has been exerted by the examiner. (From Thibodeau GA, Patton KT: *The human body in health and disease*, ed 4, St. Louis, 2005, Mosby.)

increased heart rate maintain cardiac output. Blood pressure is unaffected or characterized by a small decrease in systolic pressure, and the diastolic pressure may actually rise a few millimeters (mm) of mercury.

In contrast, for the person with FVD, systolic pressure may fall 20 mm Hg or more, accompanied by an increase in the pulse rate greater than 15 beats/minute.<sup>85</sup> The decreased volume results in compensatory increases in pulse rate as the heart attempts to increase output in the face of decreased stroke volume.

As fluid volume depletion worsens, blood pressure becomes low in all positions due to loss of compensatory mechanisms and autonomic insufficiency. Conditions such as diabetes, associated with autonomic neuropathy, can also produce orthostatic blood pressure and pulse changes (see the section on Orthostatic Hypotension in Chapter 12).

#### SPECIAL IMPLICATIONS FOR THE THERAPIST

#### 5-11

##### *Assessment of Fluid and Electrolyte Imbalance*

Assessment of fluid and electrolyte balance is based on both subjective and objective findings (Table 5-12). At the bedside or in the home health care setting, the therapist must be alert to complaints of headache, thirst, and nausea and changes in dyspnea, skin turgor, and muscle strength. More objective assessment of fluid and electrolyte balance is based on fluid intake, output, and body weight. (See Special Implications for the Therapist: Fluid Imbalances and Electrolyte Imbalances in this chapter.)

**Table 5-12** Assessment of Fluid and Electrolyte Imbalance

Area	Fluid Excess/Electrolyte Imbalance	Fluid Loss/Electrolyte Imbalance
Head and neck	Distended neck veins, facial edema	Thirst, dry mucous membranes
Extremities	Dependent pitting, edema, discomfort from weight of bed covers	Muscle weakness, tingling, tetany
Skin	Warm, moist; taut, cool feeling when edematous	Dry, decreased turgor
Respiration	Dyspnea, orthopnea, productive cough, moist breath	Changes in rate and depth of breathing sounds
Circulation	Hypertension, distended neck veins, atrial arrhythmias	Pulse rate irregularities, arrhythmia, postural hypotension, tachycardia
Abdomen	Increased girth, fluid wave	Abdominal cramps

Modified from Briggs J, Drabek C: Fluid and electrolyte imbalance. In Phipps WJ, Sands J, Marek J, eds: *Medical-surgical nursing: concepts and clinical practice*, ed 5, St Louis, 1999, Mosby.

## ACID-BASE IMBALANCES

### Overview

Normal function of body cells depends on regulation of hydrogen ion concentration ( $H^+$ ) so that  $H^+$  levels remain within very narrow limits. Acid-base imbalances occur when these limits are exceeded and are recognized clinically as abnormalities of serum pH (i.e., the measure of acidity or alkalinity of blood). Normal serum pH is 7.35 to 7.45. Cell function is seriously impaired when pH falls to 7.2 or lower or rises to 7.55 or higher (see the section on Laboratory Values in Chapter 40).

Three physiologic systems act interdependently to maintain normal serum pH: immediate buffering of excess acid or base by the *blood buffer systems*, excretion of acid by the *lungs* (occurs within hours), and excretion of acid or reclamation of base by the *kidneys* (occurs within days). The four general classes of acid-base imbalance are respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis. Table 5-13 summarizes these four imbalances (see Table 40-3).

*Acidosis* refers to any pathologic process causing a relative excess of acid in the body. This can occur as a result of accumulation of acid or depletion of the alkaline reserve (bicarbonate content,  $HC_0_3^-$ ) in the blood and body tissues.

*Acidemia* refers to excess acid in the blood and does not necessarily confirm an underlying pathologic process. The same distinction may be made between the terms *alkalosis* and *alkalemia*; alkalosis indicates a primary condition resulting in excess base in the body. Although efforts have been made to standardize acid-base terminology, these terms are often used interchangeably.

### Incidence

The incidence of acid-base imbalances in hospital settings is high. Acid-base imbalances are often related to respiratory and/or metabolic problems typical of the critically ill or injured individual. Some people have more than one acid-base imbalance at the same time.

### Clinical Manifestations

A guide to the clinical presentation of acid-base imbalances is shown in Table 5-13. Besides the major distinguishing characteristics of acid-base imbalance described

in this chapter, potassium excess (hyperkalemia) is associated with both respiratory and metabolic acidosis, and neuromuscular hyperexcitability is associated with both respiratory and metabolic alkalosis.<sup>35</sup>

### MEDICAL MANAGEMENT

**DIAGNOSIS.** Pulse oximetry is used most often to measure oxygen saturation, yet it does not provide needed information regarding the effectiveness of ventilation or the pH of the blood. A more comprehensive procedure is the arterial blood gas (ABG) test (see Table 40-18).

