

Table 13-1 Causes of Lymphedema

Primary	Secondary*
Unknown	Filariasis
Hereditary	Primary or metastatic neoplasm (benign or malignant)
Developmental abnormality	Surgery (lymph node dissection or removal)
• Aplasia	Radiation treatment
• Hypoplasia	Chemotherapy
• Hyperplasia	Severe infection
	Other surgery (e.g., multiple abdominal or pelvic surgeries)
	Lipedema
	Chronic venous insufficiency
	Liposuction
	Crush injury
	Compound fracture
	Severe laceration
	Degloving skin injury
	Burns
	Obesity
	Multiparity
	Paralysis
	Prolonged systemic use of cortisone (cortisone skin)
	HIV/AIDS
	Air travel (a "trigger" for those at risk; see Table 13-2)

HIV, Human immunodeficiency syndrome; AIDS, acquired immunodeficiency syndrome.

*Listed in approximate descending order.

distribution of secondary lymphedema caused by filariasis, but distribution may be governed by climate, with an estimated 420 million people exposed to this infection in Africa in the year 2000.⁵⁷

The WHO estimates 700,000 people in the Americas are affected today (including 400,000 in Haiti and 100,000 in the Dominican Republic). Clinical reports on the incidence of secondary lymphedema from other causes vary, with an estimated 3 million new cases in the United States each year; up to 30% of breast cancer survivors in the United States develop lymphedema sometime in their lifetime. The incidence increases after surgery and radiation when these procedures are combined.^{22,29,63}

According to Armer, "perhaps in part because of differences in measurement and diagnosis, the reported incidence of lymphedema varies greatly among persons treated with surgery and radiation for breast cancer. Through increased measurement accuracy, lymphedema incidence and prevalence following current therapeutic approaches for breast cancer treatment, cancer will be better understood, and more informed decisions about risk factors, treatment interventions, and recovery will be made."³

Etiologic Factors

The exact cause of primary lymphedema is unknown and cannot be linked to any significant traumatic event (Table 13-1). Primary lymphedema is most likely the result of



Figure 13-9

A 13-month-old with primary lymphedema of the right lower extremity, right buttock, and genital area since birth. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

lymphangiomas or malformations of the lymphatic vessel present at birth (Fig. 13-9) but sometimes delayed in symptomatic presentation. Although a small percentage of primary lymphedemas are linked to genetic causes (e.g., Milroy's disease and Meige's syndrome), most cases are not genetically linked and are more likely the result of some developmental abnormality in the fetus. A family history of lymphedema is present in only 10% to 20% of all people with primary lymphedema.²⁵

Klippel-Trenaunay-Weber syndrome (KTWS) is a rare occurrence in embryonic development and is associated with numerous anomalies. These can include varicose veins, cavernous hemangioma of the skin, and hypertrophy of bones and soft tissues in one or several extremities. In addition, dysplasia of the lymphatic system and neurogenic and visceral vascular malformations can occur. The dysplasia of the lymphatics can result in lymphedema in the involved extremities^{15,90} (Fig. 13-10).

Malformations of the lymphatic vessels associated with primary lymphedema can be divided into three types: aplastic, hypoplastic, and hyperplastic. *Aplasia* occurs when the lymphatic collectors are so few that they are considered "absent." Aplasia may also involve the absence of lymph capillaries that render the adequate collectors less functional. Aplasia is most often combined with hypoplasia; complete aplasia would result in tissues unable to support life.

Hypoplasia refers to less than the normal expected number of lymph collectors in the affected region and may also occur when collectors present are unable to function as transport vessels. Hypoplasia represents the most common cause of primary lymphedema, occurring in 75% of the cases. *Hyperplasia* accounts for 15% of primary cases and is characterized by grossly dilated and enlarged lymphatics that can become varicose. Hyperplasia can occur in the lymphatics of the superficial plexus of the skin or in the main lymph trunks. As a result of



Figure 13-10

A 50-year-old man with Klippel-Trenaunay syndrome, a lymphangiomyomatosis that caused lymphedema in both lower extremities. Note the skeletal abnormalities of the toes, the large hemangioma on the left thigh, and the venous varicosities in the lower legs. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)



Figure 13-11

A 19-year-old male with primary lymphedema of the left lower extremity (onset age 8). Lymphedema progressed to involve the buttocks and genitalia after prolonged pneumatic compression pump usage. This young man had three microsurgical procedures (lymphovenous and lympholympatic anastomoses) in an attempt to reduce the genital and extremity edema. In addition, he had two debulking surgeries, which also were unsuccessful in reducing the lymphedema. He developed chylous reflux and eventually had sclerotherapy to his leaking abdominal lymphatics, which was very successful in stopping the severe leakage of chyle from his scrotum, medial thigh, and buttock. The chyle-filled papules are visible on the posterior aspect of the thigh and calf. Notice the abnormal bulges and skin folds on the posterior thigh, which result when the debulked areas fill in with edema fluid. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

the overdistension of the vessels, the intralymphatic valve flaps do not seal, and a reflux of lymph occurs.

When this occurs in the mesenteric and intestinal lymphatics, a reflux of chyle to distal areas also takes place—that is, to the skin of the genitals, buttocks, and thighs, onto the knee joint (Fig. 13-11). Chyle is the protein-rich, milky fluid taken up by the intestinal lymphatics during digestion, consisting of lymph and triglyceride fat in a stable emulsion, and conveyed by the thoracic duct to empty into the venous system.

Lymphangiectasia refers to lymphatic hyperplasia in a deeper organ or localized area of a limb. Lymphangiomas and lymph cysts are forms of lymphangiectasia.

Secondary lymphedema occurs as the result of damage to otherwise normal lymphatic vessels or nodes from a known entity. The most common cause of secondary lymphedema worldwide is filariasis. Filariasis is a parasitic infection carried by mosquitoes in endemic regions, often found in tropical climates (Africa, South America, India, and Malaysia). The larvae of the worm are injected into the dermis with the mosquito bite. They pass into the initial lymphatics and larger collecting lymphatics and can grow to 20 cm in length and 1 to 2 cm in diameter as they mature into the adult worm forms. The adult male has a long tail that whips back and forth, damaging the fragile lymphatic walls.

The greatest damage, however, is done after the worm dies, often 5 to 10 years after the initial infection. At that time, foreign proteins from the worm body cause severe local inflammatory reactions leading to severe fibrosis

and scarring of the tissues, totally blocking the larger lymph collectors. This total blockage results in massive swelling distal to that collection site.^{44,77,90}

In the United States and other regions of the world where the filaria parasite does not exist or has been eradicated, the most common cause of secondary lymphedema is invasive procedures used in the diagnosis and treatment of cancer. Regional lymph node dissection for diagnostic staging and eradication of tumor sites disrupts the lymphatic system. Radiation therapy, reconstructive or other surgical procedures, or the combination of these procedures are well-known contributing factors to the development of lymphedema.

Local radiation treatment after surgery for cancer increases the incidence of secondary lymphedema three times that of surgery alone, probably a result of the increase in local tissue fibrosis that further impairs lymph flow through the remaining functioning lymphatic

vessels.¹⁹ If there is significant burning and blistering of the skin during radiation treatment, the risk of lymphedema is increased because of the decreased elasticity of the skin and subcutaneous tissues.⁷⁵

Other causes of secondary lymphedema include bacterial or viral infection; multiple abdominal surgeries, particularly in the obese individual; any trauma or surgery that impairs the lymphatics; or repeated pregnancies (see Table 13-1). Liposuction, done for cosmetic reasons to enhance appearance, when performed on an individual with an asymptomatic but marginal lymphatic system can trigger lymphedema in the operative limb.

Crush injuries, compound fractures, or severe lacerations or degloving injuries to the skin can significantly impair lymph flow. These types of injuries are also usually associated with damage to blood vessels. The damaged blood vessels leak fibrinogen, blocking the tissue channels and initial lymphatics and thus contributing to the development of lymphedema. Other known causes that have been reported as associated with secondary lymphedema include paralysis, lipedema, skin thinned by cortisone (sometimes referred to as *cortisone skin*), and acquired immunodeficiency syndrome (AIDS), particularly if Kaposi's sarcoma is present.¹⁹

Some medications used in the treatment of breast cancer (e.g., tamoxifen or Adriamycin) have been associated with peripheral thrombophlebitis. These medications can cause blood clots resulting in deep vein thrombosis (DVT), venous insufficiency, and eventual secondary lymphedema.

Surgery is "controlled trauma," but it is trauma nevertheless; the more extensive the procedure, the more extensive is the trauma. Surgery in individuals with a marginal lymphatic system (where the lymph transport capacity equals the normal lymph load) can cause enough of an overload to trigger lymphedema. For example, an individual undergoing a triple coronary artery bypass graft (CABG) procedure with donor veins taken from the legs may develop chronic leg edema that is often misdiagnosed as venous insufficiency or "cardiac related." This is particularly true in the older, obese individual who has poor functional mobility. If the diagnosis of lymphedema is delayed or never made and is not addressed, the individual may not be able to succeed in postoperative rehabilitation (Fig. 13-12).

In the past, most health care professionals knew about upper limb lymphedema secondary to axillary dissection for breast cancer, but many were not aware that an individual who had a CABG procedure; inguinal node dissection for melanoma of the foot, testicular cancer, or prostate cancer; or pelvic/abdominal node dissection for gynecologic cancer was at risk for lymphedema of the leg.

Anyone with postoperative leg edema after a fracture or total hip or knee replacement would not have been routinely evaluated for lymphedema 10 years ago. The combination of venous edema and lymphedema is often overlooked in the management of edema secondary to trauma. Many cases of chronic edema with recurrent infection and skin ulcerations are treated as pure venous edemas with poor results because the lymphatic component of the edema is not addressed.



Figure 13-12

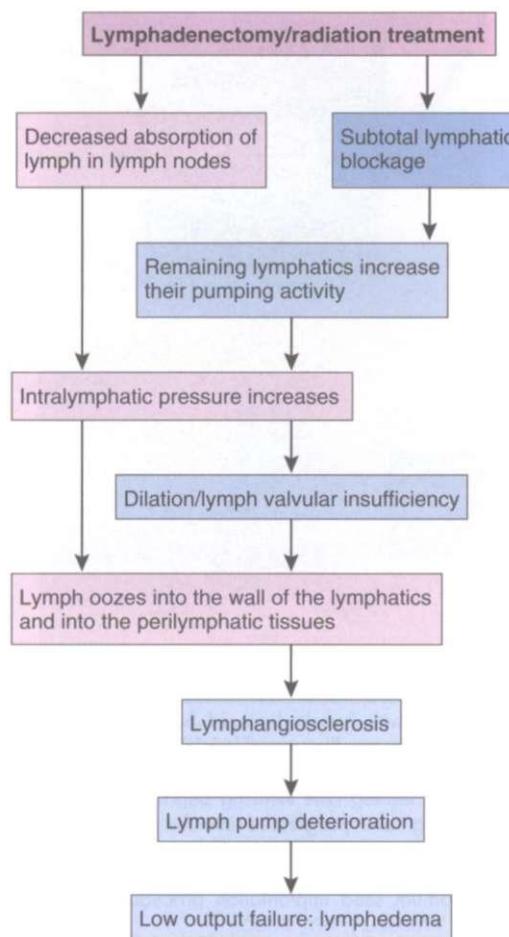
A 63-year-old man with lymphedema of both lower extremities, left greater than right. The swelling developed in the left leg 1 year after a coronary artery bypass graft (CABG) procedure in which veins were harvested from the left leg. The swelling began in the right leg, worsened in the left leg, and progressed into the abdomen after radium seed implantation for prostate cancer. This man's marginal lymphatic system was overwhelmed by the "trauma" caused by the CABG procedure and the radium seed implantation procedure. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

Pathogenesis

Lymphedema by definition is a low flow edema that occurs when the lymph transport capacity is inadequate to transport the normal volume of lymph. It is a failure of the safety valve mechanisms (Fig. 13-13). This can occur when the lymph load is normal, but the lymph transport capacity is inadequate (*decreased absorption of lymph in lymph nodes*) or when there is an increase in the lymphatic load (e.g., fluid entering the tissues) and the transport capacity is inadequate (*subtotal lymphatic blockage*).

In reality, the body adjusts the load if the capacity alters in response to changes in tissue hydrostatic pressure and other changes in homeostasis (*remaining lymphatics increase their pumping activity*), and conversely, the capacity can be adjusted if the load alters (*intralymphatic pressure increases*). When the safety valve mechanisms are no longer effective or become overwhelmed, the body's normal compensation is not enough, and lymphedema develops.

Lymphedema causes the lymphatic vessels to dilate; the valve flaps become incompetent (*dilation/lymph valvular insufficiency*), and the protein-rich lymphatic fluid refluxes to the tissue spaces (*perilymphatic tissues*). At first, a proliferation of initial lymphatic vessels occurs as the system tries to cope with the accumulation of lymphatic load. Lymph vessels can rejoin, or collateral lymphatics can develop to bypass the damaged area. In

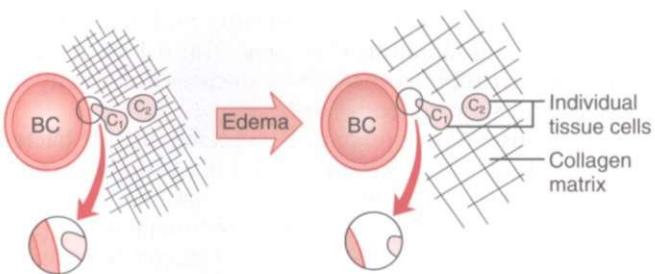
**Figure 13-13**

Pathogenesis of lymphedema. This flow chart follows the progression from an "at-risk" or latent phase of lymphedema to acute lymphedema after lymphadenectomy and/or radiation treatment to the nodal area. (Courtesy Dr. Michael Földi, June 1999.)

lymphedematous tissue, a state of chronic inflammation exists.⁶⁷ This chronic inflammation leads to progressive tissue fibrosis, resulting in a state of relative hypoxia in the tissues, further impeding tissue oxygenation and contributing to a cycle of chronic inflammation and increased risk of infection.

In either primary or secondary lymphedema, infection or delayed wound healing (the latter can be directly related to the low oxygen state caused by edema) will add to the high-protein edema. Infection in the tissues (cellulitis) or infection in the lymph vessels (lymphangitis) can cause progressive tissue fibrosis and/or scarring in the lymph vessels (*lymphangiosclerosis*). Though some recanalization and collateralization of lymph vessels take place, lymphatic function remains compromised. An increase in the size of the tissue channels occurs with an increase in the distance for the oxygen to diffuse from the capillaries to the cells (Fig. 13-14). Gas exchange and metabolism of cellular waste products are impaired.

Although the number of macrophages increases, their activity is decreased in the lymphedema fluid for reasons not clearly understood. Some theories suggest that the

**Figure 13-14**

Reduction of gas (oxygen) exchange. Even a relatively minor amount of edema, which moves the fibers and individual tissue cells (C₁, C₂) apart by only a small amount, can cause a great increase in the resistance to diffusion of gases (and other small lipid-soluble molecules) between the cells and the blood capillaries (BC). The magnified view of the distance between the BC and the tissue cell (representing the cell's oxygen supply) is greatly increased in the edematous state. The greater distance for oxygen to diffuse to nourish the cells will eventually lead to a hypoxic state. (From Casley-Smith JR, Casley-Smith JR: Modern treatment for lymphoedema, ed 5, Adelaide, Australia, 1997, lymphoedema Association of Australia.)

chronic lack of essential nutrients (e.g., oxygen) or perhaps a toxic factor produced by the stagnant proteins or the damaged tissues contribute to the deterioration of macrophage.^{22,36} In chronic lymphedema, the muscle wall of the collecting lymphatics hypertrophies, reducing the effective pumping power of these vessels (*lymph pump deterioration*).

The effect of lymphedema on the blood vessels causes a proliferation of new small blood vessels and the development of arteriovenous anastomoses. These new small vessels may leak as a result of abnormal changes in total tissue pressure in the lymphedematous region, further overloading the area. Proteins, fats, cellular waste products, and the 10% of tissue fluid volume that is not directly transported by the venous system have no alternative transport pathway from the interstitium to the venous system except via the lymphatic system. When this transport mechanism is impaired, lymphedema develops (Fig. 13-15, A). The impairment can be structural or functional.

Structural Impairment. Aging or damaged blood vessels are associated with structural impairment as fibrin physically narrows or blocks tissue channels (Fig. 13-15, B). Hypoplasia of the collecting lymphatics is also associated with the pathogenesis of structural lymphedema (Fig. 13-15, C). Primary lymphedema that manifests itself in puberty with a growth spurt and increase in tissue mass causes the body to outgrow or outstrip the capacity of the lymphatic system. The functioning vessels become overwhelmed, the walls fail, dilate, and result in valvular incompetence, causing increased peripheral intralymphatic pressures and peripheral lymphedema.

Structural lymphedema may also occur when the flaps of incompetent valves of the initial lymphatics (Fig. 13-15, D) no longer meet, allowing reflux of lymph to regions distal to the blockage. The initial lymphatics eventually dilate as well, their endothelial junctions remain open, and lymph refluxes to the tissues.

Other causes of structural lymphedema include gaps and tears in the initial lymphatic walls associated

with trauma and inflammation (Fig. 13-15, E), physical obstruction of collecting lymphatics (Fig. 13-15, F) associated with fibrosis, radiation therapy, tumor growth, surgical excision of lymphatics during tumor removal, and torn anchoring filaments (Fig. 13-15, G) associated with sudden acute edema. The latter may occur secondary to massive trauma or infection and can tear the microfilaments that connect the initial lymphatics to the interstitial tissues, resulting in the collapse of the initial lymphatics because of the high total tissue pressure.

In the case of lymphedema caused by filariasis, the adult worm blocks the vessel it is in. Damage to lymph vessels occurs from the whiplike action of the constantly motile adult worms and the toxic effects of parasite secretory and excretory products. When the worm dies, the toxins released stimulate a granulomatous reaction with

infiltration of plasma cells, eosinophils, and giant cells, further damaging the vessel and surrounding tissue as severe inflammation develops. Over time, repeated limb bacterial infections in previously damaged vessels may superimpose additional lymphatic damage.¹⁵⁻¹⁷

Functional Impairment. Anything that causes a lack of variation in total tissue pressure (TTP) causes lymphedema. Bed rest, paralysis, or prolonged immobility can severely limit changes in total tissue pressure. For example, a survey by the Lymphoedema Association of Australia reported an increase in the incidence of lymphedema and exacerbation of preexisting lymphedema after air flight.²³ It is this variation that contributes to a pressure gradient between the interstitial tissues and the intralymphatic pressure. Normally this pressure gradient stimulates the lymphangions to contract, which enhances the flow of

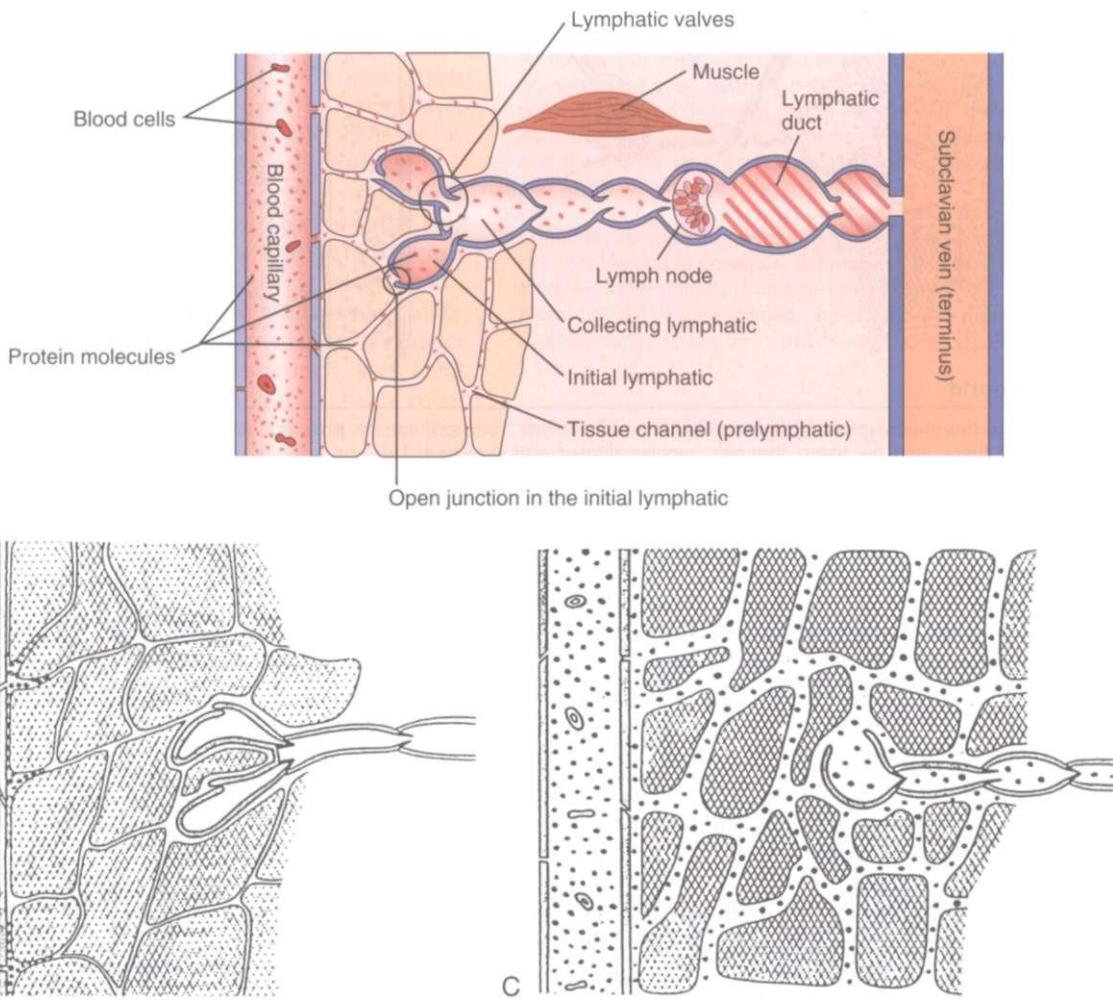


Figure 13-15

Low-flow, high-protein lymphedema caused by structural impairment. **A**, "Normal" tissue for comparison showing the passage of protein (dots) in normal tissue from the blood capillary, through the tissue channels, into and through the lymphatic system, and back to a vein. **B**, Altered interstitial tissue (e.g., too few or too narrow tissue channels). Notice that the prelymphatic channels are much narrower than in the normal tissue and the protein molecules are stacked up on the arterial side, unable to move easily through the narrow tissue channels, causing impaired lymph flow (and eventual tissue fibrosis). Inlet valves are closed because the endothelial cell junctions cannot open properly in fibrosed tissues, contributing to poor lymph drainage. **C**, Abnormally few initial lymphatics. This may occur developmentally or because some of the vessels become blocked (e.g., by fibrin). In this case, too few initial lymphatics are evident. Notice the dilation of the prelymphatic channels, the greater concentration of protein molecules in the tissue channels, and the malformed inlet valve. Low-flow, high-protein lymphedema caused by structural impairment.

Continued.

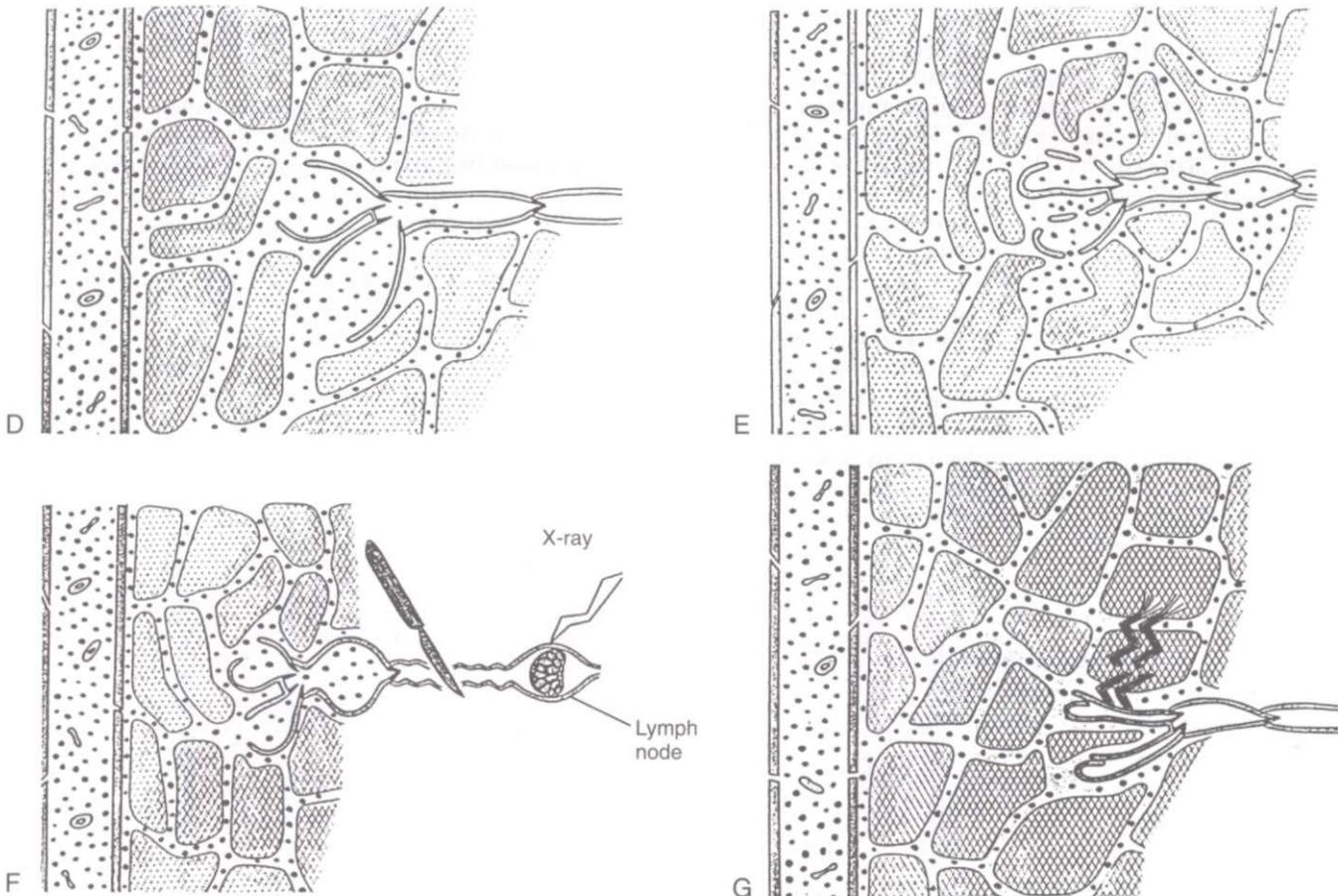


Figure 13-15, cont'd

D, Malformations of the initial lymphatics preventing their inlet-valves from sealing; the prelymphatic tissue channels are dilated, a high-protein concentration exists there, and the tissue channels become dilated and stretched. This can happen in both primary and secondary lymphedema; in secondary lymphedema, it occurs after prolonged lymphostasis from a more proximal blockage. **E**, Injuries to the walls of the very fragile initial lymphatics. Lymph refluxes into the tissue channels, causing them to dilate. The high concentration of protein in the extracellular tissues causes a chronic inflammatory response and greater risk of infection. Note the larger spaces between the tissues. This results in a larger distance for oxygen to diffuse and leads to tissue hypoxia. **F**, Iatrogenic factors (e.g., surgery, radiation, tumor growth) that damage the lymphatic ducts or larger vessels impair lymph flow from the periphery. When movement of lymph from the tissue channels into the initial lymphatics is impaired, the tissue channels dilate, lymph stasis occurs, and there is a high-protein concentration in the tissues with subsequent chronic inflammation, increased risk of infection, and progressive swelling of the limb. **G**, Anchoring filaments tearing away from the interstitial tissue. This occurs in severe edema from other causes (e.g., rapid swelling from acute lymphedema as a result of trauma can tear the anchoring filaments from the surrounding tissues). The initial lymphatics can no longer function as conduits, as they would normally. The lymphostasis this produces worsens the existing edema. (From Casley-Smith JR, Casley-Smith JR: *Modern treatment for lymphoedema*, ed 5, Adelaide, Australia, 1997, Lymphoedema Association of Australia.)

lymph from the periphery to the center of the body. When the tissue pressure does not change or vary, the force pumps remain inactive.

Other factors contributing to functional impairment of the lymphatic system may include spasm of collecting lymphatics (e.g., lymphangiospasm caused by inflammation stimulating sympathetic nerves); paralysis of the collecting lymphatics (e.g., prolonged distention leading to fatigue and ultimately, failure); and impaired contraction of the collecting lymphatics caused by physical obstruction of fibrotic tissue surrounding lymphatic vessels. This type of functional impairment is common in severe Stage II lymphedema and lymphostatic elephantiasis. If collectors cannot pump, lymph refluxes peripherally, causing overdistension of initial lymphatics, valvular incompetence, lymphatic failure, and ultimately, lymphedema.

