Lymphedema is the general term for a set of pathologic conditions in which there is excessive, regional interstitial accumulation of protein-rich fluid. It can be either a primary or acquired (secondary) condition. Lymphedema usually involves abnormalities in the regional lymphatic drainage of the extremities (either upper or lower, or both), although visceral lymphatic abnormalities can also occur. Generalized developmental insufficiency of the lymphatic circulation is not compatible with life (1).

In addition to the chronic changes in the size and structure of the subcutaneous and integumentary structures, lymphedema may have a substantial effect on quality of life and the perception of well-being (2). Patients with lymphedema manifest anxiety, depression, adjustment problems, and difficulty in vocational, domestic, social, and sexual domains (3–5). Among women who develop postmastectomy lymphedema, psychological factors may reduce compliance with available treatments (6,7).

**PATHOPHYSIOLOGY OF LYMPHEDEMA**

In contrast with venous edema, in which enhanced capillary pressure can indirectly stimulate lymph production, lymphedema is caused by a reduction in lymphatic transport. Several anatomic problems can lead to lymphatic stasis, including lymphatic hypoplasia and functional insufficiency or absence of lymphatic valves (8). Some patients may have an impairment in the intrinsic contractility of the lymphangion (the segmentally contracting, functional vascular unit of the lymphatic circulation) (8). Secondary lymphedema, which is much more common than the primary form, can develop as a consequence of any surgical, traumatic, inflammatory, or neoplastic disruption or obstruction of lymphatic pathways.

Much of the current understanding of the pathophysiology of lymphedema derives from the experimental work of Olszewski (9) in dogs. In this experimental model, mechanical interruption of lymph vessels of the limb was sufficient to produce lymphedema after a period of months to years. Before overt edema occurred, marked lymphangiographic changes were observed in the absence of detectable accumulation of interstitial fluid. Eventually, lymph collectors became fibrotic and lost their normal permeability. In addition, electron micrographs of skin lymph capillaries disclosed permanent incompetence of the interendothelial junctions. In contrast to the pattern observed in other edematous states that occasion venous hypertension, like congestive heart failure and thrombotic venous disorders, the advent of chronic lymphedema in these limbs was not accompanied by the lymphatic hypertension that might otherwise have been theoretically predicted.

Once established, lymphatic stasis fosters the accumulation of protein and cellular metabolites, such as macromolecular protein and hyaluronan, within the extracellular space. Impaired lymphatic transport produces accumulation of both macromolecular protein and of hyaluronan (10). This is followed by an increase in the tissue colloid osmotic pressure, which leads to water accumulation and increased interstitial hydraulic pressure.

Chronic lymph stasis often produces an increase in the number of fibroblasts, adipocytes, and keratinocytes in the edematous tissues. Mononuclear cells (chiefly macrophages) often demarcate the chronic inflammatory response (11,12). In most patients, there is an increase in collagen deposition, with adipose and connective tissue overgrowth in the edematous skin and subcutaneous tissues (13). Histopathologic findings in chronic lymphed-
Lymphedema include thickening of the basement membrane of lymphatic vessels, fragmentation and degeneration of elastic fibers, increased numbers of fibroblasts and inflammatory cells, and increased amounts of ground substance and pathological collagen fibers (14). Ultimately, these processes lead to progressive subcutaneous fibrosis.

**CLASSIFICATION OF LYMPHEDEMA**

The simplest classification of lymphedema relies upon a differentiation between primary and secondary causes (15). Primary lymphedemas are often classified according to the age at which the edema first appeared. Congenital lymphedema is apparent at birth or becomes recognized within the first 2 years of life. Lymphedema praecox is most commonly detected at the time of puberty, but may appear as late as the third decade of life. Lymphedema tarda typically appears after age 35 years. Recent advances within the genetic investigation of hereditary lymphedemas have permitted the identification of possible candidate genes for lymphedema-distichiasis (16). Linkage analysis of family cohorts with cholestasis-lymphedema syndrome has similarly resulted in successful chromosomal mapping of the disease locus (17). Genetic mapping of the autosomal dominant form of hereditary primary lymphedema (Milroy’s disease) (18) suggests that the disease can be ascribed to a mutation inactivates the VEGFR3 tyrosine kinase signaling mechanism that is felt to be specific to lymphatic vessels (19).