This measurement is important in the diagnosis and treatment of ventilation, oxygen transport, and acid-base problems. The test measures the amount of dissolved oxygen and carbon dioxide in arterial blood and indicates acid-bases status by measurement of the arterial blood pH. The pH is inversely proportional to the hydrogen ion concentration ( $H^+$ ) in the blood. Therefore, as the hydrogen ion concentration (LP) increases (acidosis), the pH decreases; as the hydrogen ion concentration ( $H^+$ ) decreases (alkalosis), the pH increases.

The  $P_{CO_2}$  is a measure of the *partial pressure of carbon dioxide* in the blood.  $P_{CO_2}$  is termed the *respiratory component* in acid-base measurement because the carbon dioxide level is primarily controlled by the lungs. As the carbon dioxide level increases, the pH decreases (respiratory acidosis); as the carbon dioxide level decreases, the pH increases (respiratory alkalosis).

**TREATMENT.** Treatment in acid-base imbalances is directed toward the underlying cause and correction of any coexisting electrolyte imbalance. For example, respiratory infections contributing to ventilatory failure (respiratory acidosis) are managed with appropriate antibiotic therapy, pulmonary hygiene, oxygen support, and possibly, continuous mechanical ventilation. Use of pharmaceutical agents that depress the respiratory control center is minimized. Dialysis may be indicated in renal failure (metabolic acidosis) or overdose of toxins.

### Respiratory Acidosis

Respiratory acidosis is nearly always due to hypoventilation and subsequent retention of carbon dioxide ( $CO_2$ ). In a therapy setting, respiratory acidosis is most commonly observed in the population with COPD or asthma,

**Table 5-13** Overview of Acid-Base Imbalances

Mechanism	Etiologic Factors	Clinical Manifestations	Treatment
<b>Respiratory Acidosis</b>			
Hypoventilation	Acute respiratory failure COPD Neuromuscular disease Guillain-Barré Myasthenia gravis Respiratory center depression Drugs Barbiturates Sedatives Narcotics Anesthetic CNS lesions Tumor Stroke Inadequate mechanical ventilation	Hypercapnia, restlessness, disorientation, confusion, sleepiness, visual disturbances, headache, flushing, dyspnea, cyanosis, decreased deep tendon reflexes, hyperkalemia, palpitation, pH < 7.35, $\text{PaCO}_2 > 45 \text{ mm Hg}$	Treat underlying cause; support ventilation; correct electrolyte imbalance
Excess carbon dioxide production	Hypermetabolism Sepsis Burns		
<b>Respiratory Alkalosis</b>			
Hyperventilation	Hypoxemia Pulmonary embolus High altitude Impaired lung expansion Pulmonary fibrosis Ascites Scoliosis Pregnancy*Congestive heart failure Stimulation of respiratory center Anxiety hyperventilation Encephalitis/meningitis (hepatic failure) Salicylates (aspirin overdose) Theophylline CNS trauma CNS tumor Excessive exercise Extreme stress Severe pain Mechanical overventilation	Tachypnea, hypocapnia, dizziness, difficulty concentrating, numbness and tingling, blurred vision, diaphoresis, dry mouth, muscle cramps, carpopedal spasm, muscle twitching and weakness, hyperreflexia, arrhythmias, pH > 7.45, $\text{PaCO}_2 < 35 \text{ mm Hg}$ , hypokalemia, hypocalemia (see Table 5-10)	Treat underlying cause; increase carbon dioxide retention (rebreathing, sedation)
<b>Metabolic Acidosis</b>			
Acid excess	Renal failure (acid retention) Diabetic or alcoholic ketoacidosis Lactic acidosis Starvation Ingested toxins Aspirin Antifreeze	Hyperventilation (compensatory), muscular twitching, weakness, malaise, nausea, vomiting, diarrhea, headache, hyperkalemia (cardiac arrhythmias), pH < 7.35, $\text{HCO}_3^- < 22 \text{ mm Hg}$ , $\text{PaCO}_2$ normal or slightly decreased, coma (death)	Treat underlying cause, correct electrolyte imbalance; $\text{NaCO}_3$ for severe acidosis (pH < 7.2)
Base deficit	Severe diarrhea ( $\text{HCO}_3^-$ loss) Renal failure (inability to reabsorb $\text{HCO}_3^-$ )		

*Continued.*

**Table 5-13** Overview of Acid-Base Imbalances—cont'd

Mechanism	Etiologic Factors	Clinical Manifestations	Treatment
<b>Metabolic Alkalosis</b>			
Fixed acid loss (with base excess)	Hypokalemia Diuresis Steroids Vomiting Nasogastric suctioning	Hypoventilation (compensatory); dysrhythmias, nausea, prolonged vomiting, diarrhea, confusion, irritability, agitation, restlessness, muscle twitching, cramping, hypotonia, weakness, Troussseau's sign, paresthesias, seizures, coma, hypokalemia, pH > 7.45, $\text{PaCO}_2$ normal or slightly increased	Treat underlying cause; administer potassium chloride
Excessive $\text{HCO}_3^-$ intake	Peptic ulcer Milk-alkali syndrome Excessive intake of antacids Overcorrection of acidosis Massive blood transfusion	Hypochloremia	
Excessive $\text{HCO}_3^-$ resorption	Hyperaldosteronism Cushing's disease		

COPD, Chronic obstructive pulmonary disease; CNS, central nervous system; ARDS, adult respiratory distress syndrome;  $\text{PaCO}_2$ , partial pressure of carbon dioxide;  $\text{NaCO}_3$ , sodium bicarbonate;  $\text{HCO}_3$ , bicarbonate ion.