Clinical Manifestations

Primary or secondary lymphedema is characterized by clinical signs and symptoms caused by the effects of lymphedema on the lymphatics, body tissues, and blood vessels. Lymphedema resulting from filariasis is reversible in its early stages; secondary lymphedema can be transient if damage is minor. Secondary lymphedema can develop immediately postoperative or weeks, months, or years after surgery.

Lymphedema can develop in any part of the body or limb(s). Signs or symptoms of lymphedema include a full sensation in the affected body part; a sensation of skin tightness; decreased flexibility in the hand, wrist, or ankle; difficulty fitting into clothing in one specific area; or ring, wristwatch, or bracelet tightness. In advanced cases, fistulas to the skin, joints, or gut may develop; these

are portals of entry for bacteria to invade the skin and cause recurrent infection.

Physical impairments caused by lymphedema can include increased circumferential limb girth; postural changes; tremendous discomfort (heavy, aching, or bursting sensations); neuromuscular deficits; and integumentary complications. These physical impairments can lead to functional limitations and disability along with the potential for psychosocial morbidity (e.g., social isolation, depression, or suicide).^{7,51} Healing time is increased, and all of this is occurring in a heavy, painful, and clumsy limb that is more prone to injury because of its abnormally large size and decreased functional mobility. Risk of injury is increased, whereas oxygenation and metabolism of waste and cellular debris are decreased. This is a most dangerous environment.

As the lymphedema progresses, atrophic skin changes can occur as a result of the low oxygen state, including loss of hair and sweat glands, formation of keratotic patches on the skin, and the development of papillomas (blisterlike outpocketings of the skin) that sometimes leak lymphatic fluid. Angiosarcoma (Stewart-Treves syndrome) is a rare malignancy that can develop in an advanced, chronic lymphedema that is left untreated.

Complications of Lymphedema. As lymphedema progresses, the dermal layer of the skin thickens, the skin itself dries and cracks, and ulcerations often develop. These ulcers do not heal because of the tension on the tissues from the edema and the decreased oxygen state, coupled with the subcutaneous fibrosis and chronic inflammation. As the skin and tissues stretch, skin folds and tissue flaps can develop. These folds and flaps become breeding grounds for fungal and bacterial infections that further damage skin integrity, creating new portals of entry for the bacteria as the skin macerates and cracks.

Chronic fungus (*tinea*) is common on the foot and toes of anyone with lymphedema of the legs, as well as in the groin and under the breast. This fungus can be difficult, if not impossible, to treat topically. If this *tinea* is not addressed during treatment, a successful outcome is not possible¹⁹ (Fig. 13-16).

The progressive increase in girth and weight of the affected areas contributes to pathologic alterations in the gait pattern and decreases in functional range of motion and strength caused by fatigue and inactivity. With increasing edema and subcutaneous fibrosis, tactile sensation and kinesthetic awareness are impaired, increasing the risk of injury to the affected areas.

If the edema progresses into the trunk quadrant adjacent to the lymphedematous limb, a further loss of trunk strength and function can occur. Some individuals, for example, must sleep in a recliner chair to prevent losing their independence, since they can no longer mobilize themselves and their heavy limbs in bed. A vicious cycle develops with decreasing mobility and strength leading to joint contractures, further increasing the risk to the already impaired skin integument.

The limbs may be painful and hypersensitive, and the adjacent trunk quadrants may ache and throb. Balance may be impaired, and the individual may no longer be able to shower or bathe independently, as a result of the fear of falling or inability to move the heavy limbs over



Figure 13-16

A 30-year-old male with spina bifida and lymphedema secondary to paralysis and unsuccessful plastic surgery with skin graft for a chronically itchy, 2-cm keratotic lesion on the left anterior ankle crease. **A**, Chronic ulceration complicated by fungal infection of the ulcer itself and the foot or toes. Note the hypertrophic fibrotic skin at the ankle and warty changes on the toes. **B**, After 4 weeks of CLT treatment (debridement of the ulcer was done daily in addition to the lymphatic drainage, compression bandaging, and other skin care). Exercise was not possible due to paralysis; deep abdominal breathing exercises and modified self-lymphatic drainage were taught and then practiced daily. Note that the wound healed completely and the infection resolved. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

the bath or shower ledge. Hygiene becomes a problem, further increasing the risk for fungal and bacterial infections.^{60,65}

Primary lymphedema is more common in females and affects the lower extremities most often. However, it is seen in males and in the upper extremities, too.¹⁶ Primary lymphedema can be present in many parts of the body, and if it is present from birth, the deep internal organs can be affected. Clinical cases of primary lymphedema of the lower extremities involve the buttocks, genitals, and intestines with reflux of intestinal chyle (chylous reflux/protein-losing enteropathy) through fistulae on the genitals, buttocks, and thighs (see Fig. 13-20).

This protein-losing enteropathy is a medical emergency. Severe protein loss can occur from this leakage of protein-rich chyle from the intestinal lymphatics. Individuals with primary lymphedema who complain of abdominal bloating, chronic diarrhea, or intolerance of fatty foods may also experience fluid accumulation in the abdomen and genitals from the pressure of the fluid leaking from the intestinal lymphatics into the abdomen. In some cases, these clients are treated medically or surgically with sclerotherapy to seal off these leaking lymphatics in an attempt to halt the reflux of this fluid into the abdomen.

Surgical dissection and radiation therapy involving the cervical, supraclavicular, or mandibular lymph nodes can cause secondary head and neck edema. Significant edema of the head and neck can cause severe functional impairments in speech, swallowing, and respiration, in addition

to the pain and psychologic trauma from cosmetic disfigurement. When scarring and lymphatic dysfunction are severe, treatment, such as manual lymphatic drainage (MLD), cannot always restore normal cosmesis; however, it can successfully reduce some of the edema, leading to improved function. For example, in individuals with severe edema of the throat and neck after surgery and radiation for tongue cancer, lymphatic drainage can reduce the swelling enough to allow the person to discontinue use of a tracheotomy tube previously considered permanent. Some clients are able to eat solid foods again; others with severe periorbital and lower facial edema may be able to open the eyes and read and watch television again. Although these are not "cures," they are great improvements in function that are important to individual quality of life.

MEDICAL MANAGEMENT

Remarkable progress has occurred in diagnosis and management of lymphedema in the United States since 1990. Ironically, this has occurred despite the incorrect prediction for those with breast cancer that the advent of breast-conserving lumpectomy would eliminate upper extremity lymphedema so commonly seen in individuals postmastectomy.

Many individuals who undergo lumpectomy receive axillary lymph node dissection (ALND) and radiation therapy too; these are the very factors that multiply an individual's risk of developing lymphedema. It has been reported that a 3% incidence of lymphedema after sentinel lymph node biopsy (SLNB) alone increased to 17% when the client required an axillary dissection following the SLNB.⁷⁹

Another study followed 102 women treated for breast cancer, defining lymphedema as a greater than 2 cm difference between measurement sites, and recorded lymphedema in 43.3% of women who underwent ALND alone, 22.2% of those who underwent SLNB alone, and 25% of those with combined SLNB and ALND. Overall, the proportion of women experiencing increased arm size, numbness, or firmness/tightness in the limb on their operative side was higher in the ALND group than the SLNB group.⁴

Wilke et al published data on surgical complications of SLNB in 5500 cases and reported a 6.9% incidence of "proximal upper extremity lymphedema" (change from baseline arm circumference of greater than 2 cm when compared to the contralateral arm).⁹¹ Gould et al found lower extremity lymphedema in 30% of individuals undergoing inguinal lymph node dissection in the treatment of vulvar cancer.⁴⁷

Zhang et al reported only 3% lower extremity lymphedema after inguinal node dissection (during surgery to treat vulvar cancer) when they were able to preserve the saphenous vein compared to 32% lymphedema incidence in those people who underwent inguinal node dissection and saphenous vein ligation.⁹² Thanks to advances in surgery and chemotherapy and the emphasis on early detection, many more individuals are surviving cancer for many years, living and functioning well with "limbs at risk" for lymphedema. Refinement in measurement tools, as well as the inclusion of self-reported symp-



Figure 13-17

Stemmer's sign is clearly visible as a thickening of the skin folds of the toes of this 22-month-old child with a history of primary lymphedema of the left lower extremity diagnosed at birth. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

toms, which may be present well before a 2-cm difference between measurement sites can be recorded, will hopefully lead to earlier diagnosis and management of lymphedema.³

DIAGNOSIS

Primary Lymphedema. An easy-to-perform clinical test for determining primary lower extremity lymphedema is Stemmer's sign, a thickened cutaneous fold of skin over the second toe, typically present in the early and differential diagnosis of a primary ascending lymphedema without false positive findings. It appears in the late stages of the descending lymphedema⁸⁰ (Fig. 13-17). Although it is possible to have a false negative Stemmer's sign, primary lymphedema is rarely accompanied by a false positive Stemmer's sign.

Secondary Lymphedema. The clinical diagnosis of secondary lymphedema is fairly straightforward in a limb at risk, when there is known disruption to the regional lymphatics (e.g., after axillary dissection/radiation for breast cancer or after inguinal node dissection/radiation for melanoma of the leg). A detailed medical history, including all surgical procedures and their chronology relative to the onset or worsening of the edema, is the cornerstone of a successful lymphologic evaluation. In secondary

lymphedema, most often no other diagnostic tests are needed to confirm the diagnosis.

A venous Doppler study of the edematous limb is often done to rule out a thrombus as the cause of the swelling. It is crucial to have recurrence of cancer firmly ruled out as the causative factor before initiating treatment for the lymphedema. Many oncologists will request a magnetic resonance imaging (MRI) or computed tomography (CT) scan of the chest for upper extremity swelling or the pelvis and abdomen for lower extremity swelling before initiating a referral for treatment of the lymphedema.

Lymphedema may be the first sign of cancer recurrence even years after cancer treatment. The prospect of recurrent disease is a frightening one, but it must be ruled out. Malignant lymphedema (i.e., directly resulting from neoplasm blocking a major nodal region or lymph vessel) is usually more severe and progresses more rapidly than nonmalignant secondary lymphedema.

It is often associated with severe pain and/or sensorimotor deficits, particularly in the upper extremity when the brachial plexus is involved. These symptoms must be differentiated from the pain and weakness of radiation plexopathy, which sometimes progresses more slowly, but causes the same type of functional deficits.

In cases of unexplained swelling, particularly in the lower extremities when no known trauma or surgery is evident, the clinical examination and history may not provide a definitive medical diagnosis. Although the MRI and CT scan will clearly show edema fluid in a limb or region, these tests do not give a description of lymphatic function. This type of information is obtained from a lymphoscintigram, a sophisticated nuclear medicine test (with cost comparable to the MRI or CT scan) that outlines the major lymphatic trunks in a region and provides a functional description of how much tracer material is moved, how far, and in what unit of time, compared with the "normal" values of a person of similar height and weight.

The test involves subcutaneously injecting a small amount of radioactive tracer in the web spaces of the first and second digits of either the hands or feet. The client then performs a set of standard movements for a specific time period and serial radiographs are taken. The amount of exposure from all the radiographs is approximately equal to one x-ray.

As the tracer is taken up by the lymphatics, it will outline the major lymph trunks and show the volume of tracer moved per unit of time. The presence of tracer reflux that goes back down a limb is called *dermal backflow* and gives an indication of more proximal obstruction in the deeper lymphatic collectors. When the etiologic factors of edema are unclear, this test clearly shows the functional deficits in the lymphatics. It is especially helpful in ruling out secondary lymphedema in cases of lipedema with questionable lymphedema of the legs.

TREATMENT. The primary focus in a case of lymphedema triggered by a new or metastatic cancer is to treat the cancer first and then manage the lymphedema. Input on how to minimize exacerbation of the lymphedema during

the cancer treatment is often well received, if given with the intent to provide comfort and function.

Individuals are encouraged to undergo the cancer treatment that they wish to pursue, without guilt or fear that it will worsen the lymphedema. They need to know the possibilities and risks but should not be frightened from necessary treatment for the cancer by a well-meaning health care professional.

On the other hand, the lymphedema should not be ignored. Management of the lymphedema must be coordinated with the medical team (e.g., medical oncologist, surgeon, and radiation oncologist) and the client. This communication can avoid further overloading the person with additional appointments and adding more to their daily activities than they can handle.

Medications. No clear-cut pharmaceutical drug is available to treat lymphedema, although there is hope for a safe, effective medication that will lyse the protein accumulating in the obstructed area and speed the healing process. Clinical studies have shown that the benzopyrones (Coumarin, Venalot, Daflon, and their natural counterparts, the bioflavonoids, rutin, horse chestnut, and grapeseed extract)* have some effect on increasing proteolysis and increasing macrophage activity (remember that the macrophages become inactive in the lymphedema fluid and unable to perform their immune functions). However, these substances also raise some health risks, specifically liver toxicity. Further randomized clinical trials are needed to assess efficacy and dosing.

This increased proteolysis helps to reduce the interstitial protein concentration, signaling the body to reabsorb more extracellular fluid, thereby reducing the lymphedema. These substances have been shown to soften fibrotic tissue and increase the healing of chronic ulcerations and bacterial infections in elephantiasis lymphedema, probably a result of the activity of the macrophages, stimulating the immune response.*

Diuretics work well on sodium retention edemas but do not help lymphedema, yet they continue to be prescribed. Although it is true that taking large doses of diuretics will reduce total body fluid volume, these medications do not address the cause of the lymphedema (i.e., that the lymph load is exceeding the reduced lymph transport capacity). Furthermore, diuretics may move the "water" component of the lymphatic fluid, further concentrating the extracellular protein in the tissues increasing fibrosis. Moreover, chronic use of high-dose diuretics leaves the individual at great risk for developing electrolyte disturbances.

*The benzopyrones have not been approved by the Food and Drug Administration (FDA) in the United States, and the oral Coumarin was decertified in Australia because of several cases of death associated with liver problems. Other oral benzopyrones are still available in Switzerland, France, and Germany. Topical Coumarin powder and ointment is still available through compounding pharmacists in the United States. Bioflavonoid liquid and tablets have been available in U.S. health food stores for years. They are combined with various other compounds (known as bioflavonoid complex) and necessitate taking a larger dose of the complex to receive the desired amount of bioflavonoid.

'References 15,19,24,27,40,42,58,62,69,85.

Experts agree that diuretics may be indicated in cases of malignant lymphedema. Individuals with comorbid conditions that require the use of diuretics, such as arterial hypertension, nephritic syndrome, or congestive heart disease, must be strongly advised to continue their medication and to consult with their primary physician with questions regarding their prescription.^{15,42}

Some nonsteroidal antiinflammatory drugs (NSAIDs) that are cyclooxygenase-2 (COX-2) inhibitors (e.g., Celebrex) have a warning in the package insert about leg edema being a possible side effect. This has been clinically reported in several cases with lymphedema and arthritis; the individual with arthritis may experience an increase in edema when taking these drugs.¹⁰

Other commonly prescribed drugs, such as Norvasc (used to treat hypertension) and Avandia (used to treat diabetes), can cause leg edema. Lyrica (pregabalin), a fairly new drug for neuropathy (used with diabetic neuropathy and shingles), may cause heart failure and limb edema.

Many people do have neuropathy from chemotherapy (e.g., docetaxel [Taxotere]) that is permanent and take these medications to manage the symptoms of neuropathy. Therapists must be aware of this possible side effect in any of these medications and not assume that increased edema is a result of, for example, behavioral noncompliance or a problem with fit of a compression garment.

Clients may experience similar problems as new drugs for other conditions are introduced into the market. Even if the package does not warn of edema as a possible side effect, the therapist and client must observe carefully for any early signs or symptoms associated with the use of a new prescription.

Surgery. Surgery has been used to "treat" severe lymphedema in the past with limited success. It is still done today if an individual receives no benefit from conservative treatments or does not have access to these treatments. Although numerous surgical approaches have been proposed to treat chronic lymphedema of the extremity, none has been clinically successful.⁵⁵⁻⁷⁰ Animal and cadaver studies continue investigating surgical techniques to resect tumors, reconstruct breast tissue, or perform liposuction^{45,46} that will prevent venous occlusion and subsequent lymphatic dysfunction.

Many microsurgical procedures attempt to anastomose a lymph vessel or node with a vein or with another functioning lymph vessel or lymph node. The morbidity and mortality from these procedures are significant. These procedures often fail soon after the surgery, leaving the individual with more superficial scarring that further blocks collateral lymph flow from the obstructed limb.

Debulking procedures (e.g., the Charles operation) seek to physically remove the excess fibrosclerotic connective tissue. (These procedures are rarely done in the United States except in extreme cases; debulking is still done in other countries.) These operations create extensive longitudinal scars on the involved extremities. Long incisions are made in the skin and subcutaneous tissues are removed down to the muscle and bone; the skin flaps are reapposed and sutured in place.

Although these procedures attempt to address the severely impaired cosmesis in the affected individuals,

they do not address the cause of the impairment, which is decreased lymph transport capacity. This problem is unchanged by these procedures; over time, the limbs begin to swell again, often with disfiguring asymmetrical tissue flaps, large lymph cysts called *papillomata* (up to 6 to 8 cm in diameter), or warty protrusions on the skin (see Fig. 13-11).^{19,41}

Reconstructive surgery after mastectomy is a very personal matter. Many procedures are available from the insertion of a tissue expander, followed later by the insertion of a permanent saline implant to the more extensive myocutaneous tissue flap procedures (i.e., transverse rectus abdominal muscle [TRAM] flap, free latissimus flap, or deep inferior epigastric flap [DIEP]) involving transplanting flaps of muscle and skin to the breast area to form a more "natural" breast.

The TRAM flap, which transplants the contralateral rectus abdominis muscle by tunneling it across the abdomen and up to the breast area, involves extensive scarring in the suprapubic area from hip to hip, in addition to the individual scars on the breast area. The procedure usually consists of two other minor procedures, performed separately to tattoo the areola and create a nipple. The horizontal hip-to-hip scar effectively blocks a large area of collateral lymph flow from the ipsilateral thoracic lymphotome through the abdominal lymphotome to the superficial inguinal nodes. This area of collateral lymph drainage is important for the treatment of ipsilateral upper extremity lymphedema that can develop after axillary dissection and mastectomy. In some cases, abdominal lymphedema develops after this procedure. This should not be confused with *asymmetric edema*, which may really be a hernia of the abdominal contents on the contralateral side where the abdominal muscle was removed. This occurs on rare occasions, but it must be medically diagnosed and surgically corrected.

The latissimus flap procedure also creates a long transverse scar on the ipsilateral posterolateral thorax, effectively blocking a large area of collateral lymph drainage from the upper extremity to the ipsilateral superficial inguinal nodes. This lymphatic pathway may be needed to treat an upper extremity lymphedema secondary to axillary dissection or radiation. These procedures may lead to truncal lymphedema, which is often not recognized, sometimes discounted as psychosomatic, and can cause considerable disability, impairment of function, and psychosocial distress.³⁶

PROGNOSIS. Left untreated, lymphedema is a progressive disease; current surgical and pharmacologic approaches do not bring about a "cure." Lymphedema is a life-long, chronic condition, but one that can be managed effectively with proper intervention, client education, and regular follow-up care.

SPECIAL IMPLICATIONS FOR THE THERAPIST 13-2

Lymphedema

PREFERRED PRACTICE PATTERNS

Five integument patterns are based on the level of skin involvement. Formerly, a singular pattern related to lymphatic impairment was included as part of the integumen-

tary Practice Patterns but has subsequently been moved to the section on cardiovascular/pulmonary practice. Additionally, reduced mobility and compounding psychosocial aspects may result in physical deconditioning described by Preferred Practice Pattern 6B.

Clients who develop radiation fibrosis or surgical scars from cancer surgery may also be described by integument patterns involving partial- and full-thickness skin involvement. Practice patterns are dependent on clinical presentation; additional patterns may be appropriate depending on the underlying cause of the lymphedema but may include the following:

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

7B: Impaired Integumentary Integrity Associated with Superficial Skin Involvement

7C: Impaired Integumentary Integrity Associated with Partial-Thickness Skin Involvement and Scar Formation

7D: Impaired Integumentary Integrity Associated with Full-Thickness Skin Involvement and Scar Formation

7E: Impaired Integumentary Integrity Associated with Skin Involvement Extending into Fascia, Muscle, or Bone and Scar Formation

6H: Impaired Circulation and Anthropometric Dimensions Associated with Lymphatic System Disorders

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

4B: Impaired Posture

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

4E: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Localized Inflammation

It is critical to advise those who are at risk for lymphedema of the signs and symptoms of lymphedema and to educate them on risk reduction strategies to minimize stress on their marginal lymphatic systems (Table 13-2). Great care must be taken to avoid further overloading an already compromised area by the application of various modalities or therapeutic exercises.

For clients who are free of lymphedema but receiving radiation therapy, the radiated area must be observed carefully and consistently for any signs such as blistering, discoloration, erythema (redness), or increased skin temperature changes. Any of these can be indications of developing lymphedema.

Many people do not "report" edema unless it is severe. This is common during the interview and history taking during patient/client consults. The individual's legs can be four times the size of their normal leg, yet they will say the swelling "just started" or "only just started to bother me" or "never swelled like this." When asked if they ever noticed even a little swelling in the foot or ankle, a mark when they removed socks or shoes, or swelling when it was hot or when they stood for a long time, clients often report all of these

events have occurred for years "but it never bothered me" or "it was not really bad" and so on. This behavior is particularly common in the heavier clients who do not have a perception of how overweight they are or really cannot see or reach their feet.

Lymphodynamic insufficiency is a concern when treating lymphedema. Clients, particularly those with primary lymphedema of the lower extremities, should be evaluated for abdominal and genital edema before undergoing any treatment to reduce the extremity lymphedema to avoid the complication of moving more fluid into an already overloaded abdominal area.

Throughout the episode of care, observe the areas adjacent to the lymphedematous limb or region (the ipsilateral buttock, suprapubic/genital areas, ipsilateral breast/lateral trunk, or the contralateral lower extremity in a case with pelvic/abdominal node obstruction) to ensure that treatment of the peripheral lymphedema does not create lymphedema in adjacent lymph drainage areas.

An increased risk of this fluid movement occurs when using gradient compression pump therapy to treat extremity lymphedema. Excessive shear on the skin of a lymphedematous limb or a limb at risk from vigorous massage or from a compression pump exceeding 60 mm Hg compression can tear microfilaments and collapse the initial lymphatic walls, advancing a preexisting lymphedema or triggering lymphedema in a limb at risk.

A Therapist's Thoughts

Although there have been no double-blind studies published that prove that these strategies are effective in reducing risk of developing lymphedema, the guidelines in Table 13-2 follow the common sense application of the anatomic and physiologic principles of lymphatic function.

Lymphedema specialists report countless numbers of cases in which individuals report lymphedema was triggered from a sunburn; an infection in the limb at risk; a strain or sprain injury in the limb at risk; exposure to excessive heat or overuse while cooking holiday meals; a fungal infection around the nails; repetitive lifting and scrubbing associated with spring cleaning; packing to move from one home to another; shopping, carrying, and wrapping heavy holiday packages; a bee sting on the limb at risk; or exercising without proper warmup or progression and grading of the exercise program.

Caution is advised in anyone with all three major risk factors for lymphedema: ALND, radiation therapy, and obesity. There is only anecdotal evidence that taking blood pressures (BPs) on a limb that is healed after ALND increases the risk of lymphedema. However, the therapist must remember tissue healing (not post-operative) requires a minimum of 6 weeks in the absence of multiple risk factors; indeed any risk is deemed unacceptable.⁷¹

It is likely that these anecdotal cases were in (1) persons not healed, (2) individuals at high risk of

Continued.

Table 13-2 Life-Long Precautions for Clients with Lymphedema or a Limb at Risk for Lymphedema

Risk	Activity
Infection	Maintain clean and dry skin; keep the skin supple by applying oil or bland cream; perfumed or fragranced lotions and creams can be irritating. A mild cleansing lotion, such as Cetaphil or Alpha Keri Oil, is recommended. Moisturizers with a high petroleum content (i.e., first ingredient listed is mineral oil or petrolatum) will damage the rubber/latex fibers of compression garments; check with therapist/garment manufacturer regarding safe products to use under garments. When drying, be gentle but thorough. Make certain to dry in any creases and between the digits. Watch for moist, cracking skin between the toes as a sign of fungal infection that must be treated. Avoid needlesticks, injections, vaccinations, acupuncture, electrolysis, or blood drawing on the involved extremity. If a technician is unsuccessful obtaining blood from the uninvolved arm, use legs or feet for blood drawing (unless these are at risk). Immediate treatment with cleansing, antibiotic ointment, and/or bandaging for all wounds no matter how minor (e.g., insect bites, paper cuts, hangnail, blister, burn); check often for signs of infection. Protect hands and feet at all times (e.g., socks and supportive footwear, rubber gloves for cleaning, long oven mitts, garden gloves for any outdoor work, thimble for sewing). Avoid harsh chemicals and abrasive compounds. Use extreme caution when cutting fingernails, toenails, or cuticles; creams are sometimes recommended for removing cuticles, but these are still chemicals and should not be used; use vegetable oil and gently push back cuticles with the pad of your finger, do NOT use a stick or nail file. Use electric razor to remove unwanted hair. A razor blade can cut the skin, and infection could develop. If possible, avoid blood pressure measurements on the involved extremity. Avoid constricting jewelry and clothing, especially tight underwear, underwire brassieres, socks, or stockings; avoid elastic around neck, upper arm, wrists, fingers, ankles, and toes. Avoid lifting heavy weights or carrying heavy objects with the involved extremity; no heavy handbags with over-the-shoulder straps; be extremely cautious when lifting children, as they can make sudden and unexpected movements. Avoid repetitive limb movements against resistance (e.g., pushing, pulling, rubbing, scraping, or scrubbing) that could cause sudden, rapid blood flow through muscle and tissue. Maintain an ideal body weight with proper nutrition and low-salt, low-caffeine diet; avoid smoking, using recreational or illicit drugs, and drinking alcoholic beverages. Changes in pressure gradient during air travel require use of compression garments and low-salt diet. Avoid prolonged automobile travel; if travel is necessary; take frequent breaks and exercise other precautions (e.g., elevation, hydration, loose clothing, proper nutrition, compressive garment or bandages when recommended). Avoid overheating local body parts or rise in core body temperature: use pyrogenic medications, even with low-grade fever; avoid saunas, hot tubs, hot pads, hot packs, or tanning booths; close monitoring is required during extensive exercise or marathon running. Avoid sunburn; keep the limb protected from the sun; avoid tanning booths. Chemicals such as those used in the application of artificial fingernails may cause an edematous response in some people.
Circulatory compromise	Avoid heavy breast prostheses after a mastectomy; too much pressure on the supraclavicular lymph nodes can slow and interrupt the lymphatic pathways. Do not overtire a limb at risk. If it starts to ache, lie down with the limb elevated. If your leg is involved, avoid prolonged sitting. It is better to lie down with the affected leg elevated than to sit with the leg elevated. Prolonged sitting can prevent lymphatic drainage through the gluteal region. As previously mentioned, avoid tight jewelry and clothing on the affected limb, especially if some swelling is present. Underpants, brassieres, jeans, shoes, or any other article of clothing with straps must be loose around the waist, thighs, and crotch. NO redness or indentation should be evident upon removal. Compression stockings/sleeves must not leave a compressive band at the ankle, knee, groin, or waist. It should not chafe at any point. If it does, obtain help from the therapist.
Stress to impaired lymphatic system	

For additional resources, see Box 13-2.

Modified from Boris M, Weindorf S, Lasinski B: Managing lymphedema: risk reduction strategies. In *Lymphedema therapy*, New York, 2002, Woodbury.

inflammation (e.g., comorbidity of autoimmune tissue disease or other inflammatory process affecting the limb), (3) obese persons who may have undergone radiation therapy, and (4) individuals who could have sustained trauma from improper BP measurement leading to inflammation.⁷¹ Although there is no proof that taking BP measurements on the limb at risk will trigger lymphedema, it is logical to consider that applying the BP cuff and inflating it to 200 mm Hg will

compress veins and lymphatics under the area of the cuff.

If those lymphatics were the only vessels that are functional in the limb at risk (since others were damaged or excised during regional lymph node dissection/radiation), then it would make sense to avoid further compromise of their function. If the limb at risk must be used, it is helpful to avoid inflating the cuff to more than the person's average systolic

pressure. This would limit the compression of the local lymphatics as much as possible.