In congenital lymphedema, the swelling can involve only a single lower extremity, but edema of multiple limbs, the genitalia, and even the face can be seen. Bilateral leg swelling and involvement of the entire lower extremity is more likely in congenital cases than in other forms of primary lymphedema (20).

When cases of congenital lymphedema cluster in families, an autosomal dominant pattern of transmission is most frequently described. However, isolated instances of lymphedema are much more common (21). There is a strong association between intrauterine and congenital lymphatic dysfunction and several heritable chromosomal abnormalities (15).

Lymphedema praecox, the most common form of primary lymphedema, is responsible for as many as 94% of the cases in large reported series. The estimated 10:1 ratio of females to males suggests that estrogenic hormones are involved (21). The edema is usually unilateral and is limited to the foot and calf in the majority of patients (21).

Lymphedema tarda is relatively uncommon, and accounts for fewer than 10% of cases of primary lymphedema. An alternative classification for primary lymphedema relies upon morphologic characteristics (20). Distal hypoplasia of the lymphatics is typically associated with bilateral peripheral edema of the lower extremities. There is usually a family history of similar symptoms, a female predominance, and a tendency for indolent progression. When isolated proximal obstructive hypoplasia is observed, clinical involvement of the entire limb is more likely, usually accompanied by relentless worsening of the edema. Patients who have unilateral edema involving the entire lower extremity are likely to have lymphatic hypoplasia with megalymphatics, although this syndrome is uncommon.

Secondary lymphedema develops after disruption or obstruction of lymphatic pathways by other disease processes, or as a consequence of surgery or radiotherapy. Secondary lymphedema is much more common than the primary form. Edema of the arm after axillary lymph node dissection is probably the most common cause of lymphedema in the United States (22), although its global incidence is overshadowed by filariasis, which affects more than 90 million people (23).

The reported incidence of edema after mastectomy varies substantially, from 6% to 80% among published series (22). Differences in the incidence estimates may reflect variations in the definition of edema. A recently published series suggests that, with up to 13 years of follow-up, a 14% late incidence of postmastectomy lymphedema can be expected in surgically treated patients with adjuvant postoperative irradiation (24). Furthermore, in a second recent series, 21 of 110 patients treated with breast-conserving techniques also developed chronic postsurgical arm swelling (25). Thus, despite improvements in surgical and radiotherapeutic techniques, lymphedematous complications cannot be obviated and are, in fact, not uncommon (26,27). Edema of the leg may occur after pelvic or genital cancer surgeries, particularly when there has been inguinal and pelvic lymph node dissection or irradiation. Its reported frequency varies between 1% and 47% (28,29). Pelvic irradiation increases the frequency of leg lymphedema after cancer surgery (30).

**NATURAL HISTORY OF LYMPHEDEMA**

The natural history of lymphedema is uncertain, particularly as it may be asymptomatic. For example, as late as 3 years after radical mastectomy and axillary node dissection, more than 20% of women remain free of any clinical evidence of lymphatic impairment, despite the extensive iatrogenic destruction of the lymphatic architecture in these patients (31,32). Similarly, in many forms of primary lymphedema, there may be a protracted phase of apparently normal lymphatic function, despite an inherited anatomic or functional disturbance of this microcirculation. This latent phase of lymphedema may represent...
a balance between the existing increased lymph load and a reduced outflow capacity (32). Lymphedema may become manifest when compensatory mechanisms, which may include lymphatic regeneration, become inadequate to withstand the requirement for lymphatic flow.

The precipitating factors for the appearance of overt lymphedema are not known (33). At the onset of clinical lymphedema, swelling of the involved extremity is typically described as puffy, and the disturbance may be intermittent. With chronicity, the involved structures develop the characteristic features of induration and fibrosis (13), which may be substantial (Figure 1).

In many patients, the maximal increase in girth of the involved limb is determined within the first year after onset, unless there are supervening complications like recurrent cellulitis. The propensity to recurrent soft-tissue infection is one of the most troublesome aspects of longstanding lymphedema. Microbial growth is encouraged by the surplus of fluid and accumulated proteins. Lymphatic dysfunction also impairs local immune responses (34). The impaired regional immunosurveillance of lymphedema is supported by the observed impairments in the cutaneous immune responses in patients with post-mastectomy lymphedema (34). With recurrent infections, there is progressive damage of lymphatic capillaries. In one reported series, acute cellulitis in the arm was observed in 6% of patients during 42 months of surveillance after breast cancer therapy (35).