\*In the third trimester of pregnancy, the hormone progesterone also stimulates respiration.

depressed CNS (drugs, infection, or brain injury), or whenever the diaphragm is impaired (e.g., Guillain-Barre syndrome, myasthenia gravis, or chest wall deformities); secondary to burns; and as a result of lesions of the CNS (e.g., tumor, stroke, or muscular dystrophy).

The respiratory system has an important role in maintaining acid-base equilibrium. In response to an increase in the hydrogen ion concentration in body fluids, the respiratory rate increases, causing more  $\text{CO}_2$  to be released from the lung.

Anything that impairs this  $\text{CO}_2$  exhalation causes the  $\text{CO}_2$  to accumulate in the blood, where it unites with water to form carbonic acid ( $\text{H}_2\text{CO}_3$ ), decreasing the blood pH. In addition, the kidneys begin to excrete more acid and retain more bicarbonate to further correct the acid imbalance.

Respiratory acidosis can be acute because of a sudden failure in ventilation, or chronic, as with long-term pulmonary disease (e.g., COPD). In the acute episode, the blood buffer systems cannot compensate to restore the acid-base balance because normal blood circulation and tissue perfusion are impaired. The lungs may not be functioning properly and the kidneys require more time to compensate than the acute condition permits.

Chronic respiratory acidosis results from gradual and irreversible loss of ventilatory function. Although there is increased retention of  $\text{CO}_2$ , the kidneys have time to compensate by retaining bicarbonate and thereby maintaining a pH within tolerable limits. However, if even a minor respiratory infection develops, the person is subjected to a rapidly developing state of acute acidosis because the lungs remove only a limited amount of carbon dioxide.

### Clinical Manifestations

Acute respiratory acidosis produces CNS disturbances. Effects range from restlessness, confusion, and apprehension to somnolence (sleepiness), with a fine or flapping tremor (see the section on Asterixis in Chapter 17) or coma. The person may report headaches and shortness of breath with retraction and use of accessory muscles. On examination, DTRs may be depressed. This disorder may also cause cardiovascular abnormalities such as tachycardia, hypertension, atrial and ventricular arrhythmias, and in severe acidosis, hypotension with vasodilation.

### Respiratory Alkalosis

Respiratory alkalosis, the opposite of respiratory acidosis, occurs as a result of a loss of acid without compensation and most commonly when the lungs excrete excessive amounts of carbon dioxide (hyperventilation).

Conditions associated with respiratory alkalosis fall into the following two categories:

1. *Pulmonary*, caused by hypoxemia in early stage pulmonary problems (e.g., pulmonary edema, pulmonary embolism, pneumonia, and acute asthma) and by overuse of a mechanical ventilator
2. *Nonpulmonary*, which includes anxiety, hysteria, pain, fever, high environmental temperature, pregnancy, drug toxicities (salicylates, theophylline), CNS disease (brainstem tumors, infection), and hyperthyroidism (see Table 5-13).

Hyperventilation and the subsequent respiratory alkalosis is a common finding in ICU patients.

## Clinical Manifestations

The cardinal sign of respiratory alkalosis is deep, rapid breathing, possibly exceeding 40 breaths/minute (much like the Kussmaul's respirations that characterize diabetic acidosis) (see Table 5-15). Such hyperventilation usually leads to CNS and neuromuscular disturbances such as dizziness or light-headedness (caused by below-normal CO<sub>2</sub> levels that decrease cerebral blood flow); inability to concentrate; tingling and numbness of the extremities and around the mouth; blurred vision; diaphoresis; dry mouth; muscle cramps; carpopedal (wrist and foot) spasms; twitching (possibly progressing to tetany); and muscle weakness. Severe respiratory alkalosis may cause cardiac arrhythmias, seizures, and syncope.

## Metabolic Acidosis

Metabolic acidosis is an accumulation of acids or a deficit of bases in the blood. This type of acidosis can occur with an acid gain (e.g., ketones with diabetic ketoacidosis, lactic acid with hypoxia, toxins such as ethylene glycol, and renal failure) or bicarbonate loss (e.g., diarrhea). Specific etiologic factors are listed in Table 5-13.

*Ketoacidosis* occurs when insufficient insulin for the proper use of glucose results in increased breakdown of fat. This accelerated fat breakdown produces ketones and other acids. Although the body attempts to neutralize these increased acids, the plasma bicarbonate (HC0<sub>3</sub><sup>-</sup>) is depleted.