Individuals who are obese are more likely to be hypertensive, requiring inflation of the BP cuff to higher pressure to get the baseline measure. Since obesity and weight gain during treatment are primary risk factors for lymphedema, this subset of the breast cancer population may warrant more caution; again, no data support clinical practice guidelines at this time.⁷¹

Do not apply the BP cuff above an intravenous (IV) line where fluids are infusing or an arteriovenous (AV) shunt on the same side where breast or axillary surgery has been performed, or when the arm or hand has been traumatized or diseased. Until research data support a change, it is recommended that clients who have undergone ALND avoid having BP measurements taken on the affected side.

Although it is recommended that anyone who has had bilateral ALND should have BP measurements taken in the leg, this is not standard clinical practice across the United States.⁶⁸ Leg pressures can be difficult to assess and inaccurate. Some oncology staff advise taking BPs in the arm with the least amount of nodal dissection. For clients who have had a mastectomy without ALND (i.e., prophylactic mastectomy), blood pressure can be obtained in either arm.⁵⁶

Although venipuncture is done with "sterile" technique, the reality is that the degree of "sterility" varies greatly and depends on where and in what type of facility the puncture is done and who is doing it. There is still a risk of introducing bacteria with the needlestick, as well as potential damage to the local veins and lymphatics, depending on the degree of compression under the tourniquet and how many times the person has to be punctured to get a full sample.

Again, it makes sense to err on the side of caution and to avoid using the limb at risk for venipuncture unless there is no other option. For people who have had bilateral axillary dissection this poses a problem. Many laboratories do not have anyone who is competent in venipuncture on the leg or foot. Some physicians feel that the risk of DVT in the leg is too great and will not recommend using the leg or foot to draw blood. It has been suggested to try to minimize tourniquet time or to eliminate the use of the tourniquet during venipuncture to reduce the risk of damaging lymphatics.

There are no absolutes, and these "guidelines" are just that—guidelines for clients to discuss with their physicians. Many of the other "precautions" are common sense recommendations. For example, if you knew that you had sensitive skin, you would avoid exposing that skin to harsh chemicals like those in household cleaning solutions—petroleum, ammonia, and lye-based products. In the same way, if you have never exercised in the past, you would not begin to weight train with 5-lb weights—you would build up from no weight gradually to whatever weight you could tolerate comfortably without causing muscle ache and a feeling of tightness in the limb at risk. Another example is gardening, since garden soil con-

tains rocks, insects, sharp roots, bacteria, fungus, and possibly pesticides. Wearing gloves when one gardens just makes sense to avoid the risk of getting a cut, insect bite, or exposure to some bacteria or fungus. It is important to remember that the skin on the limb at risk needs to be protected from anything that threatens the integrity of that skin. Perhaps changing the "title" of this common sense "list" from a list of "Dos and Don'ts" to "Risk-Reduction Strategies/Guidelines" will be less offensive to those who want to disregard them because there is no "scientific proof" that they are valid.

Currently, there is no cure for lymphedema. Any strategy that might delay the onset of this condition is worth pursuing. Individuals with a limb at risk should be educated about these risk-reduction strategies so that they can incorporate some or all of them into their daily activities if they so choose. It is the clients' right to choose, but they need to have appropriate information to make an informed choice.

Infection

Understanding the risk for infection is critical when evaluating and educating individuals with or at risk for lymphedema. These individuals are extremely prone to local infection from even a minor trauma, abrasion, or insect bite and must be educated in risk reduction and proper skin care to minimize their risk for recurrent infections. Ryan eloquently explains the rationale behind meticulous skin care⁷²: "The epidermis and adipose tissues . . . are likely factories of growth factors and mediators of inflammation . . . cytokines manufactured by the epidermis . . . are perhaps also responsible for recurrent inflammatory episodes . . . application of external emollients that are anti-inflammatory . . . should be looked upon as being pro-active in the management of lymphedema."

Minor irritations, local areas of redness of the skin, and minor dermatitis reactions must be observed and treated aggressively to avoid progression to a major infection. In a therapy department, the treatment environment and all equipment must be meticulously cleaned.

In a therapy setting, careful thought must be given even to everyday procedures. For example, a woman with mild Stage I upper extremity lymphedema secondary to axillary dissection developed cellulitis in her involved extremity after receiving a week of treatment for her lymphedema. Treatment involved a skin care program using moisturizer. During treatment, the jar of moisturizing cream was always open on the counter, and the therapist dipped into the jar with a bare hand, applying the cream to the client's skin, returning to the jar several times with the same bare hand that had rubbed the cream on her arm. Although the skin on the arm was intact, the client was concerned that a possible link existed between her infection and the cream that was used on others, some of whom she noted had open wounds. Although no direct proof of the connection between this clinical practice and the client's infection is available, it is a reminder of the

Continued.

need to improve our infection control on *all* clients, regardless of their "level" of risk. (See the section on Infectious Diseases in Chapter 8 and the Standard Precautions in Appendix A.)

Many people with lymphedema are unaware of the increased risk of infection or are lulled into complacency by health care professionals who tell them "not to worry" because antibiotics are available if an infection develops. Any infection further stresses the already overloaded regional lymphatic system, possibly scarring some of the remaining functioning lymphatic vessels and ultimately contributing to progressive and chronic lymphedema.

Any infection in a lymphedematous limb, even local, must be medically treated immediately without delay. Individuals must be instructed to contact the physician immediately or go to the emergency department, and they must advise the staff of the lymphedema diagnosis and the impending infection requiring antibiotics. Making this pronouncement firmly can save precious time, eliminating the need to request a referral from the infectious diseases department or obtaining cultures while the bacteria are multiplying and increasing in strength.

Orthopedic Lymphedema

Postsurgical lymphedema occurs after total knee or total hip replacement. If the individual is poorly mobile and had some degree of "swelling" in the legs preoperatively (often attributed to arthritis), the increase in edema postoperatively is often considered the normal sequelae for the procedure. Important loss of time in rehabilitation occurs for these people who are in pain and experience decreased range of motion and strength because of the increasing edema. When the edema is properly reduced and maintained, rehabilitation can progress quite well, provided that the therapist remembers the concept of limiting lymph load so as not to exceed the individual lymph transport capacity.

This clinical skill comes with experience and constant monitoring in the early stages of activity to assess which activities increase the person's subjective feeling of "congestion and fullness" in the affected areas. Heat modalities will increase superficial vasodilation and ultrafiltration, increasing edema, and therefore should be avoided. Electrical stimulation, particularly waveforms and intensities that produce sustained tetanic muscle contractions, should be used cautiously. Prolonged sustained tetanic muscle contractions (as opposed to rhythmic, reciprocal muscle contractions) can impair lymph flow in the area of skin overlying the muscle group, causing a retrograde edema distal to that site.

A past history of multiple abdominal or thoracic surgeries, vein stripping or sclerotherapy, and liposuction in the legs should remind the evaluating therapist to carefully assess signs and symptoms of lymphedema. A limb that was perceived as "less than perfect" can become a severely swollen, distorted limb, psychologically devastating the individual whose appearance was of paramount importance.

Evaluation

When evaluating an individual with suspected lymphedema (or the individual with unexplained edema of an extremity or extremities), cardiac, renal, thyroid, and arteriovenous disease must be ruled out medically.

A detailed history must be taken, including past medical history, especially cancer; information about swelling; onset and progression; tests conducted to evaluate and diagnose the condition; chronology of all surgeries; vein stripping; bypass stents; and insertion or removal of ports for administration of chemotherapy, especially biological response modifiers, as these tend to cause high levels of fluid retention and metabolic dysfunction.

It is important to keep in mind that secondary lymphedema can be the result of an orthopedic surgery or trauma that further disrupted marginal lymphatics. Individuals with extensive acute or chronic edema after trauma or surgery should be evaluated for lymphedema. Early intervention and management of this type of lymphedema can significantly minimize the complications of advanced, untreated lymphedema mentioned earlier.

In the case of a known history of cancer, lymphedema that does not respond to proper treatment may be caused by metastases blocking lymphatic flow. In such a case, treatment may result in proper lymphatic drainage, but the results would be temporary and the lymph fluid would begin to build up again. The therapist must remain alert to this possibility.

Clinical evaluation includes a detailed description of skin integrity, using body diagrams, both anterior-posterior (AP) and lateral, to draw unusual body contours. This description also includes the presence of edema or fibrosis on the trunk quadrants, the head and neck, as well as on the limbs; location and condition of scars, fibrotic areas, and open wounds; evidence of healed ulcerations; and the location of papillomas, warts, leaking edema, and/or subcutaneous fibrosis, folliculitis, and palpable nodes in the axillary or inguinal areas.

The presence of toenail fungus, presence or absence of pitting and subcutaneous fibrosis, presence or history of folliculitis, and palpable nodes in the axilla or inguinal areas should be noted.

Signs and symptoms of cording or axillary web syndrome may be present in individuals after axillary dissection. The therapist may palpate a firm cordlike structure extending from the axilla to the forearm or even to the wrist. These cords limit mobility of the shoulder and can significantly impair activities of daily living (ADLs).

Experts debate whether these are venous or lymphatic in origin or a combination of both structures, possibly caused by contracture of these vessels after being resected during axillary dissection.¹⁴ The presence or absence of pain, paresthesias, or other sensory impairments is documented. Using a visual analogue scale of 0 to 10 is the easiest documentation for this assessment.

Photographs are helpful to detail changes in skin color and texture. If a digital camera is not available, high-speed film without flash is preferable to avoid distortion of color and shadows. Accurate circumferential measurements taken at fixed intervals with standardized positioning noted are often more helpful describing the limb segments than volumetric measurements that give a total difference in overall volume of the entire limb. Volumetric measurements are particularly helpful in cases of bilateral extremity edema when no "normal" limb can be used for comparison.

An accurate history of infections in the affected areas, how these were treated, and how they responded to treatment is critical. A chronologic review of the person's previous treatments and/or interventions for lymphedema and the response to treatment is important.

Careful documentation of the individual's functional impairments related to the lymphedema is key to evaluating the outcome of any treatment that is recommended. Many individuals with chronic lymphedema have "learned to live with it" and often do not consider lymphedema as a "limitation." Tactful questioning can uncover the many compensating mechanisms employed to get through the day.

Finally, the results of specific tests used to diagnose the edema should be reviewed. Venograms and lymphangiograms involve cutdowns, and the injection of dyes into the vessels (these have been known to sclerose and damage vessels) is no longer recommended by lymphologists.^{15,40,42,58}

Lymphoscintigrams, which are useful to differentiate between venous edema, lipedema, and lymphedema, have already been discussed. Remember that a combination of these conditions can co-exist. Cases complicated by genetic lymphangiodysplasias need the intervention of an experienced lymphologist.^{15,40,42,58}

Preoperative Evaluation

A preoperative screening evaluation should record baseline measurements of both operative and nonoperative extremities. Circumferential measurements taken with a flexible tape measure are the easiest, most economic measures to take. These measurements do more accurately assess the shape and contour of a limb than a volumetric measure, which is a more precise measure of total volume of a limb.

Taylor et al found that volumes from circumferential measurements had a high validity when compared with volumes from water displacement, but they were slightly larger.⁵⁹ Tissue texture, unusual limb asymmetries or contours, skin color, strength, and functional range of motion are recorded.

Perometry, tonometry, and bioimpedance have been utilized to quantify lymphedema as well. The Perometer, an optoelectric device, calculates limb volume with infrared light that transects the limb every 3 mm. It can measure any part of a limb or limb segment and accurately calculate changes in volume in seconds. It is a valuable but expensive measurement tool. The Tonometer measures tissue compliance, and

the degree of compression provides an assessment of tissue fibrosis.¹⁷

Bioimpedance is another noninvasive technique that measures total body fluid and extracellular fluid in extremities by measuring the resistance of various tissues to the flow of an electrical current. It has been shown to detect very small differences in the extracellular volumes of arms, suggesting that this technique may be able to diagnose lymphedema in its first stage, prior to the onset of visible swelling and discomfort.³¹

There is still no consensus on what amount of limb volume change defines lymphedema. However, lymphedema is not only defined by a change in limb volume. Sensations of limb heaviness, tightness, soreness, fatigue, and pain accompany subtle changes in limb volume that may or may not be readily detectable in the early stages of lymph stasis that occur on the continuum from latent lymphedema (Stage 0) to where obvious pitting edema is present in Stage 1. Further study needs to be done to examine these factors and their relationship to the progression of lymphedema.^{5,6}

Any sensory abnormalities or neurologic impairments are noted. Risk-reduction strategies with emphasis on proper skin hygiene and recognition of the early signs of lymphedema and secondary infection are reviewed with the individual.

A list of resources, including whom to contact should a problem arise (and when available), is provided to the individual. Discussion of individual ADLs and brief task analysis of job and home can point to possible problem areas that may need to be modified to reduce the risk of triggering lymphedema from "overuse" of the postoperative extremity or reduce potential exposure to trauma, chemicals, excessive heat, or repetitive tasks.

Physical Therapy Intervention

Regardless of the training approach to lymphedema, several overall components of the following interventions may be modified, according to each individual client's needs: (1) MLD, (2) short-stretch compression bandaging, (3) exercise, (4) compression garments, (5) education (e.g., basic anatomy, skin and nail care, self-massage, self-bandaging, garment care, infection management), (6) compression pumps, and (7) psychologic and emotional support. These components make up a treatment approach referred to as *comprehensive lymphedema management* that is the same for all the combined manual lymphatic therapies and is carried out in two distinct phases: the initial intensive intervention phase and the optimization phase.

Different countries use different acronyms for this treatment approach; comprehensive lymphedema management is sometimes referred to as *complete decongestive therapy* (CDT); *combined decongestive physiotherapy* (CDP); *complex lymphedema therapy* (CLT); *decongestive lymphatic therapy* (DLT); or *complex physical therapy* (CFT). In the United States, the more common usage is CDP or CDT.

Continued.

INITIAL INTENSIVE INTERVENTION PHASE

During this phase of treatment, daily intervention requiring maximum compliance is often necessary to disperse lymph fluids through the superficial lymphatic vessel network and to prevent congestion of fluid in areas proximal to the compression bandages. Components of treatment include the following:

1. Meticulous skin care and treatment of any infections that may also include debridement of ulcers and wound care.
2. Lymphatic drainage: variations exist in specific stroke and pressure techniques such as Vodder, Leduc, Foldi, Casley-Smith; however, all schools of thought work to decongest the trunk quadrants first before addressing the lymphedematous extremity, decongesting the proximal portions of the limb first and progressively working distally to the end of the limb with the direction of flow always toward the trunk. Special strokes are available for fibrotic areas.
3. The affected limb or limbs are then bandaged with short-stretch compression bandages during the initial treatment phase and fitted with a compression garment at the completion of treatment.
4. Each individual is instructed in specific self-care, self-massage techniques, and exercises that are modified for the individual. The basic principle is to enhance the lymphatic pumping and collateral lymph flow from the involved or impaired areas into adjacent, normally functioning areas and eventually into the trunk with return to the central circulation via the right lymphatic duct and the thoracic duct.^{11,12}

OPTIMIZATION PHASE

During this second phase, the individual home program is finalized, continuing with the components of comprehensive lymphedema management from the initial intervention phase now modified for each person according to the clinical presentation and individual needs. During this phase, customized pressure gradient elastic support garments may replace compression bandaging when the limb is normal or close to normal.

Components of Comprehensive Lymphedema Therapy

Considerable advances were made in the treatment of lymphedema after Kubik's detailed description of the regional anatomy of the lymphatic system published in 1985 (see Fig. 13-7). Foldi and Foldi reported the successful results of their techniques, referred to as CDP, documenting 50% reductions in lymphedema after a 4-week course of daily CDP. Of those individuals, 50% maintained that reduction by adhering to a home program of self-MLD; exercises; and continuous compression on the affected limb using compression garments or bandages.^{38,39}

Casley-Smith and Casley-Smith presented results of another conservative treatment, referred to as *CPT*, reporting reductions of more than 60% in 618 lymphedematous limbs.²⁴

MANUAL LYMPH DRAINAGE

von Winiwarter first introduced the concepts of MLD in 1882. These techniques were improved by Vodder in the 1930s but were originally applied to improve the functioning of normal lymphatics.²³ Moreover, the reductions in edema obtained with MLD in those early years could not be maintained because of a lack of adequate compression bandages and garments. The Vodder techniques were modified by Asdonk and Leduc and later by Foldi and Casley-Smith.²¹

These major contributors have developed training programs to teach their methods; however, no standards are available in the United States for lymphedema training programs. The Lymphology Association of North America (LANA), a nonprofit organization composed of physicians, nurses, physical and occupational therapists, and massage therapists who specialize in lymphedema management, has developed standards for lymphedema therapists in the United States. This will help ensure access to adequate treatment for all individuals living with lymphedema (for more information, visit <http://www.clt-lana.org>).

MLD, a gentle, manual treatment technique consisting of several basic strokes, is designed to improve the activity of intact lymph vessels by providing mild mechanical stretches on the wall of the lymph collectors. Some proponents of MLD advise against the use of the word *massage* (e.g., manual lymphatic massage or lymphatic drainage massage) because the term *massage* means "to knead." MLD does not have kneading elements and is generally applied suprafascially, whereas *massage* is usually applied to subfascial tissues.

COMPRESSION BANDAGING

Short-stretch compression bandages applied to the lymphedematous extremity after lymphatic drainage help maintain the edema reduction achieved through the lymph drainage. Short-stretch bandages have minimal recoil and only stretch 70% of their "unstretched" length. They have a low resting pressure (i.e., when the bandaged limb is at rest, they exert minimal pressure on the skin), avoiding any skin ischemia or breakdown. Conversely, they have a high working pressure. When the muscles in the bandaged limb contract against the short-stretch bandage, the bandage provides a semirigid force, creating an increase in interstitial tissue fluid pressure, an increase in lymph uptake, and increased pumping of the collecting lymphatics. Therefore these bandages are comfortable when the limb is at rest and greatly increase the transport of lymph when the limb is in motion.

Johansson et al examined the effects of low-stretch compression bandaging alone and in combination with MLD and reported an additional 11% reduction in arm lymphedema when MLD was added to compression bandaging.⁴⁰

Long-stretch compression bandages have a low working pressure and a high resting pressure—that is, they are not very effective in increasing the transport of lymph when the bandaged limb is moving and they can become dangerously tight when the limb is at rest,

creating a tourniquet effect on the limb at rest. These are not the bandages of choice for the individual with lymphedema.

Proper bandaging techniques, using sufficient padding materials over bony prominences and to even out unusual limb contours, ensure that a gradient of pressure is achieved. This gradient must be greatest at the most distal point of the involved limb, gradually decreasing as the bandage layers reach the proximal portion of the limb. This gradient is particularly critical in limbs where large, balloonlike areas separated by a deep skinfold or ridge occur at a joint such as the ankle, knee, wrist, or elbow. According to Laplace's law, the pressure applied is inversely proportional to the radius of the limb segment bandaged—that is, the smaller the radius of the limb segment, the greater is the pressure applied by the bandage. For example, when bandaging an upper extremity with significant edema in the dorsum of the hand but a narrow wrist relative to the hand and forearm, the wrist area must be sufficiently padded to increase the radius (of the wrist limb segment) to be larger than the radius of the hand. If this is not done, the bandaging may actually cause an increase in the edema in the dorsum of the hand.²⁵

A proper compression gradient achieved with short-stretch bandages can increase tissue pressure, improve the activity of the lymphangion, and increase the efficiency of the muscle pump in the involved limb. It not only maintains the reduction in the involved limb that was achieved through lymph drainage; it can actually increase that reduction by enhancing the muscle pump during activity.

In addition, the application of varying densities of foam pieces or "chips," encased in adhesive gauze, stockinet, or fabric and applied under the compression bandages over fibrotic areas, can soften the fibrosis, allowing for further reduction of the limb.^{25,58}

Compression bandaging is usually worn 24 hours during the initial intensive phase of treatment, removed only for bathing and lymph drainage, and immediately reapplied. After the initial treatment phase, the individual is able to maintain adequate compression during the day with a compression garment. Getting the individual to understand that they must maintain some form of nighttime compression is the key to success in the optimization phase of the program.

The short-stretch bandages, because of their low resting pressure and "customized" fit, provide the optimal nighttime compression. The drawback to these bandages is that self-bandaging is time consuming and difficult for the less mobile or obese individual or person with a very large, heavy limb.

Several "compression alternatives" are now available for this purpose that use various fabric "sleeves" with foam padding and Velcro closures for easier application. Results of one clinical study reported that individuals who wore their compression garments day and night maintained their reductions during the optimization phase.

No skin problems or tissue breakdown resulted from wearing the garments to bed. It should be noted, however, that most of the involved individuals had

custom-made, low-elastic garments that were not measured and fitted until the involved limbs were fully reduced (plateau in reduction).¹²

EXERCISE GUIDELINES

Exercise activates muscle groups and joints in the affected extremity. Combining a specific exercise program for each individual with the use of sufficient compression facilitates the process of decongestion by using the natural pumping effect of the muscles to increase lymph flow while preventing limb refilling.²⁸

Most clinicians experienced in lymphedema treatment agree on basic guidelines for exercise. Any exercise program for the individual with lymphedema must follow the basic concepts of the combined approach—that is, work the trunk muscles first, followed by the limb girdle muscles, working from proximal to distal on the limb and finishing with trunk exercises and deep abdominal breathing to enhance flow through the thoracic duct.

Exercise should always be performed with a compression garment or compression bandages on the involved limb(s) to enhance the variation in total tissue pressure to facilitate increased lymph flow. Johansson et al reported an increase in limb volume in individuals exercising with a compression sleeve compared with when they exercised without the sleeve.⁵⁰ The small increases in volume were measured immediately after exercise, and limb volume returned to baseline when measured again in 24 hours.⁵⁰ In addition, therapists must remember that lymph load must not exceed lymph transport capacity or the exercise or activity will increase the lymphedema.

Lane suggests that lymph transport capacity can be impaired 27% to 49% in individuals after breast cancer treatment.⁵² The exact pathology and etiology of breast cancer-related lymphedema (BCRLE) is thought to be multifactorial and not as simple as a "stop-cock" effect. The stop-cock effect is like putting a cork in a bottle. Various factors, such as cutting lymph vessels and nodes, have the stop-cock effect of impairing flow of lymph fluid. Likewise, venous impairment/impingement, the action of inflammatory mediators, and tissue changes related to late effects of radiation are other factors that may contribute to the development of BCRLE because of this effect.

Impairment in venous circulation from surgery and/or radiation treatment may contribute significantly to impaired fluid transport in the at-risk or affected limb.⁵² Szuba et al found clinically relevant venous stasis (on evaluation of 35 radiocontrast venograms) in 5 of 7 subjects with edema of the upper extremity and venous occlusion in 2 of 7 subjects with upper extremity edema in a cohort of 365 subjects with lymphedema and suspected presence of mixed lymphatic and venous edema.⁸⁴

Certain activities are considered higher risk for exacerbating lymphedema, such as running, jogging, stair climbing machines, sports involving ballistic type movements of the involved limbs such as tennis and racquetball, and activities with risk of traumatic sprain

Continued.

or strain injuries (e.g., karate, soccer, football, hockey, and downhill skiing). Activities such as brisk walking, cycling, swimming, cross country skiing, and Tai Chi are lower risk activities. Although weight training is not contraindicated, the progression of the program must be carefully monitored to avoid overload of the limbs or trunk, causing lymph congestion and subsequent exacerbation of the lymphedema.

Ahmed et al found no increase in severity of lymphedema and no onset of lymphedema in 45 breast cancer survivors who participated in a program of weight training twice a week for 6 months.¹ These results suggest that participating in a resistive exercise program does not increase the risk for developing lymphedema or worsening lymphedema already present, although the follow-up of only 6 months is a very short time to conclude with certainty that individuals at risk would not develop lymphedema thereafter.

Participants received proper instruction in small groups to ensure that they performed proper warmup, weight-training exercise, cool-down, and stretching exercises. Throughout the course of the study, participants exercised with constant access to fitness trainers when needed. The importance of individualized instruction and proper progression of any exercise program cannot be overemphasized.

Simply stated, the greater the intensity of the exercise, the greater the oxygen demand. With increased oxygen demand comes increased blood flow to the muscles, which provides the oxygen to do the work. Signs of limb "overload" are aching; congested, full feeling; discomfort in the proximal lymph nodal area (axilla or inguinal areas); pain; throbbing; or change in skin color. If any of these signs or symptoms occurs, the activity should be discontinued and the limb should be elevated and a cold compress applied. Deep breathing exercises and some self-lymph drainage may help decongest the trunk and limbs and reduce the discomfort.⁶⁴ The individual must learn to "listen" to his or her body and grade future activity accordingly to avoid overloading the system.

There has been little clinical work done addressing strenuous exercise and lymphedema.⁶¹ Miller reported a 38% decrease in limb lymphedema after a 4- to 6-week period in 40 individuals with upper extremity lymphedema secondary to breast cancer treatment.⁶¹ These individuals followed a program of resistive exercise while wearing compression bandages on the affected limbs.

Turner et al followed 10 women after breast cancer treatment for 3 months after they participated in a moderate intensity exercise program consisting of mild strengthening exercises and cardiovascular exercises.⁶⁸ Participants reported a decrease in fatigue and improved quality of life with no precipitation or exacerbation of lymphedema.⁶⁸ Further studies are needed in this area.

COMPRESSION GARMENTS

Compression garments were never designed to "treat and reduce" lymphedema but rather were meant to

"hold" a limb that had already been reduced. Since lymphedema damages the elastic fibers of the skin, compression of the affected area is necessary to prevent reaccumulation of the lymphatic fluid.

Originally, compression garments were engineered to treat venous edema and were meant to be applied to the edema-free extremity before the individual got out of bed after a night of limb elevation. The same premise should apply to the lymphedematous extremity—that is, the edema must be reduced for the garment to work effectively.

Care must be given to the fit and function of the myriad of fabrics, compression grades, and styles available, with proper instruction given in donning and doffing. In addition, realistic expectations concerning these garments are a must to achieve client success and comfort.^{12,19,36,40,59}

Clients need to understand that blood moves into the affected extremity with each beat of the heart approximately 60 to 70 times/minute, 60 minutes/hour, 24 hours/day. When there is obstruction to lymph flow back to the central circulation at a regional lymph node basin, the only way to assist that flow is to apply external pressure over the skin of the affected extremity on a continuous basis.

Compression garments are a means to achieve this, but they are only one component of a total self-care program. However, they are an essential component. For example, a client with lymphedema in the fingers, hand, and arm will not achieve good control of the lymphedema by wearing a wrist-to-axilla compression sleeve without a glove. In fact, wearing a compression sleeve without a glove in the presence of significant finger and hand edema will actually worsen that edema. Removing the compression sleeve may allow some of the hand swelling to resorb into the forearm and make the hand appear "better" but that is not a solution to the problem—a well-fitting compression glove designed to wear with the compression sleeve is a more effective solution to the problem.

Designing, measuring, and fitting compression garments is as much art as it is science. What works for one client may be inappropriate for another. Experience and honest client/therapist communication lead to the best outcomes. Regular follow-up to evaluate the efficacy of the compression garments is important to determine when modifications in style or compression are needed to optimize client adherence.

Education and Home Program

Education begins on the first day of therapy intervention and is an absolutely essential part of both phases of the program. The clients must understand the pathophysiologic reasons why they are doing what they are doing for each component of therapy and carry this through on discharge into their home program. The success of any combined lymphedema treatment program hinges on compliance with the home maintenance program.

Client education includes instruction in the basic anatomy and physiology of the lymphatic system, the pathophysiology of the individual's particular

lymphedema, individual self-drainage pathways to follow during the exercise program, basic principles of the individual exercise program, the risk of infection and how to reduce that risk, wear and care instruction for compression bandages or garments, and individual skin care regimens.

Hands-on instruction in self-bandaging techniques requires practice and patience but is essential for the individual to master. In the home maintenance phase after initial intensive treatment, skin care and risk reduction and management of infection is the single most important component of the home program. Psychologic support, including support groups, is a critical component of a comprehensive lymphedema management program.

Maintaining reductions of lymphedema has been documented with compliance to a home program of skin care, exercise with self-lymphatic drainage, and compression garment wear. Significant decreases in micro lymphatic hypertension (measured by fluorescence microlymphography and lymph capillary pressure measurement), decreases in extremity lymphedema, and improvements in lymphoscintigraphic findings have been reported after a course of CPT.^{43,48} Individuals with less than 100% compliance with the home program lose a portion of their reductions^{12,34,53} (Figs. 13-18, 13-19, and 13-20).

SKIN CARE

Generally, for most people, an hour a day spent on exercise and garment care is reasonable for this condition. It is reasonable to spend 20 minutes twice daily on exercise and self-massage and another 20 minutes on skin care and washing or caring for compression garments. The better the individual understands the pathophysiology of the lymphedema, the greater the compliance.

Instruction in skin care includes the use of low pH or neutral pH soaps, cleansers, and moisturizers; the proper care of nails on finger and toes (see Table 13-2 and Box 12-14); use of topical antibiotic or antifungal preparations; and instruction in skin hygiene and compression garment/bandage washing for good hygiene.

The normal pH of healthy skin is acidic (less than 7.0) and accounts for the waterproof barrier of the skin surface. Repeated use of alkaline soaps and cleansers on the skin will result in the loss of this waterproof property, drying the skin and causing microscopic cracks in the skin surface, increasing the likelihood of bacterial invasion.

The elements of a personal first aid kit, including oral and topical over-the-counter or prescription antibiotics, adhesive bandages, and alcohol wipes, are discussed. The client is instructed to carry this kit whenever traveling. For older adults, poorly mobile individuals, or the visually impaired person, a caregiver can be instructed in how to inspect the lymphedematous limb or area daily for signs of skin irritation or infection.

No absolute dos and don'ts are available, but people must be cautioned to prevent lymph overload in their



Figure 13-18

A, Before treatment, an 84-year-old woman with severe, elephantitic lymphedema of her right upper extremity for 20 years, secondary to surgery and radiation treatment for breast cancer 30 years ago. Her right hand was essentially nonfunctional. She needed assist in all areas of activities of daily living (ADLs). **B**, After 20 CDT treatments, she has achieved a 77% reduction in the lymphedema in her right upper extremity and has begun to use her right hand functionally again. **C**, 4 years after CDT treatment. She follows through with a home exercise program, skin care, and compression garment wear. She has not had any additional treatments other than the initial 20, and she has improved her reduction to almost 100% in the years after treatment. She is more independent in ADLs and can even don her compression glove and sleeve with minimal assistance. [Courtesy Lymphedema Therapy, Woodbury, NY, 2006.]

work and home activities. Each individual must weigh the risk level of each activity and learn what is safe for him or her. Typically, most time is spent teaching the client self-massage, exercise, and bandaging techniques.

Although consistency in using these techniques is very important, many people suffer exacerbation of the lymphedema from an infection or skin problem, necessitating removal of the compression garment. These incidents can be minimized if the individual knows what to look for and how to proceed when an infection occurs.

Knowing the procedure for an emergency visit, who to contact, and how to advocate for their own care within the medical system should be discussed and reviewed at the time of discharge and at subsequent

Continued.

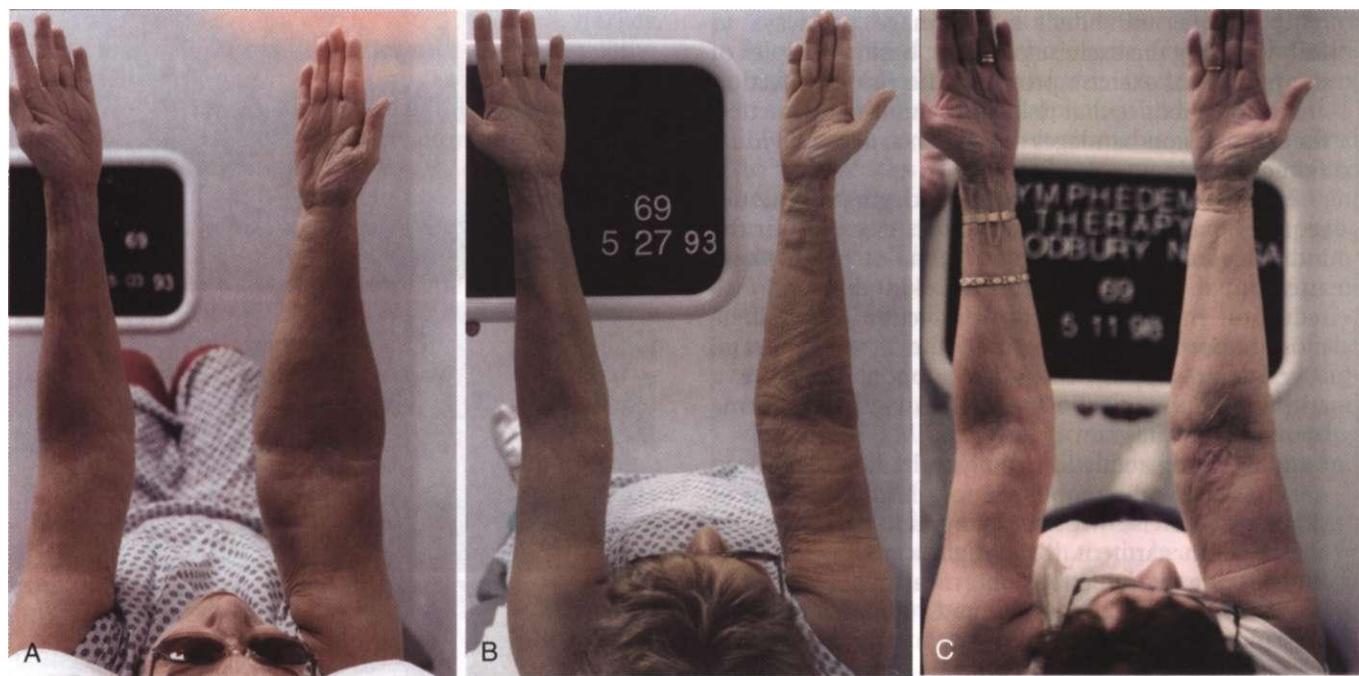


Figure 13-19

A, Before treatment, a 69-year-old woman with Stage II lymphedema of the right upper extremity of 20 years duration, secondary to breast cancer surgery and treatment. For the past few years, she has had recurrent cellulitis infections in the right arm with hospitalization several times per year to receive IV antibiotics. **B**, After 18 CDT treatments, she achieved a 57% reduction in the lymphedema in the right upper extremity. The wrinkling in her forearm and upper arm is from the compression bandaging, which was removed shortly before taking this photograph. These wrinkles are only temporary. Note the significant reduction in lymphedema. **C**, 5 years after CDT treatment. She has improved the reduction in the lymphedema of her right upper extremity to 64%. She has had no additional treatment for her lymphedema, but she follows her home program of self-massage, exercise, skin care, and compression garment wear. She has had only two cellulitis infections in the past 5 years that were treated successfully with only oral antibiotics. Note the reshaping of the forearm and upper arm since previous photos were taken. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

follow-up visits. If an infection develops, a decision must be made whether to remove compression garments or bandages, discontinue any lymphatic drainage, and discontinue exercise until the infection is under control. Circumstances occur when an infection is diagnosed in the very early stages (e.g., minor erythema may be present without pain or fever), and the physician may recommend continuing use of the compression garments if tolerated to avoid any significant increase in limb size.

Every situation is individual and unique and requires consultation with the physician and the therapist before making any changes in the management program. Any sign or symptom of infection always requires immediate medical attention.

GUIDELINES FOR JOB AND LIFESTYLE MODIFICATIONS

The same principles for exercise apply to pacing and modifying work activities and ADLs to avoid overload. Affected individuals do not necessarily have to give up a job just because lymphedema has been diagnosed. Cooperative discussion may be helpful between the therapist, the client, and the client's supervisor to implement simple task modifications ensuring client safety and comfort at work.

Some work requirements may have to be reduced, modified, or eliminated, and the supervisor should be

aware of any special needs the employee may have (e.g., the need to wear compression garments and to protect them with constant changes of vinyl gloves throughout the day in a food service job or the need for a hair stylist to rest with arm or arms elevated in between customers).

Successful management of lymphedema should mean greater "ability" for the individual, not "disability." It may be necessary to modify a workstation to provide more comfort for the individual with leg edema. Interactive education is the key to success. If the employer understands the problem of lymphedema and is assisted in providing a simple solution, everyone wins. For example, an individual with lower extremity lymphedema may need to get up from the workstation every hour and walk around for 5 minutes. A place to elevate the affected leg under the desk may be needed.

Requesting reasonable accommodations is an important goal, but sometimes, certain job tasks cannot be modified. For example, a nurse with significant upper extremity lymphedema may have difficulty getting assistance every time she needs to move and lift a patient or resident. Constant lifting and positioning heavy patients or residents can worsen an upper extremity lymphedema. In such cases, the decision rests with the individual whether a job change is

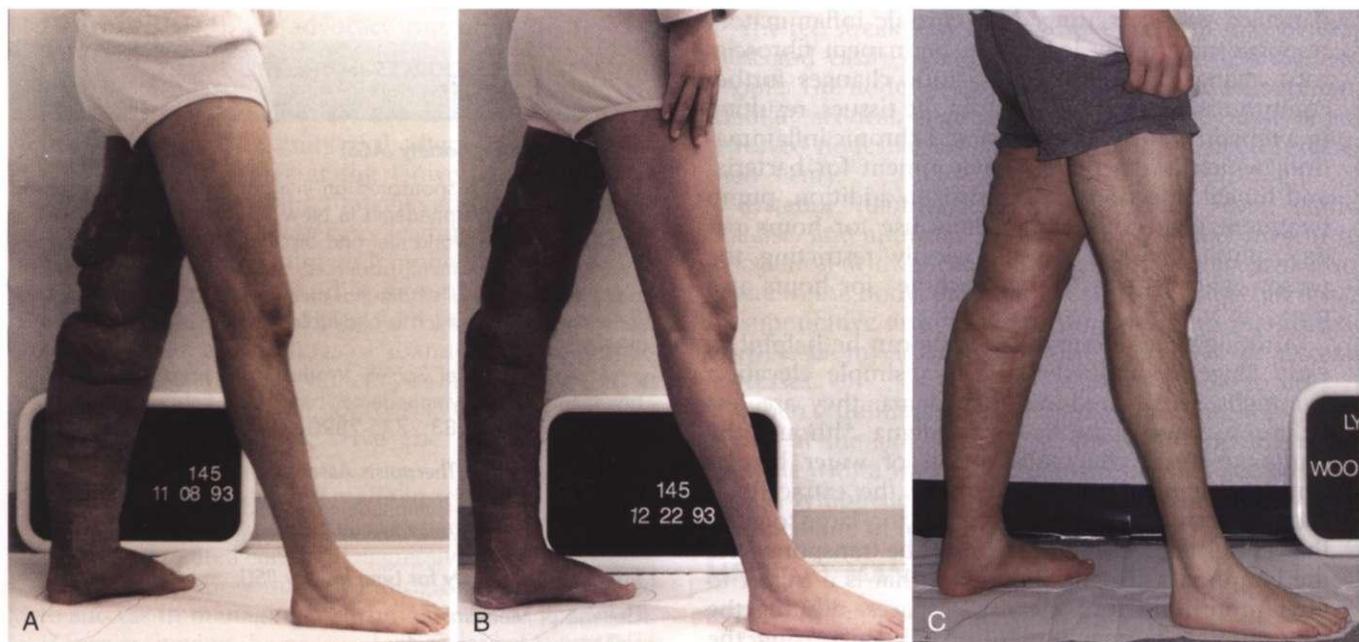


Figure 13-20

A, Before treatment, a 19-year-old male with severe Stage II primary lymphedema of the left lower extremity, progressing to the left buttock and genitals, with chylous reflux to the scrotum, buttock, and thigh. The onset of the edema was at age 8 (see Fig. 13-11). He spent most of his high school years in and out of the hospital. In the 24 months before treatment, he was hospitalized 22 times for cellulitis in the left lower extremity and placed in the intensive care unit (ICU) with septic shock three times. **B**, After one course of CDT of 30 treatments interrupted by a 2-week hospitalization (1 week in ICU) for cellulitis of the left leg and buttock with severe chylous leakage from the scrotum, buttock, and thigh. This individual went into septic shock and needed hyperalimentation to treat the hypoproteinemia (that resulted from the chylous leakage) via a central venous line. Despite the massive increase in swelling and open areas on the posterior left thigh and buttock resulting from the cellulitis, he achieved a 67% reduction in the lymphedema of his left lower extremity with reductions in the abdominal, suprapubic, and genital swelling as well. **C**, 12½ years after CDT. Note that some increase in the girth of the left lower extremity has occurred, particularly in the areas just proximal and distal to the knee, where the tissues are lax from the original debulking surgery. These areas fill in quickly without compression. Some of the girth increase is due to weight gain, now that he no longer has recurrent cellulitis and the chylous reflux is under control. This young man, having spent his high school years in and out of the hospital, was able to complete his college degree and is now a registered nurse working in an emergency department. Since his CDT treatment, he has made his lymphedema management home program a priority in his life and continues to maintain a 60% reduction in the lymphedema in his left lower extremity. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

needed or whether it will be necessary to stay and make the best of things.

Compression Pumps

Historically in the United States, a person with lymphedema was given a prescription for a compression garment and range-of-motion exercises. In some cases, treatment with a pneumatic compression pump was prescribed as the edema progressed. The degree and intensity of this treatment varied greatly because of the lack of verified, long-term scientific studies proving the efficacy of one treatment form over another.

Treatment with pneumatic compression consisted of placing the involved limb into a rubber sleeve that inflated with air from the pump, squeezing the limb, and moving fluid proximally toward the trunk. Pumps available in single or multichamber models can apply pressures from 10 to 100 mm Hg; the walls of the superficial lymphatics may collapse with greater than 60 mm Hg pressure.^{13,20,35,37}

Segers et al found significant discrepancies between target pressures set on the compression device control dial (30, 60, 80, or 100 mm Hg), and the actual pressures measured inside the cuff chamber (54, 98, 121,

or 141 mm Hg) and recommended that the devices be set at much lower target pressures (<30 mm Hg) than those typically applied in clinical practice.⁷⁸

In the presence of soft tissue injury, vigorous massage or the use of compression pumps at pressures higher than 60 mm Hg can cause severe damage to the walls of the initial lymphatic vessels (possibly by tearing the anchoring microfilaments mentioned earlier). This collapse of the initial lymphatic walls impairs lymphatic transport capacity and results in lymphedema and extravasation of lymphedema into an adjacent trunk quadrant.¹³

Atrophy or hypertrophy of the skin can further compromise lymphatic function as a result of the loss of elasticity. A network of collagen and elastin fibers surrounding the lymphatic system helps the skin respond to movement so any variable that can damage the lymph system of the skin (e.g., aging, chronic sun exposure, or prolonged use of systemic steroids) compromises the response of the tissues to movement caused by massage or pneumatic compression.

The resultant injury to the blood vessels and lymphatics causes fluid and protein to leak from the

Continued.

damaged vessels, setting up a chronic inflammatory response potentially leading to permanent fibrosclerotic changes.⁷³ These fibrosclerotic changes further compromise oxygen perfusion in the tissues, resulting in a repetitive cycle of hypoxia and chronic inflammation, which is the perfect environment for bacterial and fungal infections to flourish. In addition, pump treatment protocols require daily use for hours per day, physically and psychologically restricting the person who is "tied to the machine" for hours at a time.

Although the pneumatic pumps can be helpful in early Stage I lymphedema, when simple elevation overnight usually reduces the edema, they are less helpful in Stage II fibrotic lymphedema. Although the pumps increase the reabsorption of water by the venous system, they do not move the extracellular protein because these molecules are too large to enter the venous fenestrae. Proteins must be transported via the lymphatics. This is a situation that is a trigger to filter more fluid into the tissue spaces, diluting the concentrated protein and ultimately increasing the edema. The higher protein concentration remaining in the tissues also causes the chronic inflammatory response discussed earlier, triggering the development of more subcutaneous fibrosis. The vicious cycle of lymphedema repeats itself. The chronic inflammatory response increases the individual's risk of developing secondary infections (cellulitis/lymphangitis).

PSYCHOSOCIAL CONSIDERATIONS

Great emphasis has been given to the myriad of physical symptoms and resulting impairments associated with lymphedema. Little is reported on the psychologic distress these individuals must suffer on a daily basis. People are curious about the change in size and shape of the affected limb. Individuals are faced with tremendous alterations in body image, and many feel embarrassed. Some are scorned by a public perception that they are deformed or distorted. Those with severe leg lymphedema with chronic infections and ulcerations may leak lymphatic fluid from their limbs and experience public humiliation when people turn away from them in fear and ignorance.

Affected individuals become prisoners in their own homes, too embarrassed or afraid to go out in public. Many are judged by others who do not understand "how this could happen" and why it was not "taken care of." Individuals living with lymphedema have experienced tremendous guilt and self-doubt in the past. Many people were told by numerous medical professionals, "There is nothing to be done; just learn to live with it." Even today, physicians and therapists in this country still tell individuals with lymphedema that nothing can be done except to "elevate the limb and wear loose long sleeves or long pants."

Clinicians and researchers are realizing that individuals with lymphedema need tremendous psychologic support to cope with the problems associated with living with such a chronic condition.^{60,66} Today, innovative lymphedema treatment programs offer support groups (Box 13-2). The National Lymphedema

Box 13-2

IMPORTANT RESOURCES IN THE TREATMENT OF LYMPHEDEMA*

American Cancer Society (ACS)

In 1998, the ACS sponsored an international meeting on breast cancer-related lymphedema in New York City. Lymphologists from all over the world met and discussed current diagnosis, treatment, management, resources, professional education, and advocacy. The results from that meeting are published in the following article, which is available from the ACS at (800) 231-5355:

American Cancer Society Workshop on breast cancer treatment-related lymphedema. New York, February 20-22, 1997, *Cancer* 83:2775-2890, 1998.

American Physical Therapists Association (APTA)

Oncology Section—Lymphedema Special Interest Group (SIG). Available at <http://www.oncologypt.org>.

International Society for Lymphology (ISL)

College of Medicine
University Medical Center
1510 North Campbell Avenue
Tucson, AZ 85724
(520) 626-6118
FAX: (520) 626-0822

Available at <http://www.u.arizona.edu/~witte/ISL.htm>. A quarterly journal is available on international research on lymphedema.

Lymphoedema Association of Australia (LAA)

94 Cambridge Terrace
Malvern, SA 5061, Australia
(011) 61 (8) 8271-2198
FAX: (011) 61 (8) 8271-8776

Available at <http://www.lymphoedema.org.au>.

Lymphology Association of North America (LANA)

Available at <http://www.clt-lana.org>

Lymphatic Research Foundation (LRF)

2 Pool Drive
Roslyn, New York 11576
(516) 625-9675
FAX (516) 625-9410

Available at <http://www.lymphaticresearch.org>.

Lymphovenous Canada

Lymphovenous News is published by the Lymphovenous Association of Ontario. Available at <http://www.lymphovenous-canada.com>.

National Lymphedema Network, Inc.

Latham Square
1611 Telegraph Avenue, Suite 1111
Oakland, CA 94612-2138
Hotline: (800) 541-3259
Direct: (510) 208-3200
FAX: (510) 208-3110
(800) 541-3259

Available at <http://www.lymphnet.org>. A quarterly newsletter is available.

*The listing of any particular program or the omission of others does not denote support or preference for one method of lymphedema intervention over another. This list of resources is meant to guide the interested therapist to further information.

Network (NLN), an advocacy organization, hosts a biannual educational conference offering workshops and an opportunity to network with other affected individuals and health care providers who specialize in lymphology (the study of the lymphatic system).

Radina and Armer at the University of Missouri studied women's coping strategies and found that "the potential 'pile up' of stressors leading to vulnerability after breast cancer treatment lymphedema reported by participants included modification of daily household and work-related tasks, living with a constant reminder of the cancer, and feelings of abandonment by medicine." They state that "resiliency . . . is characterized as adjustment, adaptation, or crisis" and suggest that practitioners "need to serve the patient and the family."⁷²

Great strides are being made in recognizing lymphedema as a condition that deserves to be acknowledged and treated early and aggressively. Theoretically, all clinicians know that psychologic support is crucial to success in managing a chronic illness or condition. However, having the practical applications in place to help the individual takes a tremendous commitment in personal time and financial resources. Nevertheless, a successful lymphedema treatment program must offer ongoing support and follow-up care.

Lymphadenitis

Infections elsewhere in the body can lead to lymphadenopathy as described previously. When the lymph node becomes overwhelmed by the infection, the lymph node itself can become infected; this is called *lymphadenitis*. Lymphadenitis can be classified as acute or chronic; acutely inflamed lymph nodes are most common locally in the cervical region in association with infections of the teeth or tonsils or in the axillary or inguinal regions secondary to infection of the extremities.

In acute lymphadenitis, the lymph nodes are enlarged, tender, warm, and reddened. In the case of chronic lymphadenitis, long-standing infection from a variety of sources results in scarred lymph nodes with fibrous connective tissue replacement. The nodes are enlarged and firm to palpation but not warm or tender. The management of lymphadenitis is treatment of the underlying disorder.

Lymphangitis

Lymphangitis, an acute inflammation of the subcutaneous lymphatic channels, usually occurs as a result of hemolytic streptococci or staphylococci (or both) entering the lymphatic channels from an abrasion or local trauma, wound, or infection (usually cellulitis). The involvement of the lymphatics is often first observed as a red streak under the skin (referred to in layperson terms as *blood poisoning*), radiating from the infection site in the direction of the regional lymph nodes.

The red streak may be very obvious, or it may be very faint and easily overlooked, especially in dark-skinned people. The nodes most commonly affected are submandibular, cervical, inguinal, and axillary, in that order. Involved nodes are usually tender and enlarged (greater than 3 cm).

Systemic manifestations may include fever, chills, malaise, and anorexia. Other symptoms may present in association with the underlying infection located elsewhere in the body. Bacteremia from any cause can result in suppurative arthritis (inflammatory with pus formation), osteomyelitis, peritonitis, meningitis, or visceral abscesses.

When cellulitis results in lymphangitis, throbbing pain occurs at the site of bacterial invasion, and the client presents with a warm, edematous extremity (or possible scrotal lymphedema in males and occasionally vulvar lymphedema in females).

MEDICAL MANAGEMENT

INTACT LYMPHATIC SYSTEM

Diagnosis. Lymphangitis may be confused with superficial thrombophlebitis, but the erythema associated with lymphangitis is first seen as a red streak under the skin radiating toward the regional lymph nodes (usually ascending proximally), whereas the erythema associated with thrombosis is usually over the thrombosed vein with local induration and inflammation.

However, suppurative thrombophlebitis may develop if bacteria are introduced during IV therapy, especially when the needle or catheter is left in place for more than 48 hours. The physician will also differentiate cellulitis from soft tissue infections (e.g., gangrene or necrotizing fasciitis) that may require early and aggressive incision and resection of necrotic infected tissue.

Anyone with a history of vascular disease taking anti-coagulant medication should have a Doppler ultrasound to rule out DVT before being treated. Laboratory tests are often not required but may include blood culture (often positive for staphylococcal or streptococcal species) and culture and sensitivity studies on the wound exudate or pus.

Treatment and Prognosis. Prompt parenteral antibiotic therapy is mandatory because bacteremia and systemic toxicity develop rapidly once organisms reach the bloodstream via the thoracic duct. Antibiotic treatment may be accompanied by general measures such as heat, elevation, immobilization of the infected area, and analgesics for pain.

Appropriate wound care may include drainage of the pus from an infected wound when it is clear that an abscess is associated with the site of initial infection. An area of cellulitis should not be excised because the infection may be spread by attempted drainage when pus is not present. Treatment as described should be effective against invading bacteria within a few days.

MEDICAL MANAGEMENT

INFECTIONS WITH IMPAIRED AND AT-RISK LYMPHATIC SYSTEM AND LYMPHEDEMA

Diagnosis. Confusion of cellulitis or lymphangitis with thrombophlebitis in the individual with

lymphedema or at risk for lymphedema is common and has a disastrous impact on the severity of the lymphedema. An episode of cellulitis or lymphangitis often triggers the development of lymphedema in the individual who is at risk but has no clinical signs of edema. Improper, inadequate treatment of these infections can lead to chronic infection or inflammation and progression of the lymphedema.

The individual who has had regional lymph node dissection and/or radiation has an impaired immune response in the areas that drain to that regional nodal area. Consequently, infection can spread rapidly in those regions and any delay in treatment while awaiting blood cultures and vascular tests can cause progression of the infection.

The combination of the impaired nodal area and the inactivity of the macrophages in the lymphedematous region allows the bacteria to multiply rapidly, feeding on the high protein lymphedema fluid. It is not uncommon for a person to develop a high fever with shaking chills (105° F [40.5° C]) within 30 minutes of "feeling ill" or "feeling an ache or pain" in the lymphedematous region. It is not acceptable for these people to "wait and see" and call their physician in a day or two. They must be seen and evaluated by a physician immediately to rule out thrombosis versus cellulitis or lymphangitis and initiate appropriate treatment immediately.

The more insidious onset of local infection (cellulitis) may manifest with an area of redness on the skin that looks like a rash or sunburn. The area may be warm to touch but not initially painful, and the individual may not develop any pain or fever. In fact, cellulitis is often mistaken for an allergic reaction, thought to be a reaction to an insect bite, or a local reaction to a sprain or strain, even when these triggers were not present.

Individuals with advanced Stage 2 and 3 lymphedema may develop recurrent cellulitis that is mistaken for "normal" skin changes associated with chronic lymphedema (Fig. 13-21)

TREATMENT AND PROGNOSIS. Treatment of cellulitis or lymphangitis in the individual with lymphedema or at risk for lymphedema differs from treatment of these conditions in the individual with an intact lymphatic system. In a healthy individual, cellulitis and lymphangitis are relatively rare. Many cases of primary lymphedema are missed in young individuals who present with unexplained recurrent cellulitis in the absence of injury or trauma. Recurring cellulitis does not develop unless some underlying pathology is causing it (usually primary lymphedema).

In the healthy individual, heat is often prescribed as an adjunct to relieve pain in the inflamed area, whereas heat should *never* be applied to individuals with lymphedema or those at risk for developing lymphedema. This contraindication includes those individuals who have developed lymphedema after orthopedic surgeries.

Local heating will increase vasodilation and ultrafiltration of more fluid into the interstitial spaces, further overloading the decompensated lymphatic transport



Figure 13-21

This individual had suffered from pain, increased swelling, and itching of the skin on both legs for months. She had suffered from swollen ankles and feet as a teen and the swelling had worsened as she aged. She had seen a vascular surgeon who performed Doppler studies and ruled out deep vein thrombosis (DVT) but had no diagnosis for her problem. She had seen a dermatologist who diagnosed a contact dermatitis and prescribed topical cortisone cream. Luckily, her podiatrist referred her to a lymphedema specialist who promptly diagnosed primary lymphedema of both legs, complicated by cellulitis. (Courtesy lymphedema Therapy, Woodbury, NY, 2006.)

capacity, exacerbating the existing lymphedema, or possibly triggering lymphedema in the limb at risk, where no clinical lymphedema existed before the onset of the infection. Rest and immobilization of the involved areas are recommended measures. Cold can be applied to relieve pain.

Experienced lymphologists initiate immediate oral antibiotic therapy, usually with high doses of broad-spectrum antibiotics and periodic medical monitoring in the first 48 to 72 hours to observe the area for spread of the infection. It is imperative that the original area of redness be outlined with indelible marker to check on the progress or regression of the infection (Fig. 13-22).

If a poor response to the oral antibiotics is evident, hospitalization for IV antibiotics may be necessary. A local infection can progress to septic shock if not treated effectively. A common cause of recurrent cellulitis or lymphangitis is poor, inadequate treatment of a previous infection. A common complaint is recurrent infection in the same area of the same limb every 2 to 3 weeks. In fact, this is more likely the same infection that was never eradicated the first time. Cases like this often have a common history of administration of too short (3 to 5 days) or inadequate doses of oral antibiotics to treat the cellulitis or lymphangitis associated with lymphedema.

**Figure 13-22**

Individual with primary lymphedema in the lower extremities with cellulitis in the lower leg. Note the black line drawn by the therapist to mark the extent of the infection. This is important to monitor the course of the infection. The person was prescribed an oral antibiotic and advised by the physician that if the redness progressed proximal to the black line, she must go to the emergency room and be assessed for intravenous antibiotics. Note the severity of the swelling and fibrosis of the toes. Examination of the skin between her toes revealed that she had a fungal infection that caused the skin to macerate and crack. Bacteria can then enter the broken skin and cause a secondary bacterial infection. This is a common problem in people with lymphedema of the lower extremities. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

SPECIAL IMPLICATIONS FOR THE THERAPIST 13-3

Lymphangitis

PREFERRED PRACTICE PATTERNS

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

7B: Impaired Integumentary Integrity Associated with Superficial Skin Involvement

6H: Impaired Circulation and Anthropometric Dimensions Associated with Lymphatic System Disorders

Clinicians must remember the pathophysiology of lymphedema to understand the seriousness of these infections. Obviously, not every local infection will progress to septicemia. However, the risk is there, given the low oxygen state in the lymphedematous area, the limited response of the macrophages, and the diminished immune response in the individual with nodal dissection or irradiation, or in the case of primary lymphedema, too few, fibrosed, or poorly developed nodes.

At the first sign of infection, the affected individual must seek medical consultation immediately and discontinue all current lymphedema treatment modalities, including MLD, pumps, bandaging, and garments, until the physician determines it is safe to resume.