In the case of *renal failure*, the failing kidney cannot rid the body of excess acids and cannot produce the necessary bicarbonate to buffer the acid load that is accumulating in the body. *Lactic acidosis* occurs as excess lactic acid is produced during strenuous exercise or when oxygen is insufficient (hypoxemia). *Severe diarrhea* depletes the body of highly alkaline intestinal and pancreatic secretions.<sup>123</sup>

## Clinical Manifestations

The symptoms of metabolic acidosis can include muscular twitching, weakness, malaise, nausea, vomiting, diarrhea, and headache (see Table 5-13). If the acidosis is severe, myocardial depression and hypotension can occur. Compensatory hyperventilation may occur as a result of stimulation of the hypothalamus as the body attempts to rid itself of excess CO<sub>2</sub>. As the acid level goes up, these symptoms progress to stupor, unconsciousness, coma, and death. The breath may have a fruity odor in the presence of acetone associated with ketoacidosis.

## Metabolic Alkalosis

Metabolic alkalosis occurs when either an abnormal loss of acid or excess accumulation of bicarbonate occurs. Postoperative loss of acids through vomiting or gastric suctioning may also result in metabolic alkalosis. In the outpatient setting, diarrhea, excessive use of laxatives, diuretics, antacids, and milk (milk alkali syndrome) may also lead to metabolic alkalosis. Other causes are listed in Table 5-13.

## Clinical Manifestations

Signs and symptoms occur as the body attempts to correct the acid-base imbalance, primarily through hypoventilation. Respirations are shallow and slow as the lungs attempt to compensate by building up carbonic acid stores. Clinical manifestations may be mild at first, with muscle weakness, irritability, confusion, and muscle twitching (see Table 5-13). If untreated, the condition progresses and the person may become comatose, with possible seizures, cardiac arrhythmias, and respiratory paralysis.

## Aging and Acid-Base Regulation

The normal aging process results in decreased ventilatory capacity and loss of alveolar surface area for gas exchange; thus older adults are prone to respiratory acidosis caused by hypoventilation and to respiratory alkalosis caused by hypoxemia and subsequent hyperventilation. Older adults are often taking multiple medications for hypertension or cardiovascular disease that may contribute to hypokalemia and metabolic alkalosis. Respiratory compensation in these conditions can be compromised because of the structural and functional changes mentioned.

Aldosterone is less effective in older adults, as is ammonia buffering. These changes limit renal compensation for respiratory imbalances and place the individual at higher risk for metabolic imbalance.<sup>138,169</sup>

Older adults who are unable to excrete an acid load may develop a chronic metabolic acidosis. While the bicarbonate level and pH of the blood remain normal, mild metabolic acidosis may contribute to muscle wasting and bone loss.

## SPECIAL IMPLICATIONS FOR THE THERAPIST 5-12

### Acid-Base Imbalances

The therapist must observe clients at risk for acid-base imbalance for any early symptoms. This is especially true for people with known pulmonary, cardiovascular, or renal disease; clients in a hypermetabolic state, such as occurs in fever, sepsis, or burns; clients receiving total parenteral nutrition or enteral tube feedings that are high in carbohydrates; mechanically ventilated clients; clients with insulin-dependent diabetes; older clients whose age-related decreases in respiratory and renal function may limit their ability to compensate for acid-base disturbances; and clients with vomiting, diarrhea, or enteric drainage.<sup>138</sup> Specific reference values in acid-base disorders are listed in Tables 5-13 and 40-3.

Client and family education in the prevention of acute episodes of metabolic acidosis, particularly diabetic ketoacidosis, is essential. A fruity breath odor from rising acid levels (acetone) may be detected by the therapist treating someone who has uncontrolled diabetes.

*Continued.*

The therapist should not hesitate to ask the client about this breath odor, since immediate medical intervention is required for diabetic ketoacidosis. Dehydration occurs rapidly as a result of severe hyperglycemia. A rising pulse rate and a drop in blood pressure are critical (and often late) indicators of a fluid volume deficit caused by dehydration.

Safety measures to avoid injury during involuntary muscular contractions are the same as for convulsions or epileptic seizures. Vigorous restraint can cause orthopedic injuries as the muscles contract strongly against resistance. Placing padding to protect the person is a key to prevention of injury.

Measures that facilitate breathing are essential to client care during respiratory acidosis. Frequent turning, coughing, and deep breathing exercises to encourage oxygen-carbon dioxide exchange are beneficial. Postural drainage, unless contraindicated by the client's condition, may be effective in promoting adequate ventilation.

In the case of respiratory hyperventilation, rebreathing CO<sub>2</sub> in a paper sack is helpful, as well as encouraging the individual to hold the breath. Oxygen may be given to reduce respiratory effort and the resultant blowing off of CO<sub>2</sub> by the person who has anoxia

caused by pulmonary infection or CHF. Individuals with COPD may retain CO<sub>2</sub>; the use of oxygen is contraindicated in these clients because it can further depress the respiratory drive, causing death.

Any client receiving diuretic therapy must be monitored for signs of potassium depletion (e.g., postural hypotension, muscle weakness, and fatigue; see Table 5-10) and alkalosis (see Table 5-13). Decreased respiratory rate may be an indication of compensation by the lungs, but the physician must make this assessment. Signs of neural irritability, such as Troussseau's sign (see Fig. 5-8), may be seen when taking blood pressure measurements, and they are helpful in detecting early stages of tetany due to calcium deficiency.

## References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 192 cited references and other general references for this chapter.

# CHAPTER 6

## Injury, Inflammation, and Healing

CATHERINE C. GOODMAN

STEVEN H. TEPPER • D. MICHAEL MCKEOUGH (FIRST AND SECOND EDITIONS)

*Pathology* is defined as the structural and functional changes in the body caused by disease or trauma. Understanding the normal structure and function of the tissues is required before the discussion of pathology. The organization of the material presented in this chapter parallels the processes underlying pathology—that is, cell injury and the factors causing this injury, inflammation as a secondary response to cell injury, and tissue healing, the third step of the process toward homeostasis.

The role of nerve-immune interactions in regulation and tissue healing is just beginning to be revealed and will continue to enhance our understanding of and intervention in injury, inflammation, and recovery. A new area of science called *psychoneuroimmunology* (see description in Chapters 1 and 7) describes the influences of the nervous system on immune and inflammatory responses and how these contribute to the healing and repair process. For example, it is now clear that mast cells, T cells, neutrophils, and monocytes can directly alter tissue physiology through the release of mediators and cytokines. In addition, aging, age-related changes, and various other factors can influence homeostasis and the recovery process and are the major focus of the next two sections.

### CELLULAR AGING

Various components of cells (e.g., mitochondria, ribosomes, or cell membrane) are subject to changes associated with aging. Mitochondrial deoxyribonucleic acid (DNA) is considered a prime target for age-related changes. DNA has to replicate and maintain itself to preserve the primary genetic message. This takes place through division, which can result in alterations of the genetic code by anything that can damage DNA (e.g., physical, chemical, or biologic factors; spontaneous mutations of genes; exposure to radiation). Anything that can alter the information content of the cell can cause changes in function and affect the ability of the cell to maintain homeostasis.

The ability of a cell to resist microorganisms or to recover from injury or inflammation is dependent in part

on the underlying state or health of the cells. Age-related changes at the cellular level are present but remain difficult to measure or quantify; researchers are working toward finding satisfactory biomarkers of aging at the cellular level. Age-associated deterioration in cells leads to tissue or organ deficiencies and ultimately to the expression of aging or disease. The most well-described age-associated change in the subcellular structure (lysosomes) of postmitotic cells, especially neurons and cardiac myocytes, is the presence of a component called *lipofuscin*, an aging-pigment granule that is found in high concentrations in old cells. The explanation for the increase of lipofuscin with age and the effects of these intracellular deposits on function remains under investigation. It is suspected that pressure from this pigmented lipid on the cell nucleus may interfere with cellular function.<sup>124,142</sup>

### Theories of Cellular Aging

The aging process is often associated with impaired wound healing, but the cellular and molecular mechanisms implicated are not completely understood.<sup>37,78</sup> More than 300 theories exist to explain the aging phenomenon from a cellular level. Many of these theories originate from the study of changes that accumulate with time. In organs composed of cells that cannot regenerate, such as those of the heart and brain, the *wear-and-tear theory* may account for the decline in function of these organs. Other factors may also play a role, such as the influence of genetics suggested by the genetic hypothesis that aging is a genetically predetermined process.

*The free radical theory* of aging is the most popular and widely tested and is based on the chemical nature and wide presence of free radicals causing DNA damage and cellular oxidative stress as it relates to the aging process (see the Chemical Factors section under Mechanisms of Cell Injury in this chapter).

The discovery of the telomeres, the structure at the end of chromosomes, has added the *telomere aging clock theory* for the molecular mechanisms that lead to senescence. This theory suggests that the telomere acts as a molecular clock signaling the onset of cell senescence. Normal

human cells will not divide forever but eventually enter a viable nondividing state (senescence). The progressive accumulation of senescent cells contributes to but does not exclusively cause the aging process. Cell senescence acts as an anticancer mechanism to control the potential for cellular proliferation<sup>71,146</sup> (see further discussion in Chapter 9). Because of the close association between telomere dysfunction and malignancy, both pathologists and clinicians expect this molecule to be a useful malignancy marker.

Pathologic changes associated with aging vary from individual to individual but usually consist of reduced functional reserve caused by atrophy of tissues or organs. Resistance to infection declines with age, and pathologic processes such as atherosclerosis result in increased cardiovascular and cerebrovascular injuries or death.

Studies have shown that considerable potential exists for improving aerobic capacity by training. This observation has cellular implications. For example, mitochondria of cardiac and skeletal<sup>78</sup> muscle cells improve function under appropriate training conditions. If changes in diet and exercise or treatment with hormones or compounds, such as antioxidants (see Fig. 6-2), are able to modify damage by reactive oxygen species and the body can reestablish cellular norms, then this information has great implications for the various cellular and molecular theories on aging and our approach to the aging process.