If the infection is treated early, some physicians may allow resumption of bandaging or garments as tolerated to avoid the limb ballooning out of control as the infection is resolving. This is determined on a case-by-case basis by the physician who is familiar with the individual, follows the individual's care closely, and provides emergency treatment as needed for that person.

**Figure 13-23**

Stage I lipedema. Note that the feet are free of edema and the ankles and lower legs have pitting edema. Fatty nodules are beginning to appear on the distal thighs. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

Lipedema

Overview and Etiologic Factors

The term *lipedema* was first used by Allen and Hines to describe a symmetrical "swelling" of both legs, extending from the hips to the ankles, caused by deposits of subcutaneous adipose tissue.² The underlying etiologic factors of these fat deposits remain unknown. Although lipedema is not a disorder of the lymphatic system per se, it is often confused with bilateral lower extremity lymphedema, thus the reason for discussing it in this chapter. It occurs almost exclusively in women, may have an associated family history (20% of cases), and is usually accompanied by hormonal disorders as well.^{3,2} If present in a man, it is accompanied by massive hormonal disorder.

Fat in the lower extremities extends to the malleoli, often with flaps of tissue hanging over the foot. The feet are not affected; occasionally, lipedema is found in the arms. Typically, fatty bulges are in the medial proximal thigh and the medial distal thigh, just above the knee. Clinically, the affected individuals complain of pitting edema as the day progresses, which is relieved by prolonged elevation of the leg or legs overnight.^{19,73,74}

Stages of Lipedema

In stage I, the skin is still soft and regular, but nodular changes can be felt on palpation (Fig. 13-23). No color



Figure 13-24

Stage II lipedema. Note that obvious pitting edema on the dorsum of the feet is evident, and the tissues are beginning to hang over the medial and lateral ankles and above the knees. The discoloration at the antero-distal left lower leg is from a resolving cellulitis, secondary to the lymphedema that developed secondary to the lipedema. (Courtesy Lymphedema Therapy, Woodbury, NY, 2006.)

changes occur in the skin, and the subcutaneous tissues have a spongy feel, like a soft rubber doll. In stage II, the subcutaneous tissue becomes more nodular and tough. Large fatty lobules begin to form on the medial distal and proximal thigh and medial and lateral ankles just above the malleoli (Fig. 13-24). Pitting edema is common, increasing as the day progresses. The individual may report hypersensitivity over the anterior tibial area. Skin color changes occur in the lower leg, indicative of secondary lymphedema, which often occurs in later stage lipedema.

Pathophysiology of Lipedema⁸²

Many histologic and physiologic changes occur in lipedema. A decrease in the elasticity of the epidermis and subcutis also occurs. The basement membrane of vessels is thickened, and disturbances in vasomotion take place. The venoarterial reflex (VAR) is disturbed, causing decreased vascular resistance, increased skin perfusion, and increased capillary filtration. Under normal circumstances, the VAR is an important mechanism for the regulation of microcirculation and interstitial fluid exchange. It is measured as a ratio between skin perfusion in the

supine versus the standing position using a laser Doppler flowmeter.

Increased venous or blood capillary pressure causes increased ultrafiltration. These changes, combined with the decreased efficiency of the calf muscle pump, result in both the dependent pitting edema seen in Stage I and the secondary lymphedema that often complicates lipedema in its later stages.⁴²

Histologic changes seen in lipedema include a thinning of the epidermal layer, thickening of the subcutaneous tissue layer, fibrosis of arterioles, tearing of elastic fibers, dilated venules and capillaries, and hypertrophy and hyperplasia of fat cells. Clinical studies show enlargement of the prelymphatic channels⁸¹ and defects in capillary perfusion.⁸³ Some authors have reported no alteration in lymphatic transport,¹⁴ whereas others⁹ have reported decreased lymph outflow in those individuals with lipedema. Foldi and Foldi reported an increase in fat cell growth during lymphostasis.⁴⁰

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of lipedema is difficult if the clinician is unfamiliar with this condition. Often, these people are told that they are "fat" and should just lose weight to resolve the problem. For reasons still unknown, the fatty tissue accompanying this condition cannot be significantly decreased by diet. It is not uncommon for a diagnosis of primary lymphedema to be made. This results in frustration for the person who then seeks out lymphedema therapy with poor results.

Several significant clinical differences exist between lipedema and bilateral primary lymphedema. The feet are not involved in lipedema; although they are edematous with a positive Stemmer's sign in lymphedema, Stemmer's sign is negative in lipedema (see Fig. 13-17). The "swelling" in lipedema is symmetric, whereas in primary lymphedema, usually one limb is more involved than the other. The subcutaneous tissues feel rubbery in lipedema. In advanced Stage II lymphedema, significant subcutaneous fibrosis occurs, which feels firmer than lipedema.

Although incidences of cellulitis in stage II lipedema, usually with a component of lymphedema as well, have been reported, the frequency of cellulitis in stage II lymphedema is much higher. The time of onset of the "swelling" in lipedema is usually around puberty, and 90% of these cases have accompanying diagnoses of hormonal disturbance (thyroid, pituitary, or ovarian). This is usually not the case with primary lymphedema.

A lymphoscintigram may be helpful to differentiate between lymphedema and lipedema; however, results can be conflicting, as lymphedema often occurs to some degree in the later stages of lipedema, probably a result of impairment of lymph flow caused by the pressure of fatty tissue.

In fact, clinical cases of bilateral lower extremity lymphedema in the morbidly obese individual are seen; the onset of the lymphedema occurs after body weight exceeds 350 to 400 lbs. It is plausible to suspect that the pressure of a large apron of abdominal fat can effectively block lymph flow through the inguinal area, causing the lymphedema, but the difference between these cases and lipedema is that obesity does not cause lipedema.

Lipedema is caused by a hormonal imbalance resulting in excessive deposition of adipose tissue, most often in the lower extremities (see Figs. 13-23 and 13-24), although it can occur in the upper extremities, too.

TREATMENT AND PROGNOSIS. No effective medical treatment for lipedema is available, and the prognosis is guarded; however, significant functional improvements are possible with good program compliance and therapy intervention. Medical management involves treating the hormonal disturbance as effectively as possible and providing nutritional guidance to avoid additional weight gain. Many of these individuals have endured years of ridicule because of their physical appearance and become recluses in their homes, further limiting their activity level.

As lipedema progresses and the hypersensitivity increases, they feel less inclined to walk or exercise because of the pain. They inevitably gain more weight as a result of the inactivity and depression, often finding food their only comfort.

SPECIAL IMPLICATIONS FOR THE THERAPIST 13-4

Lipedema

PREFERRED PRACTICE PATTERNS

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

7B: Impaired Integumentary Integrity Associated with Superficial Skin Involvement

6H is not selected because although impaired anthropometric measurements are evident, these are not caused by lymphatic system disorder.

The primary goal of therapy intervention in the person with lipedema is symptomatic relief and realistic improvement of trunk and lower extremity function. Application of the combined lymphedema treatments has shown some success in relieving the pain and hypersensitivity in the lower legs and improving general mobility. Usually, a lower level of compression is needed to support a lymphedematous limb, compared with a lymphedematous limb of the same size and girth. This guideline applies to the compression garments, too.

These individuals often require more padding under the compression bandages, particularly in the anterior tibial area. They do not tolerate the heavier, denser compression fabrics and usually require a lower grade compression garment than someone with uncomplicated lymphedema. The therapist must remember, however, that later stage lipedema is often accompanied by lymphedema, too, and the treatment and management must take that factor into consideration when recommending exercise and garments.

The main goals of intervention are to decrease pain and hypersensitivity, decrease the lymphedematous component of the disease, and assist the individual in maintaining and/or reducing adipose tissue through exercise and nutritional guidance. The compression garments can help decrease the adipose tissue with exercise and weight loss. The most difficult task is fitting the compression garments. They must be custom-made because of the large size of the individual and are often uncomfortable at the waist, particularly when sitting.

Making the radical change in daily activity level is most challenging for these individuals. Providing continued support and encouragement is important. Networking is helpful and is facilitated by offering a support group, even when held on an irregular, informal basis. An hour-long educational meeting, even if only offered three or four times per year, can provide a neutral meeting place for people to begin networking.

Nothing can compare with the encouragement and hope that an individual with lipedema or lymphedema can derive from seeing and talking with someone else living with the same problem and hearing how others cope on a day-to-day basis. Therapists can learn some of the best guidance on exercise and coping with garments in a group like this.

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 95 cited references and other general references for this chapter.

CHAPTER 14

The Hematologic System

CELESTE PETERSON • CATHERINE C. GOODMAN

Hematology is the branch of science that studies the form and structure of blood and blood-forming tissues. Two major components of blood are examined: plasma and formed elements (erythrocytes, or red blood cells [RBCs]; leukocytes, or white blood cells [WBCs]; and platelets, or thrombocytes).

Delivery of these formed elements throughout the body tissues is necessary for cellular metabolism, defense against injury and invading microorganisms, and acid-base balance. The formation and development of blood cells, which usually take place in the red bone marrow, are controlled by hormones (specifically erythropoietin) and feedback mechanisms that maintain an ideal number of cells.

The hematologic system is integrated with the lymphatic and immune systems; for a complete understanding of these systems see Chapters 7 and 13. The lymph nodes are part of the lymphatic system but also part of the hematopoietic (blood-forming) system and the lymphoid system, which consists of organs and tissues of the immune system (see Fig. 7-8).

Lymph fluid passes through these nodes, or valves, which are located in the lymph channels at 1- to 2-cm intervals. As the fluid passes through the nodes, it is purified of harmful bacteria and viruses. Networks of the lymphatic system are situated in several areas of the body and may be considered primary (thymus and bone marrow) or secondary (spleen, lymph nodes, tonsils, and Peyer's patches of the small intestine).

All the lymphoid organs link the hematologic and immune systems in that they are sites of residence, proliferation, differentiation, or function of lymphocytes and mononuclear phagocytes (mononuclear phagocyte system: macrophage and monocyte cells capable of ingesting microorganisms and other antigens).

Lymphocytes are any of the nonphagocytic leukocytes (WBCs) found in the blood, lymph, and lymphoid tissues that make up the body's immunologically competent cells. They are divided into two classes: B and T lymphocytes (see the section on leukocytosis in this chapter and Chapter 7). For example, in the hematologic system, the lymphocytes of the spleen produce approximately one third of the antibody available to the immune system.

SIGNS AND SYMPTOMS OF HEMATOLOGIC DISORDERS

Disruption of the hematologic system results in circulatory disorders as well as signs and symptoms noted in the hematologic tissues themselves. The circulatory disorders can be characterized by edema and congestion, infarction, thrombosis and embolism, lymphedema, bleeding and bruising, and hypotension and shock (Box 14-1).

Edema is the accumulation of excessive fluid within the interstitial tissues or within body cavities. *Congestion* is the accumulation of excessive blood within the blood vessels of an organ or tissue. The forms of lymphedema include cerebral edema, inflammatory edema, peripheral dependent edema, and pulmonary edema. Congestion may be localized, as with a venous thrombosis, or generalized, as with heart failure (e.g., congestive heart failure [CHF]), which results in congestion in the lungs, lower extremities, and abdominal viscera.

Infarction is a localized region of necrosis caused by reduction of arterial perfusion below a level required for cell viability. Such a situation occurs as a result of arterial obstruction due to atherosclerosis, arterial thrombosis, or embolism, when oxygen supply fails to meet the oxygen requirements of organs with end arteries, such as the gastrointestinal (GI) tract, the heart, and, less often, the kidneys and spleen. Cerebral cortical neurons (cerebral infarction) and myocardial cells (myocardial infarction) are most vulnerable to ischemia, although protective collateral blood flow develops in the heart through anastomoses.

A *thrombus* is a solid mass of clotted blood within an intact blood vessel or chamber of the heart. An *embolus* is a mass of solid, liquid, or gas that moves within a blood vessel to lodge at a site distant from its place of origin (see Fig. 12-28). Most emboli are thromboemboli. Thrombosis (development of a thrombus or clot) results from pathologic activation of the hemostatic mechanisms involving platelets, coagulation factors, and blood vessel walls. Endothelial injury, alteration in blood flow (stasis and turbulence), and hypercoagulability of the blood (e.g., protein abnormalities either primary or associated with cancers) promote thrombosis and thromboembolism.

Box 14-1**MOST COMMON SIGNS AND SYMPTOMS OF HEMATOLOGIC DISORDERS**

- Edema
 - Lymphedema
 - Cerebral edema
 - Inflammatory edema
 - Peripheral dependent edema
 - Pulmonary edema
- Lymphadenopathy
- Congestion
- Infarction (brain, heart, GI tract, kidney, spleen)
- Thrombosis
- Splenomegaly
- Embolism
- Bleeding and bruising
- Shock
 - Rapid, weak pulse (late phase)
 - Hypotension (systolic blood pressure less than 90 mm Hg)
 - Cool, moist skin (late phase)
 - Pallor
 - Weak or absent peripheral pulses

Lymphedema, or chronic swelling of an area from accumulation of interstitial fluid (edema), occurs in hematolymphatic disorders secondary to obstruction of lymphatic vessels or lymph nodes. Obstruction may be of an inflammatory or mechanical nature from trauma, regional lymph node resection or irradiation, or extensive involvement of regional nodes by malignant disease.

Women who have been treated surgically for breast cancer with lymph node dissection, mastectomy, and/or radiation therapy are at double the risk of developing lymphedema of the arm and/or chest wall (see Chapter 13). When the obstruction that slows the lymph fluid exceeds the pumping capacity of the system, the fluid accumulates in the tissues in the extremity, causing edema in one or more limbs. This accumulation of fluid may become a source for bacterial growth, leading to infection, fibrosis, and possible loss of functional limb use.

Bleeding and bruising can occur from trauma of various types and are normal consequences of injury. However, when bleeding and bruising are elicited with minor trauma (e.g., brushing teeth) or bleeding continues longer than normal, there is more concern for a disorder of the blood. These symptoms are often a result of platelet abnormalities (function or quantity) such as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or von Willebrand's disease.

Purpura is a hemorrhagic condition that occurs when not enough normal platelets are available to plug damaged vessels or prevent leakage from even minor injury to normal capillaries. Purpura is characterized by movement of blood into the surrounding tissue (extravasation), under the skin, and through the mucous membranes, producing spontaneous ecchymoses (bruises) and petechiae (small, red patches) on the skin. When accompanied by a decrease in the circulating platelets, it

is called *thrombocytopenic purpura*. In the acute form, bleeding can occur from any of the body orifices such as hematuria, nosebleed, vaginal bleeding, and bleeding gums.

Shock occurs when the circulatory system (heart as well as arteries) is unable to maintain adequate pressure in order to perfuse organs. Common clinical signs include tachycardia, tachypnea, cool extremities, decreased pulses, decreased urine output, and an altered mental status. Hypotension is typically present but may be initially absent. The end result is hypoxia to end-organ tissues, particularly the kidneys, brain, and heart.

Diagnosis as to the cause of shock should include an evaluation of the heart and the peripheral arteries (systemic vascular resistance). Myocardial infarction and heart failure are problems that make it difficult for the heart to pump an adequate amount of blood to the body. Decreased blood volume (hypovolemia) from hemorrhaging or severe volume depletion (e.g., nausea, vomiting, and diarrhea) also reduces the body's ability to perfuse tissue.

Disorders that cause a decrease in the arterial pressure include sepsis (infection from any source), liver failure, severe pancreatitis, anaphylaxis, and thyrotoxicosis. The three most common classes of shock therefore are cardiogenic (heart related), hypovolemic, and causes related to reduced systemic vascular resistance, although many overlap (Table 14-1).

Lymphadenopathy is the abnormal enlargement of a lymph node(s). Lymph nodes filter lymph as it returns to the heart. Infectious organisms (e.g., Epstein-Barr virus [EBV] and tuberculosis) and autoimmune disorders (e.g., rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]) can cause an inflammatory expansion and enlargement of lymph nodes. Malignant diseases, such as lymphoma, chronic lymphocytic leukemia, and Hodgkin's lymphoma, can also cause enlarged lymph nodes.

Lymph nodes are typically "rubbery" in feel, unattached to surrounding tissue (mobile), and small (usually less than 1 cm). Inflammatory nodes may be tender to the touch, warm, and enlarged but usually remain mobile and soft. While malignant nodes are often not tender or mobile, they are firm and enlarged. Most cases of lymphadenopathy are not malignancy related, although all instances of abnormal adenopathy should be investigated.

Enlargement of the spleen, or *splenomegaly*, is present in many hematologic diseases. The spleen is normally involved in removing old or deformed erythrocytes, producing antibodies, and removing antibody-laden bacteria or cells. When the spleen exceeds normal function in one of these areas, it becomes enlarged. For example, if a client has hereditary spherocytosis and forms abnormally shaped erythrocytes, the spleen attempts to remove all these cells, thereby increasing in size to accomplish this task.

Splenomegaly is often noted in people with infectious mononucleosis or malignancies such as Hodgkin's lymphoma (where the spleen is infiltrated by disease). If the bone marrow is unable to produce cells (because of an infiltrative process), the spleen often assumes that role and becomes enlarged (extramedullary hematopoiesis).

Table 14-1 Etiologic Factors of Shock

Category of Shock	Causes
Hypovolemic	Hemorrhage (loss of blood, shock) Vomiting Diarrhea Dehydration secondary to decreased fluid intake, diabetes mellitus (diuresis during diabetic ketoacidosis or severe hyperglycemia), diabetes insipidus, inadequate rehydration of long-distance runner Addison's disease Burns
Cardiogenic	Arrhythmias Acute valvular dysfunction Acute myocardial infarction Severe CHF Cardiomyopathy Obstructive valvular disease (aortic or mitral stenosis) Cardiac tumor (atrial myxoma)
Reduced systemic vascular resistance	Bacteremia; overwhelming infections Spinal cord injury Pain Trauma Vasodilator drugs Burns Thyrototoxicosis Pancreatitis Anaphylaxis Liver failure

SPECIAL IMPLICATIONS FOR THE THERAPIST

14-1

Hematologic Disorders

Hematologic conditions alter the oxygen-carrying capacity of the blood and the constituents, structure, consistency, and flow of the blood. These changes can contribute to hypocoagulopathy or hypercoagulopathy, increased work of the heart and breathing, impaired tissue perfusion, and increased risk of thrombus.

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 risk.⁴⁴ Precautions and interventions for the client with lymphedema are discussed in Chapter 13 (see Table 13-2).

Platelet disorders require special consideration by the therapist during exercise. Decreased platelets are associated with the risk of life-threatening hemorrhage; physical therapy intervention must be tailored to the individual's platelet levels. For example, platelet levels between 40,000 and 60,000 μl face an increased risk of postsurgical or traumatic bleed. Low-load resistance exercise is permitted with 1- to 2-pound weights. Safe exercise includes walking, stationary bicycling

with light resistance, and minimal activities of daily living.

For clients with platelet levels in the 20,000 to 40,000 range, low-intensity exercise with no weights or resistance up to 2 pounds is permitted but with no resistance during stationary biking. Activity and exercise restriction is even more stringent when platelet levels are below 20,000. Below 10,000, spontaneous central nervous system (CNS), GI, and/or respiratory tract bleeding may occur.²⁰⁵ In all cases clients are monitored carefully for any signs of bleeding. Guidelines vary from one geographic region to another and even from center to center within a single geographic location.

Splenomegaly

Because splenomegaly is often associated with conditions characterized by rapid destruction of blood cells, it is important to follow the usual precautions for anyone with poor clotting abilities (e.g., see Special Implications for the Therapist: The Anemias in this chapter).

The client must be taught proper breathing techniques in conjunction with ways to avoid activities or positions that could traumatize the abdominal region or increase intracranial, intrathoracic, or intraabdominal pressure.

The person with a small or absent spleen is more susceptible to streptococcal infection, which calls for prevention techniques such as good handwashing (see Boxes 8-4 and 8-5 and Appendix A).

Exercise and Sports

Exercise training can induce blood volume expansion immediately (plasma volume) and over a period (erythrocyte volume) and is associated with healing, improved quality of life, and improved exercise capabilities in cases of anemia from hemorrhage, trauma, renal disease, and chronic diseases. The reestablishment of erythropoiesis through exercise and effects of exercise on blood volume in other groups remain unknown but are a potential area for further investigation and consideration in the clinical setting.^{62,165}

Improvements in athletic performance with exogenous erythropoietin (referred to as "blood doping") have been documented as improvements in running time and maximal oxygen uptake. However, these effects are not without risk for increased blood viscosity and thrombosis, with potentially fatal results. Until a definitive test is developed for detection of exogenous erythropoietin, the therapist must remain aware of this potential problem.^{172,173}

Monitoring Vital Signs

Clients in whom shock develops may exhibit orthostatic changes in vital signs. A drop in systolic blood pressure of 10 to 20 mm Hg or more, associated with an increase in pulse rate of more than 15 beats/min, may indicate a depleted intravascular volume.

The therapist is unlikely to see a client with acute hypovolemia; hypovolemia is more likely the result of dehydration, as in the case of the long-distance runner

or the client with severe diarrhea or slow GI tract bleeding. The aging population is especially vulnerable to development of unknown slow intestinal bleeding, especially with the use of aspirin or nonsteroidal antiinflammatory drugs (NSAIDs).

Clients with peripheral neuropathies or clients taking medications such as certain antihypertensive drugs may be normovolemic and experience an orthostatic fall in blood pressure but without associated increase in pulse rate. If any doubt exists, the client should be placed in the supine position with legs elevated to maximize cerebral blood flow. The Trendelenburg position, in which the head is lower than the rest of the body, is no longer used because of the increased difficulty of breathing in this position.

AGING AND THE HEMATOPOIETIC SYSTEM

Although blood composition changes little with age, the percentage of the marrow space occupied by hematopoietic (blood-forming) tissue declines progressively. The percentage of bone marrow fat is equal to the person's age, reaching a plateau at around age 50 years.

Other changes include decreased total serum iron, total iron-binding capacity, and intestinal iron absorption but with increased total body and bone marrow iron; increased fragility of plasma membranes; a rise in fibrinogen and increased platelet adhesiveness; red cell rigidity; and early activation of the coagulation system. Platelet morphology (form and structure) does not appear to change with age, but platelet count and function have been found to vary from normal to increased or decreased.

The cumulative effect of these changes appears in the form of disturbed blood flow in older subjects, leading to the development or aggravation of various circulatory disorders, especially hypertension, stroke, and diabetes. In addition, correlations found between hematologic changes and changes in behavioral patterns and some cognitive functions suggest that hematologic changes contribute to other changes associated with aging as well.⁵

Age-related changes in the peripheral blood include slightly decreased hemoglobin and hematocrit, although levels remain within the normal adult range. Low hemoglobin levels noted in aging adults can be caused by iron deficiency (usually via blood loss such as ulcer, telangiectasia, colon polyps, or cancer) or can be associated with a long-standing condition such as rheumatologic conditions often seen in a therapy practice (referred to as *anemia of chronic disease*). Vitamin B12, which is required to produce blood cells, and the subsequent development of anemia (resulting from a B12 deficiency) with its hematologic, neurologic, and GI manifestations, are discussed later in this chapter.

Aging is also associated with a decreased number of lymph nodes and diminished size of remaining nodes, decreased function of lymphocytes, and decline in cellular

immunity owing to altered T-cell function (see the section on Effects of Aging on the Immune System in Chapter 7). The effect of aging on quantity, form, and structure of lymphocytes is not well documented.

BLOOD TRANSFUSIONS

Advances in treating hematologic/immunologic disorders through blood transfusions and bone marrow transplantation have provided new success in long-term treatment and a cure for some previously fatal disorders (see Chapter 21). Modern blood banking and transfusion medicine have developed techniques to administer only the blood component needed by the client, such as packed RBCs for anemia or cryoprecipitate for bleeding disorders.

Clients in a therapy setting who have undergone numerous surgical procedures (e.g., traumatic injuries) or elective orthopedic or cardiac procedures may also receive autologous blood transfusions (i.e., reinfusion of a person's own blood) when significant blood loss may be a complication and a transfusion may be anticipated.

The development of recombinant human erythropoietin (rHuEpo, EPO, or Epogen), with its ability to stimulate erythropoiesis and elevate RBCs, has reduced the need for blood transfusion in a variety of clinical situations (e.g., chronic renal disease, hematologic malignancies, cancer-related anemia, and surgical procedures, especially joint arthroplasty and cardiac procedures).

Reaction to Blood and Blood Products

Febrile Nonhemolytic Reaction

Because blood products are most often donated from another person, reactions may occur. The most common transfusion-related reaction is a febrile, nonhemolytic reaction (occurring in 0.5% to 1% of erythrocyte transfusions and 30% of platelet transfusions). The condition is characterized by an increase in temperature by more than 1° F during or soon after the transfusion. These reactions are a result of either donor leukocyte cytokines or alloantibodies of the recipient directed against the leukocytes of the donor.

Treatment includes stopping the transfusion, checking the blood for a direct hemolytic process (in the laboratory), and administering antipyretics or corticosteroids. Symptoms are usually transient, and the removal of donor leukocytes from the blood (leukocyte reduction) can reduce the risk of another similar reaction (Box 14-2).

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury occurs in as many as 1 in every 2000 transfusions.¹⁰⁸ This reaction may present with mild shortness of breath or appear clinically similar to adult respiratory distress syndrome. With appropriate respiratory intervention, most people recover without permanent pulmonary damage.¹⁵⁴ Other complications may include transmission of disease (human immunodeficiency virus [HIV], hepatitis, cytomegalovirus), iron overload, air embolism, hypotension in clients

Box 14-2**SIGNS AND SYMPTOMS OF REACTIONS TO BLOOD AND BLOOD PRODUCTS****Febrile, Nonhemolytic Transfusion Reaction**

- Fever, chills
- Headache
- Nausea, vomiting
- Hypertension
- Tachycardia

Transfusion-Related Acute Lung Injury

- Pulmonary edema
- Acute respiratory distress
- Severe hypoxia

Acute Hemolytic Transfusion Reaction

- Fever, chills
- Nausea, vomiting
- Flank and abdominal pain
- Headache
- Dyspnea
- Hypotension
- Tachycardia
- Red urine

Delayed Hemolytic Transfusion Reaction

- Unexplained drop in Hb—anemia
- Increased bilirubin level—jaundice
- Increased lactate dehydrogenase (LDH) level

Allergic Reactions

- Hives, rash
- Wheezing
- Mucosal edema

Anaphylaxis

- Abrupt hypotension
- Edema of the larynx
- Difficulty breathing
- Nausea
- Abdominal pain
- Diarrhea
- Shock
- Respiratory arrest

Septic Reactions

- Fever, chills
- Hypotension
- Headache
- Back, chest, abdominal pain
- Shortness of breath

Circulatory Overload

- Red face
- Shortness of breath
- Tachycardia
- Orthopnea
- Hypertension
- Headache
- Seizures

taking angiotensin-converting enzyme inhibitors,¹¹⁵ and circulatory overload when blood is administered rapidly in large amounts.

Acute Hemolytic Transfusion Reaction

Less common (only 1 in every 25,000 transfusions) but more severe is the acute hemolytic transfusion reaction. This is due to ABO incompatibility: typically a mistake is made by giving the wrong blood to a person or blood is mislabeled. Symptoms begin soon after the transfusion is begun (see Box 14-2). Erythrocytes are destroyed intravascularly with resultant red plasma and red urine.

The mortality rate is high, ranging from 17% to 60%. The transfusion is immediately terminated and the client given cardiovascular support. Renal failure, disseminated intravascular coagulation, and severe hypotension may occur.

Delayed Hemolytic Transfusion

Delayed hemolytic transfusion reactions occur when the donated erythrocytes are quickly removed from the circulatory system because of an alloantibody. There are often asymptomatic reactions that are noted only because there was not a rise in the hemoglobin following the transfusion.

Allergic Reaction

If the client reacts to the donated plasma an allergic reaction may occur, with associated hives, rash, mucosal edema, wheezing, and other respiratory symptoms. These types of reactions are more typical with fresh frozen plasma and platelet transfusions and are seen in about 1% to 3% of all transfusions. Antihistamines and/or corticosteroids aid in treating the symptoms, and pre-medication prior to the next transfusion may help reduce or prevent subsequent reactions.

Anaphylaxis

True anaphylaxis is rare (approximately 1 in 20,000 to 50,000 transfusions) and may occur with or without allergic reactions. Symptoms include acute onset of hypotension and edema of the larynx with associated difficulty breathing. Nausea, abdominal pain, and diarrhea may accompany the reaction. This reaction can be severe and fatal and is associated with shock, respiratory failure, and vascular collapse. The earlier the symptoms occur, the more severe the reaction. Treatment consists of immediately discontinuing the transfusion, administering epinephrine and corticosteroids, and providing cardiovascular and respiratory support.