## CELL INJURY

Understanding cell injury, inflammation, and tissue healing serves as a solid foundation for the other topics presented in this text. We begin by acknowledging that the structural and functional changes produced by pathology start with injury to the cells that make up the tissues. Mild injury produced by stressors leads to sublethal alterations of the affected cells, whereas moderate or severe injury leads to lethal alterations. After cell injury, the body reacts by initiating the process of inflammation. The amount, type, and severity of the inflammatory reaction are dependent on the amount, type, and severity of the injury. As part of the healing process, the inflammatory process is responsible for the removal of the injurious agent, removal of cellular debris, and the initiation of the healing process. The healing process occurs to allow restoration of structure and function whenever possible.

To achieve complete restoration of function, regeneration of the damaged tissue must occur. Often, regeneration of the tissue is not possible, and the body must settle for tissue repair by nonfunctional, connective tissue (fibrosis or scar tissue). This connective tissue helps maintain structural integrity but has none of the functional properties of the original cells and tissues.

### Mechanisms of Cell (Tissue) Injury

Cells may be damaged by a variety of mechanisms. The most important mechanisms are listed in Box 6-1. Each of these mechanisms leads to either a reversible (sublethal) or irreversible (lethal) injury. Whether the injury

### Box 6-1

#### MECHANISMS OF CELL INJURY

- Ischemia (lack of blood supply)
- Infectious agents
- Immune reactions
- Genetic factors
- Nutritional factors
- Physical factors
- Chemical factors

is reversible is dependent on the cell's ability to withstand the derangement of homeostatic mechanisms and its adaptability (i.e., ability to return to a state of homeostasis). Reversing the injury and achieving homeostasis are determined by a combination of factors including the mechanism of injury, length of time the injury is present without intervention, and the severity of the injury.

#### Ischemia

At the tissue or organ level, ischemia is defined as blood flow below the minimum necessary to maintain cell homeostasis and metabolic function. This can be due to a reduction in flow or an increase in metabolism of the tissue beyond the capability of the arterial vascular system. Insufficient blood flow results in a critical reduction in oxygen delivery to the tissue that is partial (hypoxia) or total (anoxia), a decreased delivery of nutrients, and decreased removal of waste products from the tissue. The lack of oxygen leads to loss of aerobic metabolism. The resulting reduction in adenosine triphosphate (ATP) synthesis leads to accumulation of ions and fluid intracellularly. The cells swell and their function is compromised. This concept is discussed further in the section on Reversible Cell Injury in this chapter.

Hypoxia or anoxia may occur under many circumstances, including obstruction of the respiratory tree (e.g., suffocation secondary to drowning), inadequate transport of oxygen across the respiratory surfaces of the lung (e.g., pneumonia), inadequate transport of oxygen in the blood (e.g., anemia), or an inability of the cell to use oxygen for cellular respiration (e.g., chemical poisoning).<sup>26</sup>

Ischemia is usually the result of arterial lumen obstruction and narrowing caused by atherosclerosis and/or an intravascular clot called a *thrombus*. Ischemia, resulting in myocardial infarction (MI) and stroke (lack of blood flow to the heart or brain, respectively), can cause death of tissue (necrosis) and accounts for two of the three leading causes of mortality in industrialized nations.

#### Infectious Agents

Infectious agents, such as bacteria, viruses, mycoplasmas, fungi, rickettsiae, protozoa, prions, and helminths (see Chapter 8), may also cause cell injury or death. Bacterial and viral agents are responsible for the vast majority of infections. Bacterial infections cause cell injury primarily by invading tissue and releasing exotoxins and endotoxins that can cause cell lysis and degradation of extracellular matrix and aid in the spread of the infection. Injury

can also result from the inflammatory/immunologic reactions induced by bacteria in the host. For example, exotoxins may be released by clostridial organisms that cause gas gangrene, tetanus, and botulism.

*Clostridium tetani*, for example, releases an exotoxin that is preferentially absorbed by the alpha motor neurons and delivered into the central nervous system (CNS). Once inside the CNS, the exotoxin crosses the synapse of the anterior horn cell and interferes with release of inhibitory neurotransmitters. This disruption of homeostasis eventually causes the activation of motor neurons that in turn cause involuntary muscular contractions (tetanus).<sup>130</sup>

When microorganisms or their toxins are present in the blood, a condition called *sepsis* can occur. Endotoxins released from gram-negative bacteria induce the synthesis of cytokines (extracts of normal leukocytes such as tumor necrosis factor [TNF] and interleukins [ILs]) that are responsible for many of the systemic manifestations of sepsis (see Box 6-5).

In sepsis, endothelial cell damage, loss of plasma volume, and maldistribution of blood flow result in hypovolemia. Cardiovascular collapse may ensue and lead to a condition called *septic shock*. The detection of an infectious agent initiates an inflammatory reaction designed to contain and inactivate the pathogen, but the magnitude of this defensive response by the host may also cause cellular or tissue destruction in the infected area.