Septic Reactions

Rarely, septic reactions can occur secondary to bacterial contamination of blood products, principally platelets (they are not stored at cold temperatures). In March 2004, all blood banks began to routinely screen platelets for bacterial contamination with a subsequent reduction in septic reactions. Symptoms of such reactions include fever/chills; hypotension; headache; back, chest, and abdominal pain; and shortness of breath. Culture of the product and appropriate antibiotics and cardiovascular support are the mainstays of treatment.

Transfusion as a source for hepatitis (B and C) has been reduced since the initiation of donor screening for the hepatitis antibody. People with hemophilia who received coagulation factor concentrates before 1984 have been at highest risk among transfusion recipients because of exposures to pooled blood products prepared from thousands of donors. The availability of nonhuman plasma factors has virtually eliminated the transmission of viruses among people with hemophilia.

The risk of HIV infection by transfusion is low overall, calculated at 1 in 1 million transfusions. The risk of HIV transmission by blood transfusion has been continually reduced through the elimination of high-risk individuals from blood donor pools and the use of more sensitive screening. Acquired immune deficiency syndrome (AIDS) has developed in a small percentage of people receiving transfusion of RBCs, platelets, or commercial coagulation factor concentrates. AIDS has also been reported in infants after neonatal exchange, but the majority of pediatric cases were associated with maternal transmission from mothers with HIV.

Bloodless Medicine

Bloodless medicine and surgery is the use of technologic and pharmaceutical techniques to minimize blood loss and avoid the use of allogenic blood transfusions. Bloodless medicine and surgery programs began over the last 20 years to meet the needs of Jehovah's Witnesses, whose beliefs do not allow blood transfusions.

In recent years the number of bloodless medicine programs has increased due to a growing number of individuals seeking this type of treatment to avoid potential exposure to bloodborne pathogens or because of a family history of transfusion reactions.¹⁶⁹

As bloodless programs have grown, researchers have found other advantages to avoiding blood transfusions. The length of time banked blood spends in storage can affect the hemoglobin molecule's ability to release the oxygen it is carrying, potentially decreasing its oxygen-carrying capacity. Furthermore, cold storage of blood can negatively affect an RBCs elasticity, potentially leading to its early destruction.^{140,169}

Candidates for Bloodless Procedures

The first step in ensuring successful use of bloodless techniques is a thorough history, including a history of any personal or family history of bleeding abnormalities.^{70,140} Any history of bleeding abnormalities requires further evaluation.

Preoperative blood work is needed to detect anemia, since individuals with low preoperative hemoglobin levels are more likely to need a transfusion.⁷¹ Bloodless techniques can still be used if a low hemoglobin level is increased by giving recombinant human erythropoietin and iron.^{140,177}

Bloodless Techniques

During surgical procedures, there are a variety of techniques that are used to avoid the need for a blood transfusion. *Minimally invasive surgery* can significantly reduce blood loss, as does meticulous surgical technique. Tech-

nologic advances, such as the gamma knife, harmonic scalpel, and argon beams, have also improved the surgeon's ability to achieve hemostasis during procedures by coagulating vessels while causing less tissue damage.⁷⁰

Another technique, acute *normovolemic hemodilution*, removing a quantity of a person's blood and replacing it with intravenous crystalloid and colloid solution to maintain volume, can also be used.

With acute normovolemic hemodilution, fluid loss during a procedure is mainly the crystalloid/colloid solution, which limits loss of RBCs while preserving clotting factors. At the conclusion of the surgical procedure, the withdrawn blood is returned to the patient. Since this process is completed through a closed circuit, it is acceptable to most Jehovah's Witnesses.^{170,177}

Cell salvage techniques can be used in the intraoperative and postoperative phases to retransfuse lost blood. These techniques have been associated with infection and hemolysis but are believed to be safe as part of an overall blood loss management program.¹⁷⁰

Postoperatively, steps should be taken to minimize blood loss by close observation for bleeding, with immediate steps being taken to regain hemostasis (halt bleeding). Additionally, postoperative phlebotomy should be kept to a minimum and the blood drawn using microsampling techniques.^{70,170} Use of recombinant human erythropoietin and iron should be continued as needed during the postoperative phase.

Finally, clinician acceptance of low hemoglobin levels is essential in bloodless medicine and surgery. Research has shown that the body can tolerate lower hemoglobin levels than would be thought acceptable without compromising oxygen delivery. Hemoglobin levels alone should not be used as the deciding factor for a blood transfusion. The individual's condition and comorbidities should also be taken into account.¹⁶⁹

The advances in bloodless medicine and surgery have led to use of these techniques in many surgical procedures, including the Whipple procedure, joint replacements, and coronary artery bypass.¹⁴⁰

SPECIAL IMPLICATIONS FOR THE THERAPIST

14-2

Blood Transfusions

Most blood transfusion reactions occur during the actual transfusion and are not of consequence to the therapist, but when autologous transfusion is unavailable or inappropriate, the therapist must be alert for any signs of adverse reaction. Among the most common transfusion reactions are febrile, nonhemolytic transfusion reactions and delayed hemolytic transfusion reactions. Clinical symptoms from these reactions are typically mild and can usually be prevented on subsequent transfusions.

One of the most severe, but uncommon, reactions is the acute hemolytic transfusion reaction. This is due to antigen-antibody reactions resulting from blood type incompatibility with clumping of cells, hemolysis, and release of cellular elements into the serum.

Continued.

Signs and symptoms indicating such a reaction are listed in Box 14-2.

Occasionally, a client may develop an allergic reaction observed as dyspnea or hives; the latter may be brought to the therapist's attention after local modality intervention. The therapist may also be the first to recognize early signs of hepatitis (jaundice), especially changes in sclerae or skin color or reported changes in urine (dark or tea colored) and stools (light colored or white).

Bloodless Medicine

Therapists who work where bloodless techniques are used must have an awareness of the impact of lower hemoglobin levels on a person's ability to participate in therapy, especially exercise. Therapists should review blood work prior to each therapy session, looking specifically at hemoglobin levels. Routine vital signs and pulse oximetry need to be monitored throughout the therapy sessions.

Finally, patients/clients need to be observed closely to monitor how they are tolerating sitting, standing, and therapeutic activities. Although no studies have yet documented the relationship between hemoglobin levels and safe activity levels in therapy, patients participating in the Englewood Hospital and Medical Center (Englewood, NJ) bloodless medicine program have tolerated therapeutic activities with hemoglobin levels in the 7 to 9 g/dl range.

DISORDERS OF IRON ABSORPTION

Hereditary Hemochromatosis

Hemochromatosis is an autosomal recessive hereditary disorder characterized by excessive iron absorption by the small intestine. Most inherited forms of the disease are caused by abnormalities of the *HFE* gene located on chromosome 6. Although the exact mechanism of this gene is unknown, two hypotheses exist that may explain the pathology of the disease.

Pathogenesis

The *crypt hypothesis* suggests that the abnormal protein product of *HFE* is unable to interact with transferrin and leads to a decrease in absorption of iron by the intestinal crypt cells. This then triggers an inappropriate increase in iron absorbed by the intestinal villus cells.

The second hypothesis is based on a recently discovered peptide hormone produced by the liver, hepcidin, that appears to be the master regulator of iron homeostasis in human beings and other mammals. Hepcidin levels increase when iron plasma is high but is not produced when iron plasma is low. Hepcidin inhibits the release of iron by macrophages, but in its absence macrophages can release needed iron.

The product of *HFE* most likely plays a role in regulating the production of hepcidin; thus an abnormal gene

product would alter iron metabolism, leading to increased absorption despite already high iron plasma levels.¹⁴⁷

Most likely these two hypotheses are interrelated. Abnormalities of the hemochromatosis gene occur in 1 in every 200 people of Northern European descent, although not all people with the gene will develop the disease. Hemochromatosis is present at birth but remains asymptomatic until the development of iron overloading and onset of symptoms between ages 40 and 60 years (sometimes as early as age 30 years). The prevalence is equal among men and women, but men experience symptoms five to 10 times more often than do women (menstruation and pregnancy help to slow progression of the disorder).

Clinical Manifestations

The body typically absorbs iron at a rate equal to body requirements. But in hemochromatosis, there is an uncoupling between absorption and body needs. Excess iron is slowly deposited in cells, particularly in the liver, pancreas, heart, and, to a lesser extent, other endocrine glands (e.g., the pituitary gland).

Early signs and symptoms can include weakness, chronic fatigue, myalgias, joint pain, abdominal pain, hepatomegaly, elevated hemoglobin, and elevated liver enzymes. Continued iron overload leads to tissue damage. The liver is the most commonly affected organ, and clients may present with hepatomegaly without liver enzyme abnormalities. If the disease progresses without treatment, cirrhosis with liver failure may ensue.

Other complications of untreated hemochromatosis include diabetes mellitus, cardiac myopathy (with associated CHF) and arrhythmias, "bronzing" of the skin (from iron deposition in the dermis and increase of melanin), destructive arthritis, and impotence (men) or decreased libido (women) and sterility.

MEDICAL MANAGEMENT

DIAGNOSIS. Diagnosis can best be made through blood tests. The most sensitive test is the measurement of transferrin saturation. Levels higher than 60% in men and 50% in women are suggestive of the disease. If the client has a family history of the disease, genetic testing may be diagnostic. Ferritin levels greater than 1000 ng/ml (without evidence of inflammation) also suggest an iron overload state.

Definitive diagnosis requires a liver biopsy with measurement of iron stores; however, positive results from the genetic and blood tests may be sufficient for diagnosis. A liver biopsy is helpful when assessment of liver damage is required. In families where hemochromatosis has been previously diagnosed, all first-degree blood relatives should be genetically screened for hemochromatosis. Careful monitoring of affected family members can be done through blood tests. Monthly monitoring is required for those with known hemochromatosis.

TREATMENT. Treatment should begin early in the disease process, when iron levels exceed normal values. Medical intervention consists of weekly to twice-weekly therapeutic phlebotomy. This is performed until iron stores are at

normal levels, with ferritin levels less than 50 ng/ml (for some clients this may take 1 to 2 years), after which maintenance therapy is done as needed to maintain appropriate levels (about once every 3 months).

Chelating agents (i.e., agents that bind iron) may be given parenterally in cases where anemia or protein loss is severe. Phlebotomy, however, is less expensive and safer. Affected individuals are instructed to avoid ingesting alcohol since it increases the risk of developing cirrhosis nearly tenfold.

PROGNOSIS. The prognosis is good, with normal life expectancy as long as the iron levels remain in the normal range and the disease has not caused organ damage. With treatment, liver function improves, cardiac failure may be reversed, skin color lightens, and about 40% of clients with diabetes mellitus have improved glycemic control. Cirrhosis does not improve with therapy and 30% go on to develop hepatocellular carcinoma. Hypogonadism and arthropathy typically do not improve with treatment, and joint symptoms may actually progress despite therapy.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-3

Hemochromatosis

PREFERRED PRACTICE PATTERNS

4E: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Localized Inflammation

Arthropathy occurs in 40% to 60% of individuals with hemochromatosis and can be the first manifestation of the disease.⁶⁶ The arthropathy associated with hemochromatosis is not reversible and often continues to progress even with effective medical intervention.

Osteoarthritic manifestations are diverse, with minimal joint inflammation at first. The affected individual may report twinges of pain on flexing the small joints of the hand, especially the second and third metacarpophalangeal joints. Involvement of these joints often helps to distinguish hemochromatosis-related arthropathy from osteoarthritis.

Acute joint presentation can occur with progression that involves the large joints, including the hips, knees, and shoulders, accompanied by destruction to the joint, severe impairment, and resulting disability. Hemochromatosis may be associated with calcium pyrophosphate dihydrate deposition disease. This presents as an acute inflammatory arthritis.¹⁷⁵

Therapeutic intervention is essential in providing flexibility, strength, and proper alignment to promote function, prevent falls, and prevent the loss of independence in activities of daily living. The therapist can be very helpful in evaluating the need for assistive devices, orthotics, and splints toward these goals.

DISORDERS OF ERYTHROCYTES

The Anemias

Definition

Anemia is a reduction in the oxygen-carrying capacity of the blood from an abnormality in the quantity or quality of erythrocytes (RBCs). The World Health Organization (WHO) has defined anemia in terms of the level of hemoglobin: less than 14 g/100 ml for men and less than 12 g/100 ml for women. Different ranges exist for men and women, infants and growing children, and different metabolic and physiologic states.

These normal values must be evaluated on an individual basis; normal levels may be inadequate if tissue oxygen delivery is impaired by pulmonary insufficiency, cardiac disorders, or an increase in hemoglobin oxygen affinity, whereas low levels may be appropriate if tissue oxygen requirements are decreased, as in the case of hypothyroidism.

Overview

Anemia is not a disease but rather a symptom of many other disorders, such as dietary deficiency (anemia due to folate or vitamin B12 deficiency); acute or chronic blood loss (iron deficiency); congenital defects of hemoglobin (sickle cell diseases); exposure to industrial poisons; diseases of the bone marrow; chronic inflammatory, infectious, or neoplastic disease; or any other disorder that upsets the balance between blood loss through bleeding or destruction of blood cells and production of blood cells.

Many types and causes of anemia exist; not all are discussed in this text. The most common anemias observed in a therapy setting fall into five broad disease-related categories: (1) iron deficiency associated with chronic GI blood loss secondary to NSAID use; (2) chronic diseases or inflammatory diseases, such as RA or SLE; (3) nutritional conditions (e.g., malabsorption syndrome leading to vitamin B12, folate, or iron deficiency; alcohol abuse leading to folate deficiency); (4) infectious diseases such as tuberculosis or AIDS; and (5) neoplastic disease (bone marrow failure). Anemia with neoplasia may be a complication of chemotherapy (e.g., with cisplatin, carboplatin, or taxol administration), as a consequence of radiation to the pelvis, or bone marrow infiltration.

Anemias are classified according to etiologic factors (Box 14-3) or morphology (form/structure) (Box 14-4). Descriptions of anemias based on erythrocyte morphology refer to the size and hemoglobin content of the RBC. In some anemias, variations occur in size (e.g., anisocytosis) or shape (e.g., poikilocytosis) of erythrocytes.

Etiologic Factors and Pathogenesis

Anemia results from (1) excessive blood loss, (2) increased destruction of erythrocytes, or (3) decreased production of erythrocytes. Anemia is the most common hematologic abnormality; only the anemias most commonly observed in rehabilitation or therapy settings are discussed here, using the three etiologic categories from Box 14-3 as a guideline.

Box 14-3
CAUSES OF ANEMIA
Excessive Blood Loss (Hemorrhage)

- Trauma, wound
- GI cancers
- Angiectasia
- Bleeding peptic ulcer
- Excessive menstruation
- Bleeding hemorrhoids
- Varices, diverticulosis

Destruction of Erythrocytes (Hemolytic)

- Mechanical (e.g., microangiopathic hemolytic anemia, damage by a mechanical heart valve)
- Autoimmune hemolytic anemia (AIHA)
- Hemoglobinopathies (e.g., SCD)
- Enzyme defects (e.g., glucose-6-phosphate dehydrogenase deficiency)
- Parasites (e.g., malaria)
- Hypersplenism
- Cell membrane abnormalities (e.g., hereditary spherocytosis)
- Thalassemias

Decreased Production of Erythrocytes

- Chronic diseases (e.g., RA, tuberculosis, cancer)
- Nutritional deficiency (e.g., iron, vitamin B12, alcohol abuse, folic acid deficiency)
- Cellular maturational defects (e.g., thalassemias, cytotoxic or antineoplastic drugs)
- Decreased bone marrow stimulation (e.g., hypothyroidism, decreased erythropoietin production)
- Bone marrow failure (e.g., leukemia, aplasia)
- Bone marrow replacement (myelophthisis, neoplasm)
- Myelodysplastic syndromes (sideroblastic anemia)

Box 14-4
ANEMIA CLASSIFIED BY MORPHOLOGY

- Normocytic (normal size)
- Macrocytic (abnormally large)
- Microcytic (abnormally small)
- Normochromic (normal amounts of Hb)
- Hyperchromic (high concentration of Hb)
- Hypochromic (low concentration of Hb)
- Anisocytosis (various sizes)
- Poikilocytosis (various shapes)

The underlying pathogenesis can be multifactorial and depends on the condition causing the anemia. A number of physiologic compensatory responses to anemia occur, depending on the rapidity of onset and duration of anemia and the condition of the individual. In acute-onset anemia with severe loss of intravascular volume, peripheral vasoconstriction and central vasodilation occur to preserve blood flow to the vital organs.

If the anemia persists, small-vessel vasodilation will provide increased blood flow to ensure better tissue oxygenation. These vascular compensations result in decreased systemic vascular resistance, increased cardiac output, and tachycardia, resulting in a higher rate of

delivery of oxygen-bearing erythrocytes to the tissues. Other compensatory mechanisms include an increase in plasma volume to maintain total blood volume and enhance tissue perfusion and stimulation of erythropoietin production to increase new erythrocyte production.

Excessive Blood Loss. Excessive blood loss, such as occurs with GI bleeding in the client with a history of aspirin or NSAID use, is a cause of anemia seen in a therapy practice. Slow, chronic GI blood loss from medication or any GI disorder (e.g., peptic and duodenal ulcers, gastritis, GI cancers, hemorrhoids, diverticulosis, ulcerative colitis, and colon polyps) can result in iron-deficiency anemia.

Destruction of Erythrocytes. Destruction of erythrocytes (hemolysis) can occur as a result of congenital RBC membrane abnormalities, lack of necessary enzymes needed for normal metabolism, autoimmune processes, or infection. All but the autoimmune processes are discussed elsewhere in this chapter.

Autoimmune hemolytic anemia (AIHA) is caused by an autoantibody that attaches to the RBC, leading to its destruction. The most common form of AIHA is warm antibody-mediated, an immunoglobulin (Ig) G autoantibody that binds to erythrocytes at body temperature. Macrophages are attracted to the attached autoantibody and release enzymes that begin to destroy the cell membrane. The resultant spherical cells are removed by the spleen.

Cold agglutinin disease is another autoimmune hemolytic process caused by IgM autoantibodies that bind to erythrocytes at temperatures less than 37° C and trigger complement fixation and clumping of erythrocytes. These complement-laden erythrocytes may be destroyed intravascularly or removed by the liver. Hemolytic anemia can be idiopathic or a result of collagen vascular diseases (e.g., SLE), lymphoproliferative diseases (e.g., chronic lymphocytic leukemia or lymphoma), or other malignancies. Medications such as dapsone, penicillin, quinidine, quinine, and methyldopa can also cause AIHA.

Decreased Production of Erythrocytes. Anemias resulting in the underproduction of RBCs usually stem from either a lack of erythropoietin (as seen in kidney disease) or an inability of the bone marrow to respond to erythropoietin. Hyporesponsiveness of the bone marrow may be a result of a nutrient deficiency or a chronic disease such as RA, SLE, tuberculosis, or cancer.

Nutritional deficiency as a cause of anemia can occur at any age. Iron, vitamin B12 and folate are among the most important vitamins and minerals in the production of hemoglobin and the formation of erythrocytes. Iron is necessary for DNA synthesis, oxygen transport, and respiration. Iron deficiency can occur secondary to blood loss (RBCs are the principal site of iron storage), malabsorption, normal growth, and pregnancy. Menstruating women, pregnant women, growing children, lower socioeconomic groups, and older adults (as a result of economic constraints, lack of interest in food preparation, and poor dentition) are the most common groups to develop iron-deficiency anemia.

Vitamin B12 (cobalamin) is required for DNA synthesis. Deficiency of the vitamin may infrequently occur due to a lack in the diet (the body is very efficient at retaining

cobalamin) but most often develops because of an absence of intrinsic factor (IF).

Normally, after cobalamin is ingested it combines with R binders in the stomach and then binds to IF in the small intestine. IF is produced by gastric parietal cells and is required for cobalamin absorption in the terminal small bowel. Without IF, cobalamin is not absorbed.

Pernicious anemia is an anemia due to a loss of IF. Antibodies against the membrane of gastric parietal cells cause an atrophy of these cells, resulting in a lack of IF production. Destruction of IF production sites may also occur with gastrectomy (see the section on Aging and the Gastrointestinal System in Chapter 16).

Other causes of vitamin B12 deficiency include bacterial overgrowth in the lumen of the intestine (competes for vitamin B12), surgical resection of the ileum (eliminates the site of vitamin B12 absorption), severe Crohn's disease, and, more rarely, dietary deficiency (e.g., strict vegetarian diet) and tapeworm infection. Crohn's disease can cause sufficient destruction of the ileum to retard vitamin B12 absorption.

Folic acid deficiency is a common cause of decreased production of erythrocytes. Folic acid deficiency has many causes, but it usually results from inadequate dietary intake, chronic alcoholism, malabsorption syndromes, anorexia, and consumption of overcooked food. In anemia due to folic acid deficiency associated with alcoholism, not only is the diet poor in folate, but alcohol inhibits the enzyme needed to absorb folate.

The common occurrence of folic acid deficiency during the growth spurts of childhood and adolescence and during the third trimester of pregnancy is explained by the increased demands for folate required for DNA synthesis in these circumstances. Pregnant women need six times the normal amount of folic acid to meet the needs of the developing fetus. Long-term use of anticonvulsants (e.g., primidone, diphenylhydantoin, phenobarbital), antimetabolites administered for cancer and leukemia, and certain oral contraceptives may interfere with folate absorption.

Anemia of chronic disease is very common in the therapy setting. It is characterized by a modest reduction in hemoglobin (9 to 11 g/dl), the presence of inflammation (secondary to a disease), and decreased responsiveness of the bone marrow to erythropoietin. Many diseases associated with inflammation have accompanying elevated levels of cytokines and interferons. The production of hepcidin, a protein synthesized by the liver, is induced by the presence of interferon 6 (IF-6); hepcidin both inhibits the absorption of iron from the gut and the release of iron from macrophages for bone marrow use. Clients with an underlying chronic illness usually do not need iron, and anemia of chronic disease does not respond to iron.

Bone marrow disorders constitute another source of anemia caused by decreased production of erythrocytes in a therapy practice. Aplastic anemia, marrow replacement with fibrotic tissue or tumor, acute leukemia, and infiltrative disease (e.g., lymphoma, myeloma, and carcinoma) fall into this etiologic category.

Anemias of radiation-induced bone marrow failure occur because the bone marrow stem cells are destroyed



Figure 14-1

Normal nail (right) compared with nail referred to as koilonychia and sometimes called spoon-shaped nails or spoon nails (left). They are thin, depressed nails with lateral edges turned up and are concave from side to side. They may be idiopathic, congenital, or a hereditary trait and are occasionally due to iron-deficiency anemia. (Reprinted from Swartz MH: *Textbook of physical diagnosis*, ed 5, Philadelphia, 2006, Saunders.)

and mitosis (cell division) is inhibited, preventing the synthesis of RBCs. Antimetabolites used in cancer therapy also cause bone marrow failure by blocking the synthesis of purines or nucleic acids required for synthesis of DNA within the cell. Aplastic anemia may result from either damage to the stem cells or immune-mediated destruction of the stem cells.

Clinical Manifestations

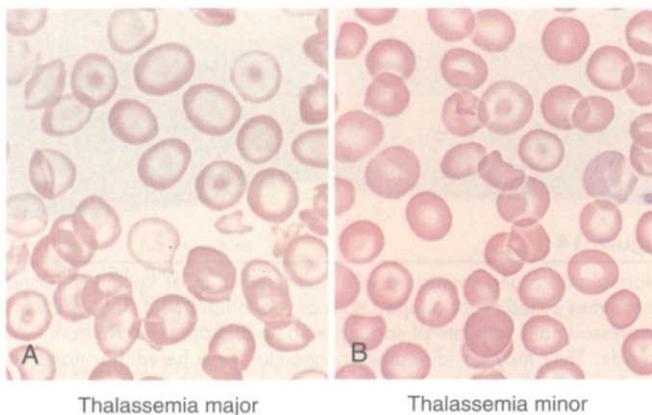
Mild anemia often causes only minimal and usually vague symptoms such as fatigue until hemoglobin concentration and hematocrit fall below half of normal. As the anemia progresses, general signs and symptoms caused by the inability of anemic blood to supply the body tissues with enough oxygen may include weakness, dyspnea on exertion, easy fatigue, pallor or yellowing of skin (especially the palms of the hands, fingernails, mucosa, and conjunctiva), tachycardia, increased angina in preexisting coronary artery disease, leg ulcers (sickle cell), and, occasionally, koilonychia (Fig. 14-1).

Pallor in dark-skinned people may be observed by the absence of the underlying red tones that normally give brown or black skin its luster. The brown-skinned individual demonstrates pallor with a more yellowish-brown color, and the black-skinned person appears ashen or gray.

Neuropsychiatric complications such as dementia, ataxia, psychosis, and peripheral neuropathies can develop in cases of B12 deficiency. These abnormalities are caused by lesions in the spinal column, the cerebrum, and peripheral nerves. The lack of cobalamin initially leads to demyelination of the nerves followed by axonal degeneration. Axonal death may result if cobalamin deficiency persists.

Reversal of symptoms may be possible if treatment is initiated before permanent damage to the nerves. The findings typically consist of a symmetric sensory neuropathy that begins in the feet and lower legs, although rarely it may involve the upper extremities, especially fine motor coordination of the hands. This upper extremity neuropathy may clinically manifest as problems with deteriorating handwriting.

Affected individuals may also describe moderate pain or paresthesias of the extremities, especially the feet. Individuals may interpret the neuropathy as difficulty with

**Figure 14-2**

Thalassemia is a hemolytic hemoglobinopathy anemia characterized by microcytic, short-lived RBCs caused by deficient synthesis of Hb polypeptide chains. Classification of type depends on the chain involved (α -thalassemia, β -thalassemia). β -Thalassemia occurs in two forms: thalassemia major and thalassemia minor. Characteristic bull's-eye or target cells are shown here in both forms. (Reprinted from Damjanov I, Linder J: *Pathology: a color atlas*, St Louis, 2000, Mosby.)

locomotion when, in fact, they are experiencing the loss of proprioception. The affected individual may need to hold on to the wall, countertops, or furniture at home due to difficulties maintaining balance. An associated positive Romberg's sign may be present. Loss of motor function is a late manifestation of B12 deficiency.

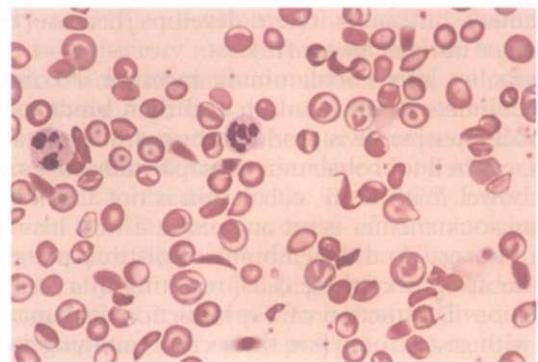
Although a symmetrical neuropathy is the usual pattern, B12 deficiency occasionally presents as a unilateral neuropathy and/or bilateral but asymmetrical neuropathy. CNS manifestations range from mild cognitive changes to dementia to frank psychosis. Clients may present with personality changes and/or inappropriate behavior.

Complications depend on the specific type of anemia; severe anemia can cause heart failure and hypoxic damage to the liver and kidney with all the signs and symptoms associated with either of those conditions. Anemia in the presence of a coronary obstruction precipitates cardiac ischemia.

MEDICAL MANAGEMENT

DIAGNOSIS. Anemia in the early stages often goes unnoticed since symptoms may not be recognized until hemoglobin concentration is reduced to half of normal. Once symptoms become pronounced or noted on routine laboratory tests, the diagnosis is most often made by blood tests.

The RBC indexes indicate if the RBCs are normal (normocytic), larger than normal (macrocytic, as seen with B12 and folate deficiency), or smaller than normal (microcytic, as seen with thalassemias and iron deficiency). The peripheral smear may reveal structural characteristics, which give clues to the underlying cause of the anemia. For example, target cells (bull's-eye erythrocytes) are often associated with thalassemia (Fig. 14-2) and microspherocytes can be seen in warm antibody-induced hemolysis, whereas sickled erythrocytes are noted with sickle cell disease (Fig. 14-3).

**Figure 14-3**

Target and sickle cells typical of sickle cell anemia (x200). (Reprinted from Goldman L: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, WB Saunders. Courtesy Jean Shafer.)

Personal and family history may point to congenital anemia, and a physical examination may elicit signs of primary hematologic diseases such as lymphadenopathy, hepatosplenomegaly, skin and mucosal changes, stool positive for blood, or bone tenderness.

Following these initial tests, more specific laboratory tests can be done to verify the diagnosis. These may include a complete blood cell count (CBC), an iron profile, serum ferritin, reticulocyte count, haptoglobin, B12 level, folate level, and lactate dehydrogenase.