Viruses kill cells by one of two mechanisms (Fig. 6-1) and are the consequence of complete redirection of the cell's biosynthesis towards viral replication. The first is a direct cytopathic effect usually found with ribonucleic (RNA) viruses. These viruses kill from within by disturbing various cellular processes or by disrupting the integrity of the nucleus and/or plasma membrane.

Virally encoded proteins become inserted into the plasma membrane of the host cell (forming a channel) and alter the permeability of the cell membrane to ions. The resulting loss of the ionic barrier leads to cell swelling and death. DNA type viruses also kill cells through an indirect cytopathic effect by integrating themselves into the cellular genome. These viruses encode the production of foreign proteins, which are exposed on the cell surface and recognized by the body's immune cells.

Immunocompetent cells, such as the T lymphocyte, recognize these virally encoded proteins inserted into the plasma membrane of host cells and attack and destroy the infected cell. When the immune system is compromised or if the number of invading microorganisms overwhelms the immune system, disease (and the symptoms of illness) occurs.

### Immune Reactions

Although the immune system normally functions in defense against foreign antigens, sometimes the system becomes overzealous in its activity, leading to hypersensitivities ranging from a mild allergy to life-threatening anaphylactic reactions or autoimmune disorders (attacking oneself). The mechanisms by which the immune system can lead to cell injury or death include antibody attachment, complement activation, and activation of the

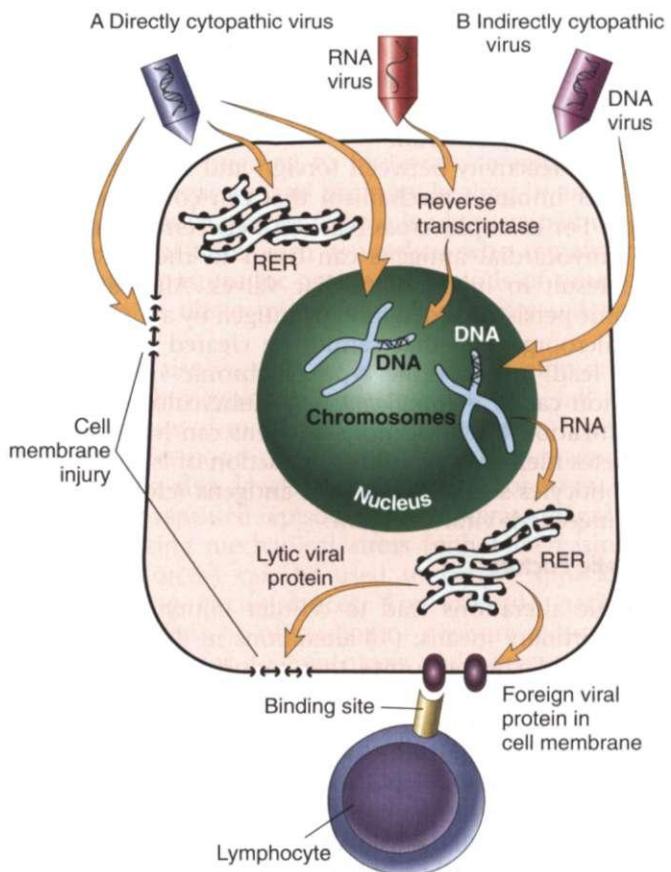


Figure 6-1

Mechanisms of cell destruction by viruses. A, Direct cytopathic effect: RNA virus inserts itself in a receptor on the cell membrane and is brought into the cell. The RNA virus is altered into DNA by reverse transcriptase. The DNA within the nucleus of the cell forms various types of RNA that allows for protein synthesis in the rough endoplasmic reticulum (RER). The protein formed inserts itself into the cell membrane, forming a channel that allows ions and extracellular fluid to enter, leading to cell lysis (directly killing the cell). B, Indirect cytopathic effect mediated by immune mechanisms: DNA virus inserts itself in a receptor on the cell membrane and is brought into the cell. The DNA virus within the nucleus of the cell forms various types of RNA that allow for protein synthesis in the RER. This foreign viral protein inserts into the cell membrane and becomes a neoantigen. This neoantigen will be recognized by the T lymphocytes that will react to and kill (indirectly) the infected cell. (From Damjanov I: *Pathology for the health-related professions*, ed 3, Philadelphia, 2006, WB Saunders.)

inflammatory cells (e.g., neutrophils, macrophages, T and B lymphocytes, mast cells, and basophils).

Cell injury and disease can be caused by the immune system in numerous ways. For example, allergies are caused by the presence of high numbers of a specific antibody-E (IgE) on the surface of specialized cells (mast cells and basophils, which release histamine), resulting in mild, moderate, or severe allergic reactions. Examples of mild reactions include the runny nose and watery eyes caused by a mild allergic response.

Moderate reactions include severe hypoxia caused by asthmatic bronchoconstriction. Severe reactions can result in a potentially life-threatening circulatory collapse seen in anaphylaxis (a whole-body allergic

reaction). The presence of what would normally be considered optimal ratios of antigen to antibody in the circulation may lead to damage of filtration in the kidney because of excess deposition of antigen-antibody complexes in the glomeruli.

Cross-reactivity between foreign and host antigens is another immune mechanism that can compromise the body. For example, cross-reaction between streptococcal and myocardial antigens can occur in rheumatic fever and result in injury of cardiac valves. Alternately, the chronic persistence of a foreign antigen by a foreign body or microorganism that cannot be cleared by the body may lead to a specific type of chronic inflammatory reaction called a *granuloma* (e.g., tuberculosis). Finally, sensitization to endogenous antigens can lead to type 1 diabetes mellitus caused by destruction of islet cells by T lymphocytes sensitized by islet antigens released during an antecedent viral infection.

### Genetic Factors

Genetic alterations lead to cellular injury or death by three primary means: (1) alterations in the structure or number of chromosomes that induce multiple abnormalities, (2) single mutations of genes that cause changes in the amount or functions of proteins, and (3) multiple gene mutations that interact with environmental factors to cause multifactorial disorders. These genetic alterations can be severe enough to cause fetal death in utero, resulting in spontaneous abortion. Some may cause congenital malformations, whereas others do not manifest pathologic alterations until midlife such as Huntington's chorea. Down syndrome is an example of an alteration in the number of chromosomes that results in multiple abnormalities. This condition, caused by the abnormal presence of a third chromosome in the twenty-first pair, includes cardiac malformations, increased susceptibility to severe infections, cognitive and developmental delays, and increased risk of leukemia and Alzheimer's dementia.

Sickle cell anemia, low-density lipoprotein (LDL) receptor deficiency, and α-antitrypsin deficiency are examples of single gene mutations. In the case of α-antitrypsin deficiency, the deficiency in a protease inhibitor causes enhanced degradation of elastic tissue surrounding the alveoli of the lungs, which in turn leads to emphysema. Examples of multiple gene mutations that can cause disease include hypertension and type 2 diabetes mellitus. In type 2 diabetes mellitus, obesity and other environmental factors induce the expression of the diabetic genetic trait.

### Nutritional Factors

Imbalances in essential nutrients can lead to cell injury or cell death. For example, deficiencies of essential amino acids interfere with protein synthesis. Synthesis of proteins is required to replace cell proteins lost through normal catabolism, through growth, and in preparation for cell replication. Cell replication is essential for the healing processes after cell injury and the replacement of cells lost through normal turnover.

The consequence of protein malnutrition is a condition called *kwashiorkor*; marasmus, another form of

### Box 6-2

#### CONNECTIVE TISSUE SYMPTOMS ASSOCIATED WITH VITAMIN C DEFICIENCY

- Reduced collagen tensile strength (scurvy)
- Altered capillary structure (petechiae and hemorrhage)
- Osteopenia (bone pain and pathologic fractures)
- Skin and gum lesions
- Impaired skin and wound healing (decreased collagen formation, lack of scar formation, impaired vascularization)
- Bilateral femoral neuropathy
- Muscle weakness
- Joint pain and effusions
- Edema

From Bucci LR: *Nutrition applied to injury rehabilitation and sports medicine*, Boca Raton, Fla, 1995, CRC Press.

### Box 6-3

#### RISK FACTORS FOR VITAMIN C DEFICIENCY

- Inadequate food intake (anorexia, chronic dieters, older adults, bedridden individuals)
- Malabsorption syndromes
- Moderate to severe physical injury or emotional stress
- Pregnancy and lactation
- Use of tobacco products (smoking or chewing)
- Obesity
- Alcoholism
- Rheumatoid arthritis
- Kidney dialysis (hemodialysis or peritoneal dialysis)
- Diabetes mellitus
- Oral contraceptives
- Drugs or medications (e.g., salicylates, corticosteroids, tetracycline)

From Bucci LR: *Nutrition applied to injury rehabilitation and sports medicine*, Boca Raton, FL, 1995, CRC Press.

malnutrition, is a consequence of generalized dietary deficiency. These two diseases are still leading causes of death in impoverished countries. In many industrialized countries, excessive nutrient intake leads to obesity and its many complications.

Nutritional imbalance can also occur as a result of abnormal levels of either vitamins or minerals. These nutrients function as cofactors for biosynthetic reactions or are essential components of proteins or membranes; their deficiency usually affects selected cells or tissues. For example, a deficiency of iron leads to anemia, and the presence of excessive amounts of iron in the tissues can cause damage by the formation of free radicals.

Vitamin C (ascorbic acid) deficiency can be associated with a wide range of connective tissue symptoms (Box 6-2). Frank deficiencies of ascorbate are uncommon in the United States, although certain population groups may be at increased risk for deficient intake sometimes referred to as *biochemical scurvy* (Box 6-3).

### Physical Factors

Trauma and physical agents can lead to cell injury and/or death. Blunt trauma caused by motor vehicle accidents is