TREATMENT. Treatment of anemia is directed toward alleviating or controlling the causes, relieving the symptoms, and preventing complications. It is critical that the underlying cause of anemia is determined so that appropriate treatment can be given. For example, endoscopy to identify the source of GI blood loss for a client with a long-term history of NSAID use would indicate the need to stop taking the medication and prescribe the use of proton pump inhibitors (see Chapter 16).

Treating the underlying cause can include the replacement of deficient vitamins and minerals (e.g., vitamin B12, folate, or iron) or corticosteroids for warm-antibody AIHA. The anemia of cold agglutinin disease is typically mild, requiring only a warm environment, while bone marrow transplantation may be required for malignancies. Immunosuppressive therapy with antithymocyte globulin and cyclosporine is the initial treatment for clients with aplastic anemia, and individuals with kidney disease are given erythropoietin or darbepoetin.

PROGNOSIS. The prognosis for anemia depends on the etiologic factors and potential treatment for the underlying cause. For example, the prognosis is good for anemia related to nutritional deficiency but poor for lymphoproliferative diseases. Likewise, treatment is aimed at correcting the underlying pathogenesis.

Untreated or misdiagnosed B₁₂ deficiency can be progressive, resulting in irreversible neurologic damage. Anemia in the older adult (age 85 years or older) is associated with an increased risk of death. Although anemia was once considered a normal consequence of aging, it is now recognized as a sign of other disease in the older

adult (e.g., hip fracture, RA, erosive gastritis, peptic ulcer, malnutrition, cirrhosis, ulcerative colitis) requiring further assessment.⁸⁹

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-4

The Anemias

PREFERRED PRACTICE PATTERNS

Practice patterns depend on manifestations of clinical signs and symptoms, complications, and the system(s) affected (e.g., dyspnea, angina, tachycardia associated with cardiovascular/pulmonary system; peripheral neuropathy associated with the nervous system).

Exercise and Anemia

The impact of anemia on functional recovery in the acute care or rehabilitation setting and the theoretical risk of increased morbidity and mortality during prescribed therapeutic exercise have not been thoroughly investigated. Further study is indicated to examine the implications for anemia on functional recovery and cardiopulmonary complications during rehabilitation.⁴⁹

The following guidelines should be used until proven protocols are developed. Exercise for any anemic person should be approved by the physician. Diminished exercise tolerance may be expected in anyone with anemia along with easy fatigability, depending on the cause of the anemia. Increased physical activity increases the demand for oxygen, which may not be adequately available in the circulating blood. Pacing and training that distribute the intensity of the workload over time can be used to promote physiologic recovery.⁴⁴ For the sedentary aging adult, decreased activity can mask exercise intolerance; observe carefully for any changes in mental status.

The prevalence of iron-deficiency anemia is likely to be higher in athletic populations and groups, especially in younger female athletes, than in sedentary individuals. In anemic individuals, iron deficiency decreases athletic performance and impairs immune function, leading to other physiologic dysfunction.

Although it is likely that blood losses secondary to exercise, such as foot-strike hemolysis or iron loss through sweat, may contribute to anemia, nonathletic causes must also be considered. Dietary choices explain much of a negative iron balance, but the GI and genitourinary systems must be evaluated for blood loss.¹⁷³

Evidence also exists for increased rates of RBC iron and whole-body iron turnover. The young female athlete may want to consult with medical or dietary consultants about the use of low-dose iron supplements during training.^{18,208}

Research has shown that people with chronic renal failure who have severe anemia are able to exercise but must do so at a lower intensity than the normal population. The maximum oxygen consumption ($\text{V}_{\text{O}_{\text{max}}}$) for the anemic client is at least 20% less than that for the normal population. Exercise testing and prescribed exercise(s) in anemic clients must be initiated with

extreme caution and should proceed gradually to tolerance and/or perceived exertion levels.⁵⁷¹⁴¹

Precautions

Knowing the underlying cause of the anemia may be helpful in identifying red flag symptoms indicating the need for alteration of the program or medical referral. For example, GI blood loss associated with NSAID use may worsen suddenly, precipitating a crisis in a therapy setting.

It is not uncommon for clients to present with both anemia and cardiovascular disease, precipitating angina (see Special Implications for the Therapist: Angina Pectoris in Chapter 12). New studies show that the amount of oxygen-carrying hemoglobin (Hb) circulating in the blood of older women is an independent risk factor for mobility problems. Hb perceived as mildly low and even low-normal (12g/dl) in women at least 70 years old increases the likelihood of difficulty performing daily tasks by 1.5 times.^{33a,33b}

The therapist may identify older adults who have a difficult time with general mobility, such as walking more than one block, climbing a flight of stairs, or doing housework. When they have difficulty, they become more sedentary, resulting in a decline in independence. The condition of mildly low Hb is no longer considered clinically benign, as mortality risk has been shown to be lower with higher Hb levels.³³⁰ It may be appropriate to request assessment of Hb levels and/or communicate with the physician about the potential harm of low-normal Hb levels.

Bleeding under the skin and easy bruising in response to the slightest trauma often occur when platelet production is altered (thrombocytopenia) secondary to hypoplastic or aplastic anemia. This condition necessitates extreme care in the therapy setting, especially any intervention requiring manual therapy or the use of any equipment, including modalities and weight-training devices. Splenomegaly associated with some types of anemia requires precautions in performing soft tissue techniques in the left upper quadrant, especially up and under the rib cage; indirect techniques away from the spleen are indicated.

Decreased oxygen delivery to the skin results in impaired healing and loss of elasticity as well as delaying wound healing and healing of other musculoskeletal injuries. If the anemia is caused by vitamin B12 deficiency (e.g., pernicious anemia, pregnancy, hyperthyroidism), the nervous system is affected.

Alteration of the structure and function of the peripheral nerves, spinal cord (myelin degeneration), and brain may occur. Paresthesias, especially numbness mimicking carpal tunnel syndrome; gait disturbances; extreme weakness; spasticity; and abnormal reflexes can result. Permanent neurologic damage unresponsive to vitamin B12 therapy can occur in extreme cases when intervention has been delayed.

Monitoring Vital Signs

Tachycardia may be the first change observed when monitoring vital signs, usually accompanied by a sense

Continued.

of fatigue, generalized weakness, loss of stamina, and exertional dyspnea. Systolic blood pressure may not be affected, but diastolic pressure may be lower than normal, with an associated increase in the resting pulse rate.

Resting cardiac output is usually normal in people with anemia, but cardiac output increases with exercise more than in nonanemic people. As the anemia becomes more severe, resting cardiac output increases and exercise tolerance progressively decreases until dyspnea, tachycardia, and palpitations occur at rest.

DISORDERS OF LEUKOCYTES

Alterations in blood leukocyte (WBC) concentration and in the relative proportions of the several leukocyte types are recognized as measures of the reaction of the body to infection, inflammation, tissue damage, or degeneration. In many instances, these alterations give useful indications of the nature of the pathologic process and may be seen in association not only with acute infections but also with many chronic ailments treated by the therapist.

Leukocytes may be classified in three main groups: granulocytes (basophils, eosinophils, neutrophils), monocytes, and lymphocytes. *Granulocytes* (granular leukocytes) contain lysing agents within their granules that are capable of digesting various foreign materials. The main type of granulocyte is the neutrophil, also called the *polymorphonuclear leukocyte*; these are usually not found in normal "healthy" tissue and are referred to as the first line of hematologic defense against invading pathogens.

Granulocytes are also involved in the pathophysiology of organ damage in ischemia/reperfusion, trauma, sepsis, or organ transplantation. Basophils and eosinophils are involved with allergic reactions and respond to parasitic and fungal infections.

Monocytes are the largest circulating blood cells and represent an immature cell until it leaves the blood and travels to the tissues. Once migrated, monocytes form macrophages when activated by foreign substances, such as bacteria. Monocytes/macrophages participate in inflammation by synthesizing numerous mediators and eliminating various pathogens.

Lymphocytes are further divided into B and T cells. B lymphocytes are responsible for the humoral portion of the immune system and are known to secrete antibodies that react with antigens and initiate complement-mediated destruction or phagocytosis of foreign pathogens, particularly bacteria. T lymphocytes are in control of cell-mediated immunity and are able to recognize and destroy cells altered by viruses.

These cells are also responsible for coordinating the immune response through the release of lymphokines and inflammatory modulators, creating a cell-to-cell communication with B cells and monocytes. The exact role or function of leukocytes during inflammatory processes remains the subject of considerable investigation.

Box 14-5

CAUSES OF LEUKOCYTOSIS

- Acute hemorrhage
- Infection (viral, bacterial, or fungal)
- Malignancies (leukemia, lymphoma, non–small cell lung cancer, multiple myeloma)
- Myeloproliferative disorders
- Glucocorticosteroid therapy
- Trauma (e.g., burns)
- Tissue necrosis (e.g., infarction)
- Inflammation (autoimmune-mediated, such as myositis or vasculitis)

Leukocytosis

Definition and Etiology

Leukocytosis, defined as an increase in the number of leukocytes in the blood, may occur as a result of a variety of causes (Box 14-5) and may also occur as a normal protective response to physiologic stressors such as strenuous exercise, emotional changes, temperature changes, anesthesia, surgery, pregnancy, some drugs, toxins, and hormones.

Leukocytosis develops within 1 or 2 hours after the onset of acute hemorrhage and is greater when the bleeding occurs internally (e.g., into the peritoneal cavity, pleural space, or joint cavity, or as a result of a skull fracture with associated intracranial bleed or subarachnoid hemorrhage) than when the bleeding is external.

Leukocytosis is a common finding in and characterizes many infectious diseases recognized by a count of more than 10,000 WBCs/mm³ (see Table 40-7). An elevated WBC count (greater than 50,000/mm³, with the majority of cells being neutrophils and neutrophil precursors) in response to a serious underlying process is referred to as a leukemoid reaction (see Box 14-5).

Leukocytosis frequently results from an increase in circulating neutrophils (neutrophilia), recruited in large numbers in the course of infections and in the presence of some rapidly growing neoplasms (e.g., leukemia, non–small cell lung cancer, renal cell carcinoma, and gastric carcinoma). The counts may be especially high in tumors with significant necrosis. Some tumors can also release hormone-like substances that cause leukocytosis.

Clinical Manifestations

Clinical signs and symptoms of leukocytosis are usually associated with symptoms of the conditions listed in Box 14-5 and may include fever, headache, shortness of breath, symptoms of localized or systemic infection, and symptoms of inflammation or trauma to tissue.

MEDICAL MANAGEMENT

DIAGNOSIS, TREATMENT, AND PROGNOSIS. Major leukocyte functions are accomplished in the tissues so that the leukocytes in the blood are in transit from the site of production or storage to the tissues, even in normal people. Variations in the blood concentrations of each

leukocyte type may be of brief duration and easily missed or may persist for days or weeks. Laboratory tests for detecting leukocyte abnormalities include total leukocyte count, leukocyte differential cell count (see Chapter 40), peripheral blood morphology, and bone marrow morphology.

Treatment is directed toward the underlying cause of the change in leukocytes and control of any infections. Prognosis depends on the etiology of the leukocytosis.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-5

Leukocytes

It is important for the therapist to be aware of the client's most recent leukocyte (WBC) count before and during episodes of care if that person is immunosuppressed. At that time, the client is extremely susceptible to opportunistic infections and severe complications.

The importance of good handwashing (see Boxes 8-4 and 8-5) and hygiene practices cannot be overemphasized when treating immunocompromised clients. Some centers recommend that people with a WBC count of less than 1000/mm³ or a neutrophil count of less than 500/mm³ wear a protective mask. Therapists should ensure that these people are provided with equipment that has been disinfected according to standard precautions.

Leukopenia

Definition and Etiology

Leukopenia, or reduction of the number of leukocytes in the blood below 5000/ml (see Chapter 40), can be caused by a variety of factors such as HIV (or other viral infection such as hepatitis), alcohol and nutritional deficiencies, drug-induced condition, and connective tissue disorders (e.g., SLE). It can occur in many forms of bone marrow failure, such as that following antineoplastic chemotherapy or radiation therapy or in overwhelming infections.

People with leukemia, lymphoma, myeloma, and Hodgkin's lymphoma have serious underlying WBC abnormalities that contribute to the risk of infection associated with leukopenia. Unlike leukocytosis, leukopenia is never beneficial. As the leukocyte count decreases, the risk for various infections increases.

The risk of infection from leukopenia after bone marrow radiation has been reduced with continued improvements in medical treatment. The use of naturally occurring glycoproteins to help collect blood stem cells administered after chemotherapy reduces the duration of blood cell reduction and prevents the serious problems encountered in the past.

These glycoproteins are hematopoietic growth factors called colony-stimulating factors (CSFs) or, more specifically, granulocyte colony-stimulating factor (G-CSF), or filgrastim (Neupogen). Growth factors move the stem cells from the bone marrow into the peripheral blood

and can result in a temporary tenfold to hundredfold increase in the numbers of circulating stem cells at the time of bone marrow recovery. Filgrastim not only increases the number but also the function of granulocytes.

Clinical Manifestations

Leukopenia may be asymptomatic (and detected by routine tests) or associated with clinical signs and symptoms consistent with infection such as sore throat, cough, high fever, chills, sweating, ulcerations of mucous membranes (e.g., mouth, rectum, vagina), frequent or painful urination, or persistent infections.

MEDICAL MANAGEMENT

DIAGNOSIS AND TREATMENT. As with leukocytosis, diagnosis is by laboratory testing for leukocyte abnormalities. Treatment is directed toward elimination of the cause of the reduced leukocytes and control of any infections. Pharmacologic therapy includes the use of antibiotics, antifungal agents, and CSF drugs such as filgrastim (Neupogen). This drug markedly assists in decreasing the incidence of infection in people who have received bone marrow-depressing antineoplastic agents.

Basophilia

Basophils are a subtype of leukocytes involved in inflammatory and allergic reactions. Their granules contain heparin (an anticoagulant but without significant systemic effects), histamine (the cause of most of the systemic symptoms), chondroitin sulfate, platelet-activating factor, and other proteins.

The antibody IgE is the most common stimulator of basophilic degranulation. IgE may be secreted in response to the body's detection of a foreign particle (such as insect venom or some drugs). The histamine and other proteins released by the basophil lead to a local inflammatory and allergic response. This response varies from person to person. Some clients may have reactions that are not modulated and develop anaphylaxis, asthma, urticaria (hives), and allergic rhinitis. Basophilia is primarily associated with myeloproliferative disorders, particularly chronic myeloid leukemia.

The remaining categories (e.g., basophilia/basopenia, eosinophilia/eosinopenia, neutrophilia/neutropenia) are all types of leukocytosis or leukopenia. The specific type is determined when the leukocyte differential (WBC count) determines the percentage of each type of granular and nongranular leukocyte.

Eosinophilic

Following the maturation and release of eosinophils from the bone marrow into the circulation, they soon migrate into tissue. These tissues are in areas that have contact with the external environment, such as the skin, GI tract, genital tract, and lungs. Eosinophils can be recruited to areas of inflammation by various antibodies and interleukins and stimulated to release chemokines, growth factors, cytokines, peroxidase, and other modulating proteins.

Chemokines are any of a group of low-molecular-weight cytokines (e.g., interleukins) identified on the basis of their ability to induce chemotaxis (cell movement; see Fig. 5-10) or chemokinesis (cell activity due to the presence of a chemical substance) in leukocytes in inflammation. Chemokines function as regulators of the immune system and may play roles in the circulatory system and CNS.

Eosinophils, however, are not central participants in defending the body against most infections but do play key roles in fighting parasitic infections, such as hookworm or strongyloidiasis. Eosinophils are also involved in allergic reactions such as asthma, cutaneous reactions, and other hypersensitivity states.

An elevation in the number of eosinophils in the blood, eosinophilia (eosinophil count greater than 500/ μ l) is seen most often in allergic reactions to drugs (aspirin, sulfonamides, penicillins), in hay fever, eczema, collagen vascular diseases (RA, eosinophilic fasciitis, periarteritis nodosa), and malignancies (Hodgkin's lymphoma, mycosis fungoides, chronic myeloid leukemia, cancer of the stomach, pancreas, and lung).

Idiopathic hypereosinophilia syndrome (counts from 50,000 to 100,000/ μ l), eosinophilic leukemia, and Loeffler's syndrome are uncommon illnesses are but associated with dramatic eosinophilia. Increased levels of eosinophils were also identified during outbreaks of *eosinophilia myalgia syndrome*, a connective tissue disease induced by the ingestion of contaminated L-tryptophan supplements, sometimes taken for insomnia or back pain.⁴³

Neutrophilia

Granulocytes assist in initiating the inflammatory response, and they defend the body against infectious agents by phagocytosing bacteria and other infectious substances. Generally, the neutrophils (the most plentiful of the granulocytes) are the first phagocytic cells to reach an infected area, followed by monocytes; neutrophils and monocytes work together to phagocytose all foreign material present.

Granulocytosis (an excess of granulocytes in the blood) or *neutrophilia* (increased number of neutrophils in the blood) are terms used to describe the early stages of infection or inflammation. The capacity of corticosteroids or alcohol to diminish the accumulation of neutrophils in inflamed areas may be due to their ability to reduce cell adherence.

The many potential causes of neutrophilia include inflammation or tissue necrosis (e.g., after surgery from tissue damage, severe burns, myocardial infarction, pneumonitis, rheumatic fever, RA); acute infection (e.g., *Staphylococcus*, *Streptococcus*, *Pneumococcus*); drug- or chemical-induced causes (e.g., epinephrine, steroids, heparin, histamine); metabolic causes (e.g., acidosis associated with diabetes, gout, thyroid storm, eclampsia); and neoplasms of the liver, GI tract, or bone marrow. Physiologic neutrophilia may also occur as a result of exercise, extreme heat/cold, third-trimester pregnancy, and emotional distress.

Neutropenia

Neutropenia is the condition associated with a reduction in circulating neutrophils (less than 2500/ μ l). Causes are either acquired or congenital. Acquired neutropenias are typically a result of toxicity to neutrophil precursors in the bone marrow. This may be due to drugs (e.g., NSAIDS, sulfonamides, penicillins, anticonvulsants) or infectious agents (e.g., hepatitis B, cytomegalovirus, EBV, HIV). Other drugs can cause an autoimmune-related peripheral destruction of neutrophils, leading to neutropenia.

Other causes of neutropenia include carcinoma of the lung, breast, prostate, and stomach and malignant hematopoietic disorders that can occupy enough of the bone marrow to cause global marrow failure with resultant pancytopenias (all cell lines are decreased in number). Congenital causes usually come to attention early in life and are much less common than acquired causes.

The longer an individual exists without neutrophils, the higher the risk for significant infection. Drug-induced neutropenia generally resolves in 10 to 12 days, while administration of GCSF may shorten the time to resolution.

Lymphocytosis/Lymphocytopenia

Lymphocytosis occurs most commonly in acute viral infections, especially those caused by EBV. Other causes include endocrine disorders (e.g., thyrotoxicosis, adrenal insufficiency) and malignancies (e.g., acute and chronic lymphocytic leukemia).

Lymphocytopenia may be acquired or congenital. Acquired lymphocytopenias can be attributed to abnormalities of lymphocyte production associated with neoplasms and immune deficiencies and destruction of lymphocytes by drugs, viruses, or radiation.

Other causes include corticosteroid therapy, severe systemic illnesses (e.g., military tuberculosis), SLE, sarcoid, or severe right-sided heart failure. For individuals with AIDS, lymphocytopenia can be a major problem, increasing their susceptibility to viral illnesses, malignancies, and fungal infections.

Monocytosis

Monocytosis, an increase in monocytes, is most often seen in chronic infections, such as tuberculosis and subacute endocarditis, and other inflammatory processes, such as SLE and RA. Monocytosis is present in more than 50% of people with collagen vascular disease (see Box 12-17).

Clients with sarcoid or other granulomatous processes may also have elevated monocytes. Monocytosis also exists as a normal physiologic response in newborns (first 2 weeks of life). Although not common, monocytes can go through a transformation, becoming leukemia, or an elevation of normal monocytes can be seen in malignancies such as Hodgkin's and non-Hodgkin's lymphoma. Monocytosis can be indicative of bone marrow recovery following a drug-induced loss of granulocytes.

NEOPLASTIC DISEASES OF THE BLOOD AND LYMPH SYSTEMS

Hematologic malignancies include diseases in any hematologic tissue (e.g., bone marrow, spleen, thymus) that arise from changes in stem cells or clonal (genetically identical cells) proliferation of abnormal cells. The primary hematologic disorders that result from stem cell abnormalities include the myeloproliferative disorders (e.g., polycythemia vera, essential thrombocythemia, chronic myeloid leukemia, and myelofibrosis with myeloid metaplasia) and acute myeloid leukemia. Myelofibrosis is the replacement of hematopoietic bone marrow with fibrous tissue such as fibroblasts and collagen.

Multiple myeloma and plasma cell diseases arise from clonal proliferation of abnormal plasma cells. Lymphoid malignancies are also a clonal proliferation of malignant cells and can be categorized according to the malignant cell type: B-cell, T-cell/natural killer cell, and Hodgkin's lymphoma. For ease of discussion, the leukemias are presented together.

Bone Marrow and Stem Cell Transplantation

Bone marrow transplantation (BMT) is often a treatment choice for many of the neoplastic diseases of the blood and lymph systems. Both BMT and the more recent technique of stem cell transplantation are discussed in Chapter 21.

The Leukemias

Leukemia is a malignant neoplasm of the blood-forming cells that replaces the normal bone marrow with a malignant clone (genetically identical cell) of lymphocytic or myelogenous cells. The disease may be acute or chronic based on its natural course; acute leukemias have a rapid clinical course, resulting in death in a few months without

treatment, whereas chronic leukemias have a more prolonged course. The four major types of leukemia are acute or chronic lymphocytic and acute or chronic myeloid leukemia (Table 14-2).

When leukemia is classified according to its morphology (i.e., the predominant cell type and level of maturity), the following descriptors are used: *lympho-*, for leukemias involving the lymphoid or lymphatic system; *myelo-*, for leukemias of myeloid or bone marrow origin involving hematopoietic stem cells (see Fig. 21-6); *-blastic*, for leukemia involving large, immature (functionless) cells; and *-cytic*, for leukemia involving mature, smaller cells. If classified immunologically, T-cell/natural killer cell and B-cell leukemias are described.

Acute leukemia is an accumulation of neoplastic, immature lymphoid or myeloid cells in the bone marrow and peripheral blood. It is defined as more than 30% blasts in the bone marrow (the WHO classification accepts 20% as the definition of leukemia).

Chronic leukemia is a neoplastic accumulation of mature lymphoid or myeloid elements of the blood that usually progresses more slowly than an acute leukemic process and permits the production of greater numbers of more mature, functional cells. With rapid proliferation of leukemic cells, the bone marrow becomes overcrowded with abnormal cells, which then spill over into the peripheral circulation. Crowding of the bone marrow by leukemic cells inhibits normal blood cell production.

The three main symptoms that occur as a consequence of this infiltration and replacement process are (1) *anemia* and reduced tissue oxygenation from decreased erythrocytes, (2) *infection* from neutropenia as leukemic cells are functionally unable to defend the body against pathogens, and (3) *bleeding tendencies* from decreased platelet production (thrombocytopenia) (Fig. 14-4).

Leukemia is not limited to the bone marrow and peripheral blood. Abnormalities in the CNS or other organ systems can result from the infiltration and replacement of any tissue of the body with nonfunctional leukemic cells or metabolic complications related to leukemia.

Table 14-2 Overview of Leukemia

	ALL	CLL	AML	CML
Incidence (% of all leukemias)	20%	25%	40%	15%-20%
Adults	30%	100% (common)	80% (most common)	95%-100%
Children	65%-70% (most common)	NA	20%	2%
Age	Peak, 3-7 years 65+ (older adults)	50+ years	Mean, 63 years; incidence increases with age from 45-80+ years	Average, 66 years (mostly adults)
Etiologic factors	Unknown; chromosomal abnormalities; Down syndrome (high incidence)	Chromosomal abnormalities; slow accumulation of CLL lymphocytes	Benzene; alkylating agents; radiation; myeloproliferative disorders; chromosome abnormalities	Philadelphia chromosome; radiation exposure
Prognosis	Adults: 40% Children: 80% survival	Poor cytogenetics: median, 8 years; good cytogenetics: median, 25 years Median survival, 10-14 years	Adults: Poor cytogenetics, 10%; intermediate cytogenetics, 40%; good cytogenetics, 60%	Moderately progressive with new treatment; current survival rate unknown

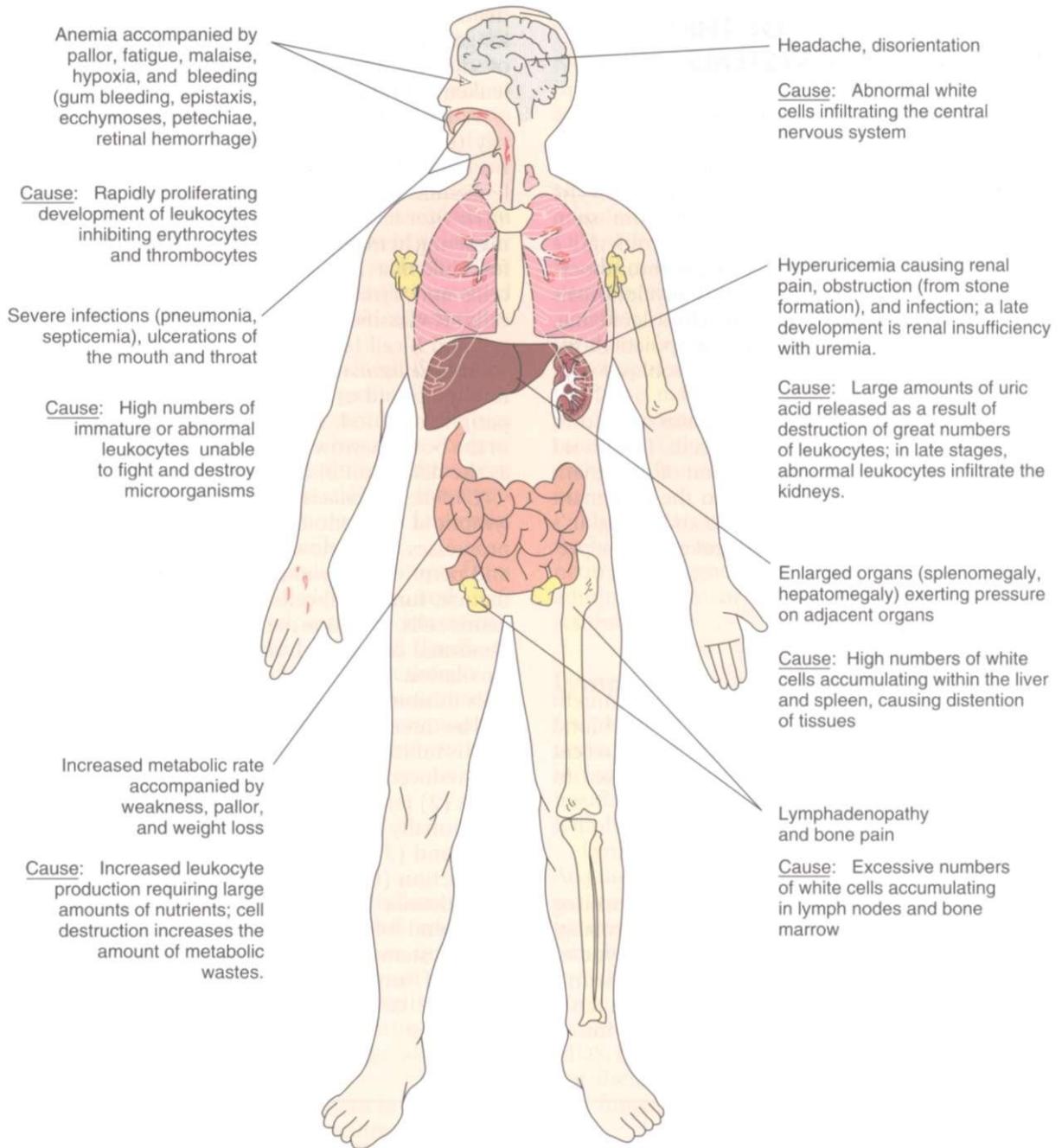


Figure 14-4

Pathologic basis for the clinical manifestations of leukemia. (Modified from Black JM, Matassarin-Jacobs E, editors: *Luckmann and Sorensen's medical-surgical nursing*, ed 4, Philadelphia, 1993, W.B. Saunders.)

Leukemia is a complex disease that requires careful identification of the subtype for appropriate treatment. Molecular probes can be used to establish a morphologic diagnosis of the type of leukemia, which then determines treatment and prognosis. These analyses are sufficiently sensitive to detect one leukemic cell among 100,000 or even in 1 million normal cells. Because of this extreme sensitivity, molecular markers have generally been used to determine the presence or absence of a few leukemic cells remaining after intensive therapy, so-called *residual disease*.

Over the last 25 years, death rates for leukemia have been falling significantly (57% decline) for children and more modestly for adults under 65 years. These declines in mortality reflect the advances made in the biologic and pathologic understanding of leukemia, technologic advances in medical care, and subsequent treatment that is more specifically targeted at the molecular level.

The aim of treatment is to bring about complete remission, or no evidence of the disease, with return to normal blood and marrow cells without relapse. For leukemia, a complete remission that lasts 5 years after treatment often

indicates a cure. Future clinical and laboratory investigation will likely lead to the development of new, even more effective treatments specifically for different subsets of leukemia. The development of new chemotherapeutic and biologic agents combined with refined dose and schedule and stem cell transplantation has already contributed to the clinical success of treatment.

Acute Leukemia

Acute leukemia is a rapidly progressive malignant disease that results in the accumulation of immature, functionless cells called *blast cells* in the bone marrow and blood that block the development of normal cell development.

The two major forms of acute leukemia are *acute lymphoblastic leukemia* (ALL) and *acute myelogenous leukemia* (AML). Lymphocytic leukemia involves the lymphocytes and lymphoid organs, and myelogenous leukemia involves hematopoietic stem cells that differentiate into myeloid cells (monocytes, granulocytes, erythrocytes, and platelets).

Acute Myelogenous Leukemia

Incidence and Risk Factors. AML is the most common leukemia in adults, constituting 80% of adult acute leukemias, while only 20% of AML patients are children. AML remains a rare disease, with about 12,000 cases per year.¹⁵

The incidence of AML increases with each decade of life, with the median age at onset of 63 years.¹⁴ People over the age of 70 years have a twelvefold increase of developing AML. Most cases of AML develop for unknown reasons, while some cases occur following treatment for another cancer (chemotherapy or radiation induced) or from a preexisting myelodysplastic syndrome.

Two types of chemotherapy treatment-related AML are described. The first typically occurs 5 to 7 years following exposure to an alkylating agent and is often heralded by a dysplastic phase. The other appears shortly after exposure to a topoisomerase II inhibitor (1 to 3 years) and lacks a dysplastic phase. Abnormalities in chromosome 7 are often seen in treatment-related AML and carry a worse prognosis than those cases that are idiopathic.¹⁶

Other risk factors for AML include previous radiation exposure and chemical/occupational exposure (e.g., benzene, herbicides, pesticides, cigarette smoking). Persons with uncommon genetic disorders, such as Down syndrome or Fanconi syndrome, also have a higher incidence of developing acute leukemia than the general population.

Pathogenesis. AML is a heterogeneous group (not all the same) of neoplastic myeloid cells. Myeloid stem cells have the capability of differentiating into granulocytes, monocytes, erythrocytes, and platelets; neoplastic changes can occur along any line, resulting in many subtypes of AML.

Current techniques allow for cytogenetic analyses that can reveal specific chromosomal abnormalities where portions of a chromosome translocate (move) and fuse with another gene, creating a fusion gene. It is these

abnormalities that lead to the development of leukemia, either allowing the cell to divide without regulation or failing to undergo programmed cell death (apoptosis).

Clinical Manifestations. Initial clinical indications of AML are related to pancytopenia (reduction in all cell lines), reflecting leukemic cell replacement of bone marrow. Clients often have infections due to a lack of neutrophils or bleeding secondary to platelet deficiency (thrombocytopenia).

Spontaneous bleeding or bleeding with minor trauma often occurs in the skin and mucosal surfaces, manifested as gingival bleeding, epistaxis, mid-cycle menstrual bleeding, or heavy bleeding associated with menstruation (see Fig. 14-4). Petechiae (small, purplish spots caused by intradermal bleeding) are common clinical manifestations of thrombocytopenia particularly noted on the extremities after prolonged standing or minor trauma.

Fatigue, loss of energy, and shortness of breath with physical exertion are common due to anemia. Leukemia cells may infiltrate the skin (known as leukemia cutis), seen most often in the acute monocytic or myelomonocytic subtypes of AML. Leukemia cutis may present as multiple purplish papules or as a diffuse rash (Fig. 14-5).

Modest splenomegaly is seen in 50% of clients with AML, whereas lymphadenopathy is uncommon. Discomfort in the bones, especially of the sternum, ribs, and tibia, caused by expanded leukemic marrow may occur. In the older adult, the disease can present insidiously with progressive weakness, pallor, a change in sense of well-being, and delirium.

CNS involvement is uncommon, occurring in only 1% to 2% of adults presenting with AML.¹⁰ These people present with symptoms similar to meningitis (e.g., headache, stiff neck, and fever). Some clients may develop cerebral bleeding or meningitis due to pancytopenia. In a small number of cases, AML may be more subtle, presenting at first with progressive fatigue and normal blood counts.

MEDICAL MANAGEMENT

DIAGNOSIS. Initial blood tests often reveal an elevated leukocyte count with an excessive amount of immature cells although low counts may be seen, especially in the elderly. Uncommonly initial counts may be normal. Diagnosis usually requires a bone marrow biopsy and aspiration in order to view bone marrow architecture and perform further tests.

Since most AML does not involve the CNS, lumbar punctures are not needed unless clinically indicated. Diagnosis involves several laboratory tests. First, immunophenotyping of blasts from peripheral blood or bone marrow is done in order to determine lineage of the cells (e.g., myeloid vs. lymphoid).

Treatment is determined by lineage, and AML treatment differs from ALL treatment. AML can be subdivided into various subtypes or classifications, and each subtype may receive varying initial therapy. The FAB system (French-American-British classification, first published in 1976) describes eight subdivisions classifying AML according to cell morphology and according to how the cells react to various stains.



Figure 14-5

A, Leukemia cutis in an individual with monoblastic leukemia. **B**, Another example of leukemia cutis in the form of erythematous nodular tumors. (A, Reprinted from Hoffman R: *Hematology: basic principles and practice*, ed 4, Philadelphia, 2005, Churchill Livingstone. B, Reprinted from Noble J: *Textbook of primary care medicine*, ed 3, St Louis, 2001, Mosby.)

The WHO has recently provided a revised classification of AML, retaining many aspects of the FAB system but adding cytogenetic information (chromosomal abnormalities) with associated prognosis (Table 14-3).¹⁰ Although the cytogenetic abnormalities do not determine initial therapy, they do guide postremission therapy and provide prognostic information.¹⁵

The FAB system is clinically useful and widely accepted. The WHO classification is still undergoing changes as research provides more insight into the cytogenetic abnormalities of AML. Some recent abnormalities that have been identified include mutations of the *FLT3* gene (found in about 30% of AML cases and associated with a poor prognosis) and *NPM* mutations (identified in 60% of AML cases with normal cytogenetics).

TREATMENT. The diagnosis of acute leukemia is a medical emergency, especially if the WBC count is high (greater than 100,000/ml), placing the person at risk for cerebral hemorrhage caused by leukostasis (obstruction of and damage to blood vessels plugged with rigid, large blasts).

Treatment decisions are based on the subtype of AML. Most induction (initial) treatment protocols utilize aggressive combination chemotherapy in order to eradicate the neoplastic cells and restore normal hematopoiesis. Supportive care, including fluids, blood product replacement, and prompt treatment of infection with broad-spectrum antibiotics, is frequently needed during the 3- to 4-week hospitalization required for bone marrow recovery. Significant complications occur during this period, with a death rate of 5% to 10%.¹⁵

Induction chemotherapy is followed by consolidation chemotherapy, which is intended to maintain a complete remission. Consolidation treatment is administered in a cyclic fashion over 2 to 4 months.

The discovery of mutations and translocations that may be causing leukemia has led to the development of

Table 14-3 Revised Classification of AML

FAB Classification	Incidence	WHO Classification	Prognosis
M0	AML, minimal differentiation	3%-5%	With t(8;21)(q22;q22)
M1	AML without maturation	15%-20%	With t(15;17)(q22;q12)
M2	AML with maturation	25%-30%	With inv(16)(p13q22)
M3	Acute promyelocytic leukemia	10%-15%	With 11q23 abnormalities
M3v	Acute promyelocytic leukemia variant, microgranular		Related to therapy for other cancers
M4	Acute myelomonocytic leukemia	20%-30%	With multilineage dysplasia
M4eo	Acute myelomonocytic leukemia with eosinophilia		Not otherwise categorized: use FAB categories
M5a	Acute monoblastic leukemia, poorly differentiated	2%-9%	Poor
M5b	Acute monocytic leukemia, differentiated		Intermediate and heterogeneous
M6	Acute erythroleukemia	3%-5%	
M7	Acute megakaryoblastic leukemia	3%-5%	

FAB, French-American-British.

The FAB classification system, first published in 1976, describes eight subdivisions classifying AML according to cell morphology and how the cells react to various stains.

Modified from Jaffe ES, Harris NL, Stein H, editors: *Pathology and genetics of tumours of haematopoietic and lymphoid tissues*. Vol 3 of World Health Organization classification of tumours, Lyon, France, 2001, IARC Press.

targeted therapeutic agents. One example is tretinoin. It is used against acute promyelocytic leukemia and targets the t(15;17) translocation. Experimental drugs are in clinical trials for persons with *FLT3* mutations, and other agents will be designed in hopes of targeting the genetic abnormalities without affecting normal cells.

PROGNOSIS. If left untreated, all leukemias are fatal. With induction treatment, approximately 80% of clients younger than 60 years achieve remission. The rate of remission decreases as age increases over 60 years.

According to the WHO classification, persons with AML with favorable cytogenetics (good prognosis) have a 60% 5-year survival rate, whereas those with a poor prognosis have only a 10% 5-year survival rate. Clients with an intermediate prognosis (the majority of AML cases) have a 40% 5-year survival rate.

Improvement in outcomes for people with a poor prognosis is a major goal of clinical research. Because this group rarely remains in remission after consolidation therapy, current protocols include allogeneic, unrelated-donor or cord-blood transplantation following induction (e.g., transplant done in first remission). Consolidation therapy is offered to those people with good prognostic cytogenetics. Autologous transplantation and consolidation therapy are the options for clients with normal cytogenetics but an intermediate risk for recurrence.

Acute Lymphoblastic Leukemia

Incidence and Risk Factors. In contrast to AML, ALL is diagnosed more frequently in children. Of the 4000 cases of ALL identified each year, two thirds occur in children while only one third are diagnosed in adults.¹⁵⁶ Yet of the 1500 annual deaths, almost two thirds occur in adults.

Like AML, most ALL cases develop for unknown reasons. A few risk factors have been identified including significant exposure to radiation and infection with HTLV-1 (human T-cell lymphoma/leukemia virus). Persons with genetic disorders such as Down syndrome also have an increased risk.

Questions have been raised as to whether electromagnetic fields, such as those generated in high-voltage power lines, increase the risk of developing ALL. Currently large studies are ongoing with initial data suggestive of no increased risk or a very slight increased risk. Answers should be available at the conclusion of these studies. Burkitt's lymphoma can form a type of ALL that responds poorly to treatment.

Pathogenesis. Abnormal cytogenetics or translocations and mutations are frequently seen in ALL cases. These genetic changes lead to abnormal cell growth and division or inability of the cells to decrease their growth and die (scheduled cell death or apoptosis). These various abnormalities are associated with poor or good prognosis. For instance, leukemic cells with more than 50 chromosomes (hyperdiploidy) and the translocation t(12;21) have a good prognosis. More than 50% of children with ALL have this defect, while only 10% of adults have it. Leukemic cells with less than 45 chromosomes are difficult to treat and carry a poor prognosis. Trans-

locations t(4;11) (50% of infant cases) and t(9;22) (50% of adults over the age of 50 years) also have a poor prognosis).¹⁵⁶

Clinical Manifestations. ALL exhibits clinical signs and symptoms resulting from an abnormal bone marrow that is unable to engage in normal hematopoiesis. Fever and frequent infections indicate a lack of normal neutrophils, while easy bleeding and bruising are indicative of thrombocytopenia. Clients are often tired as a result of anemia.

ALL is more likely than AML to have leukemic cells spread to extramedullar sites. The CNS is frequently involved, causing headache, weakness, seizures, vomiting, difficulty with balance, and blurred vision.⁹ Testicles in males and ovaries in females commonly harbor leukemic cells and are difficult to reach with chemotherapy agents.

Bone and joint pain from leukemic infiltration or hemorrhage into a joint may be the initial symptoms (more common finding in children than adults). Involvement of the synovium may lead to symptoms suggestive of a rheumatic disease, especially in children.

Hepatosplenomegaly and lymphadenopathy (particularly in the mediastinum) are frequently encountered along with an enlarged thymus. If thymic swelling is significant, the client may exhibit difficulty breathing or upper extremity swelling from increased pressure on the bronchus or superior vena cava (superior vena cava syndrome), which requires immediate attention.

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of ALL is similar to that of AML (see diagnosis of AML above). The peripheral blood smear is examined, and additional special tests are performed using peripheral blood and bone marrow. A bone marrow biopsy and aspirate are required for many of these tests.

Bone marrow is used to perform flow cytometry/immunophenotyping to determine if the leukemic cells are myeloid or lymphoid in origin (rarely there are cells that express features of both). Cytogenetic studies are performed to aid in prognosis and assist in determining subsequent treatment. This is accomplished by culturing bone marrow cells or performing fluorescent in situ hybridization.

Since ALL commonly involves the CNS, a lumbar puncture is done to collect cerebral spinal fluid for analysis. As with AML, ALL is a heterogeneous group of lymphoid leukemias with varying prognoses. The FAB classification of ALL includes the three subtypes L1, L2, and L3, while an expanded classification that relies on flow cytometry and cytogenetics establishes six subtypes: (1) early pre-B-cell ALL, (2) common ALL, (3) pre-B-cell ALL, (4) mature B-cell ALL (Burkitt's lymphoma), (5) pre-T-cell ALL, and (6) mature T-cell ALL.

TREATMENT. ALL treatment protocols vary depending on age, subtype of ALL, and genetic abnormalities associated with risk of recurrence. For example, mature B-cell ALL has a good prognosis and is treated with short-term intensive chemotherapy. Other subtypes require remission-induction therapy (initial intensive

combination chemotherapy designed to induce a complete remission).

Clients with CNS involvement receive intrathecal chemotherapy periodically throughout their treatment, and those at high risk for CNS relapse may receive cranial radiation. Intensification therapy (consolidation) is administered following successful remission-induction treatment. This consists of a reinduction treatment (a readministration of induction agents) followed by cyclic use of other chemotherapy agents over a period of 2 years or longer, termed continuation therapy.

Selection of these agents is based on risk of recurrence, age, and subtype. Drugs, dosages, and scheduling can be individualized. For ALL subtypes at high risk, allogeneic BMT is offered. Adults frequently require transplantation and can achieve long-term survival rates of 45% to 75%.⁵⁷

Ninety-eight percent of children and 85% of adults achieve a complete remission following remission-induction therapy. With such favorable results, efforts are being made to reduce toxicities associated with aggressive combination chemotherapy, especially in children with standard risk of ALL with favorable cytogenetics.

A recent analysis has shown that children who survive cancer go on to develop significant long-term medical problems including other cancers, heart disease, cognitive dysfunction, joint replacement, and hearing/vision loss.¹³⁷ Some of the strategies being implemented in protocols include a dose reduction of vincristine in infants, the omission of cranial irradiation in girls and young children (attempts are being made to completely omit irradiation for all people with ALL), and a dose reduction of methotrexate in clients with Down syndrome.

Another strategy is to provide targeted agents. Imatinib mesylate (Gleevec) is available for the treatment of cancers with the t(9;22) translocation. The use of targeted drugs reduces toxicity and alleviates the requirement of adjuvant agents.

PROGNOSIS. Children with ALL do better than adults (the older the client, typically the worse the prognosis). The cure rate of children is approximately 80%, while adults average a 40% cure rate. Continuing research into the cytogenetics has provided significant prognostic information regarding various abnormalities.

T-cell ALL carries the best prognosis, while mature B-cell ALL is associated with the worst. ALL classified as L3 has a poor prognosis as well as those leukemic cells with the Philadelphia chromosome [t(9;22)] or t(4;11) translocation. Pre-B-cell ALL has an intermediate prognosis, while clients requiring 4 to 5 weeks to achieve complete remission with induction chemotherapy have a poor prognosis.

Chronic Leukemia

Chronic leukemia is a malignant disease of the bone marrow and blood that progresses slowly and permits numbers of more mature, functional cells to be made. Chronic leukemia has two major groups: chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL), each with several subtypes.

These are entirely different diseases and are presented separately. CML is also known as chronic myelogenous leukemia or chronic myelocytic leukemia. Other less-common forms include prolymphocytic leukemia (terminal transformation of CLL) and hairy cell leukemia (accounting for only 1% to 2% of adult leukemias).

Chronic Myeloid Leukemia

Incidence and Etiologic Factors. CML is a neoplasm of the hematopoietic stem cell. The genetic abnormalities created in the stem cell are the result of acquired injury to the DNA and passed on to all related cell lines, resulting in increases in myeloid cells and clonal anomalies in erythroid cells and platelets. This leads to abnormal cells in peripheral blood and marked hyperplasia in the bone marrow.

CML accounts for 15% of all leukemias, with approximately 4600 cases diagnosed per year. This type of leukemia occurs mostly in adults, with only 2% developing in children. Although the exact etiologic factors are unknown, the incidence of CML is increased in people with severe radiation exposure. No chemical or other environmental risk factors are known to cause CML.

CML was the first form of leukemia with a known genetic predisposition (Philadelphia chromosome [Ph]; named after the city in which researchers first observed the chromosome). The specific genetic anomaly is a translocation that fuses the long arm of chromosome 22 to chromosome 9. Detached pieces of chromosome 9 adhere to the broken end of chromosome 22 and vice versa. This translocation occurs only in the stem cell and in the various blood cells derived from that stem cell. The chromosomes of the cells in other tissues are normal.

Pathogenesis. CML originates in the hematopoietic stem cell (i.e., this cell has the ability to develop into any one of several blood cells; see Fig. 21-6) and involves overproduction of myeloid cells. The genetic defect detected in CML cells is called the Philadelphia chromosome. This translocation [t(9;22)] was the first consistent chromosomal anomaly identified in a cancer and is now detected in all cases of CML and known to be the cause of CML.

The abnormal chromosome develops from the accidental translocation and fusion of the *BRC* gene on chromosome 22 and the *ABL* gene on chromosome 9, creating a unique gene (*BRC-ABL*). The *BRC-ABL* gene encodes for an abnormal protein product that acts as a tyrosine kinase, resulting in a dysregulated proliferation signal.

Tyrosine kinase is an enzyme that is necessary for normal cell growth. In normal cells the enzyme turns on and off as it should, but in people with CML this enzyme appears to be in the permanent "switched on" state, eliminating the normal checks and balances on proliferation.

Unlike AML, CML permits the development of mature WBCs that generally can function normally. This important distinction from acute leukemia accounts for the less-severe early course of the disease.¹⁵⁹

Clinical Manifestations. Presenting signs and symptoms are often quite nonspecific. The most typical symptoms at presentation are fatigue, anorexia, and weight loss, although approximately 40% of affected individuals

are asymptomatic. Sweats, malaise, and shortness of breath during physical activity are also reported.

Splenomegaly is present in 50% of all cases, with thrombocytosis being very common. Discomfort on the left side of the abdomen from the enlarged spleen is not uncommon.

The natural history of CML is a progression (over years) from a proliferative phase (chronic phase), into an accelerated phase (more symptoms but not acute leukemia), to an aggressive acute leukemia (blast crisis) that can be rapidly fatal within months.

MEDICAL MANAGEMENT

DIAGNOSIS. Early in the disease process, only vague symptoms or routine blood analysis may herald the disease. Peripheral blood counts and smears often demonstrate an abnormal leukocytosis, which leads to further testing. The peripheral blood smear will often reveal a wide range of cells in a variety of stages. Basophilia may also be seen. The appearance of both mature and immature cells in the peripheral blood is suggestive of CML but must be differentiated from other myeloproliferative disease.

As with other leukemias, laboratory findings, including blood and bone marrow testing, assist in establishing the diagnosis. The genetic abnormality in blood cells (Ph chromosome) is almost invariably present and may be detected in either the peripheral blood or bone marrow using fluorescent in situ hybridization, polymerase chain reaction (PCR) analysis, or karyotyping.

TREATMENT AND PROGNOSIS. Recent research has significantly changed the treatment and prognosis of CML. In fact, because of the prolonged survival seen with current treatments, the long-term survival rate is unknown. Knowledge that the cause of the disease was an abnormal *BCR-ABL* gene led to the development of the drug imatinib mesylate (Gleevec), designed to target and inhibit tyrosine kinase (it blocks adenosine triphosphate from interacting with the abnormal protein product).

In studies comparing the previously used regimen of cytarabine and interferon, imatinib mesylate produced a 95% complete hematologic remission (blood and bone marrow look normal) compared to only 56% for the combination therapy. Imatinib mesylate is also better tolerated, with fewer adverse effects. After 18 months of treatment, 87% of clients were able to achieve a complete cytogenetic remission (cells lack the *BCR-ABL* gene) compared to only 35% on the combination therapy.¹³⁵

Clients with evidence of the translocation in cells are at risk for relapse. Those without evidence of the abnormal clone had long-term CML-free survival. Investigations are still ongoing to determine the optimal length of treatment and long-term side effects. Some people will develop a relapse of CML that is resistant to imatinib mesylate. New drugs (e.g., nilotinib, dasatinib) have been and are being developed that can be used simultaneously with imatinib or in clinical situations where the leukemia is resistant to imatinib.¹⁹⁵

For those clients with CML that is not responsive to these new treatments (or for individuals who are unable to tolerate imatinib), combination therapy can control

the symptoms for a time. Allogeneic BMT continues to be an option that may provide a cure. This should be performed during the proliferative phase (chronic phase) within the first year of diagnosis. For those people who develop blast crisis, treatment is similar to acute leukemia treatment. If a remission is induced, these clients become candidates for BMT.

Chronic Lymphocytic Leukemia

Incidence and Etiologic and Risk Factors. CLL is a common type of adult leukemia, accounting for 25% to 30% of all leukemias with almost 10,000 cases per year.⁹¹ The incidence of CLL increases with advancing age; 90% are older than 50 years, and men are affected more often than women. CLL may occur in as many as 3% of people over the age of 70 years.

The cause of CLL is also unknown but a few environmental factors have been implicated, such as farming pesticides and the chemical warfare herbicide Agent Orange, although conclusive evidence is lacking. Some groups of people may have a genetic predisposition, including persons with a first-degree family member with CLL.²⁰⁴

Pathogenesis. The cell type responsible for more than 95% of the cases of CLL is the B cell (T-cell CLL is uncommon). When a normal B cell is stimulated by an antigen, it enters a proliferative phase, creating clones able to fight infection. It is during this stage that a cell may develop a mutation and predispose it to become cancerous. A mutation allowing the cell to continue to proliferate places that cell at an advantage but the human host at a disadvantage. With continuous exposure to this antigen and the aid of stromal cells, cytokines, and chemokines, cells would be stimulated to proliferate and avoid apoptosis (programmed cell death), potentially leading to cancer.

CLL cells may develop from this type of cell since most initial CLL cells lack major cytogenetic abnormalities (translocations are uncommon). As the mutated B cell continues to divide, more mutations develop, creating a heterogeneous group of abnormal cells. Different mutations appear to affect the course of the disease.

Mutations in the immunoglobulin-forming genes can proffer a prolonged, milder course of disease or a more aggressive, symptomatic illness. For example, clients with no or few V gene mutations or multiple CD38+ or ZAP-70+ mutations followed an aggressive, often fatal course, while cancerous clones with few CD38+ or ZAP-70+ mutations resulted in a more indolent course.³⁴ ZAP-70+ is a protein normally found in T lymphocytes and is responsible for transferring signals inside the cell.

There are few unifying mutations except the deletion of 13q14.3, which is present in more than half of all people with CLL.¹²³ The frequency of this mutation suggests that the genes in this region offer the clonal cells an advantage over other cells. Other mutations are noted to be in genes that control apoptosis or confer chemotherapy resistance, resulting in a poor prognosis.

Clinical Manifestations. In the early stages of the disease, most clients remain asymptomatic or complain of vague, nonspecific symptoms such as fatigue or enlarged lymph nodes. Depending on the mutations present in the abnormal clone, clients may experience a prolonged, indolent course with few symptoms.

Those people with more aggressive CLL develop pancytopenia (with accompanying symptoms of infections, hemorrhage, and significant fatigue) and decreased immunoglobulin levels (also resulting in infections). With progression of the disease, clients may develop lymphadenopathy, splenomegaly, hepatomegaly, weight loss, bone pain, and bone marrow infiltration. Approximately 10% to 25% of clients develop the complication of AIHA,¹⁴⁴ and immune thrombocytopenia occurs in 2% of cases.²⁴

MEDICAL MANAGEMENT

DIAGNOSIS. Examination of the peripheral blood smear, CBC, and flow cytometry are performed to make a diagnosis. Bone marrow examination is not required but may be helpful. Staging is established according to the Rai and Binet systems.

The Rai system recognizes five stages (0 to IV) conferring a low (stage 0), intermediate (I, II), and high (III, IV) risk of progression. This staging determines which clients should receive treatment and when, but this staging system does not provide reliable prognostic information.

TREATMENT. CLL has been difficult to treat and typically is without a cure. Better understanding of the pathogenesis of CLL is leading to improved treatments, but most initial treatment is based on clinical staging.

Low-risk clients require careful monitoring and frequent examinations with treatment initiated if symptoms worsen or if there is evidence of progressive leukemia. Intermediate- and high-risk clients are treated with chemotherapy (fludarabine and chlorambucil) accompanied by monoclonal antibodies. Alemtuzumab is the only Food and Drug Administration approved monoclonal antibody for the treatment of CLL, although rituximab is frequently used because of its better side-effect profile.

Immunomodulating agents (agents that change signals sent to the abnormal cells) are currently being studied and may prove to be beneficial as an adjuvant therapy.³² The use of autologous transplant for the treatment of CLL has increased recently but remains a successful option in a limited number of cases.

PROGNOSIS. CLL continues to be a fatal disease with a significant impact on life expectancy, but in the last few years a trend toward an improvement in overall survival has taken place.

Prognostic information can be provided by analysis of mutations, which in the future may also better determine when therapy should be initiated (if an indolent course is most likely, therapy can be withheld until needed; an aggressive CLL may require therapy sooner). Since cytogenetic testing is not widely available, identification of the proteins ZAP-70+ or CD38+ may prove reliable surrogate markers for determining prognosis.³⁴

Clients who present in Rai stage III to IV have an average life expectancy of 3 years, while those with less-aggressive leukemia may never require treatment (depending on the age at diagnosis). About 70% of people with CLL eventually require treatment.⁹⁵

As mutations are discovered, they are being related to prognosis. As previously discussed, CLL, which displays ZAP-70+ or CD38+ mutations, has a poor prognosis, while mutations in the immunoglobulin heavy-chain variable region have a good prognosis (median survival of 25 years). Overall, CLL has a median life expectancy of 10 to 14 years.

SPECIAL IMPLICATIONS FOR THE THERAPIST 14-6

Leukemia

PREFERRED PRACTICE PATTERNS

Practice patterns are determined on an individual basis depending on clinical presentation and response to medical intervention or other treatment measures.

Like all cancers, medical innovations in the treatment of leukemia are increasing the patient's lifespan while increasing the likelihood of treatment side effects. Strengthening and energy-enhancing programs during cancer treatment may reduce the disabling fatigue and other effects of chemotherapy and radiation therapy.

Precautions

The period after chemically induced remission is critical for each client, who is now highly susceptible to spontaneous hemorrhage and defenseless against invading organisms. The usual precautions for thrombocytopenia, neutropenia, and infection control must be adhered to strictly. The importance of strict hand-washing technique (see Boxes 8-4 and 8-5) cannot be overemphasized. The therapist should be alert to any sign of infection and report any potential site of infection, such as mucosal ulceration, skin abrasion, or a tear (even a hangnail). Precautions are as for anemia, outlined earlier in this chapter.

Anticipating potential side effects of medications used in the treatment of leukemia can help the therapist better understand client reactions during the episode of care. 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. Exercise intensity and duration and activity modifications are necessary for clients with anemia.

Clients with a history of prolonged corticosteroid use should be assessed for muscle weakness and avascular necrosis of the hips and shoulders.

Joint Involvement

Arthralgias or arthritis occurs in approximately 12% of adults with chronic leukemia, 13% of adults with acute leukemia, and up to 60% of children with ALL. Articular symptoms are the result of leukemic infiltrates of the synovium, periosteum, or periarticular bone or of secondary gout or hemarthrosis. Asymmetrical involvement of the large joints is most commonly observed. Pain that is disproportionate to the physical findings may occur, and joint symptoms are often transient.