The clinical presentation of soft-tissue infection in lymphedema can be variable, from very subtle exacerbations of lymphedema characterized by skin changes without fever, to rapidly progressive soft tissue infection with high fever and systemic toxicity. Recurrent attacks of cellulitis further damage the cutaneous lymphatics, worsen the skin quality, and aggravate the edema.

In very rare cases, chronic lymphedema may be complicated by the local development of malignant tumors such as lymphangiosarcomata, which can be either sclerotic plaques or multicentric lesions with blue-tinged nodules or bullous changes (36). Other cutaneous malignancies that have been observed in association with chronic lymphedema (37) include lymphoma, melanoma (38), squamous cell carcinoma (39), and Kaposi’s sarcoma (40).

**DIAGNOSIS OF LYMPHEDEMA**

In most patients with advanced lymphedema, the characteristic clinical presentation and physical findings estab-
lish the diagnosis with near certainty (41). However, early in the natural history, or with presentations of mild or intermittent swelling, it may be more difficult to distinguish lymphedema from other edematous states. Several physical features distinguish lymphedema from other causes of chronic edema of the extremities. Among these are the classic changes of cutaneous and subcutaneous fibrosis (peau d’orange), and the Stemmer sign, which is an inability to tent the skin on the dorsum of the digits of the feet. Although the Stemmer sign has not been validated, it was initially reported to discriminate patients with lymphedema (42). Lymphedema in the legs often produces preferential swelling of the dorsum of the foot, as well as the characteristic blunt, “squared-off” appearance of the digits in the involved extremity.

When the physical examination does not conclusively support the diagnosis of lymphedema, additional evidence may be necessary to confirm impaired lymphatic function. Available tests include isotopic lymphoscintigraphy, indirect and direct lymphography, lymphatic capillaryscopy, magnetic resonance imaging (MRI), and ultrasonography. Direct lymphography is generally limited to the evaluation of candidates for lymphatic surgery. Isotopic lymphoscintigraphy is the most commonly used test and is generally considered to be the gold standard for the diagnosis of lymphedema. A radio-labeled macromolecular tracer (e.g., sulfur colloid) is administered into the subdermal, interdigital region of the affected limb. The lymphatic transport of the radiolabeled macromolecule can be monitored in a semiquantitative fashion with a gamma camera. Major lymphatic trunks and lymph nodes can be visualized. Typical abnormalities in lymphedema include absent or delayed transport of tracer, absent or delayed visualization of lymph nodes, crossover filling with retrograde backflow, and dermal backflow (43–45). In a series of more than 700 patients, peripheral lymphatics were visualized readily (46). These imaging techniques can also be used to monitor the effects of therapy and to facilitate invasive therapies for chylous reflux (the reflux of intestinal lymph to the skin as a consequence of lymphatic valvular incompetence) (47).

Magnetic resonance imaging and computerized tomographic (CT) imaging allow the objective documentation of structural changes attributable to lymphedema (48). The characteristic absence of edema within the muscular compartment helps to distinguish lymphedema radiographically from other forms of edema. In addition, the honeycomb distribution of edema within the epifascial plane, along with thickening of the skin, is characteristic of lymphedema. The anatomic delineation of lymphatic and nodal architecture derived from MR imaging can complement the functional assessment provided by lymphoscintigraphy (45,49).

Less commonly employed techniques include tissue tonometry (50,51) and bioelectric impedance analysis (52–55). These techniques allow detection of small changes in tissue turgor and may have utility in the detection of subclinical states of lymphatic impairment, as well as in the serial assessment of the response to treatment.

DIFFERENTIAL DIAGNOSIS

Chronic Venous Insufficiency and Postphlebitic Syndrome

This common condition is often confused with lymphedema of the legs. Its distinguishing clinical features include aching discomfort in the lower extremities during sitting or standing and chronic pruritus, particularly overlying the incompetent communicating veins (56). Physical findings include cutaneous deposits of hemosiderin, dusky discoloration and venous engorgement with dependence, cutaneous varicosities, and if advanced, ulceration of the skin.

Myxedema

This special form of edema arises when abnormal deposits of mucinous substances accumulate in the skin as a result of thyroid disease (57). Hyaluronic acid-rich protein deposition in the dermis produces edema that, in turn, disrupts structural integrity and reduces the elasticity of the skin. In thyrotoxicosis, this process is focal in the pretibial region (58); in hypothyroidism, the myxedema is more generalized. Myxedema is characterized by roughening of the skin of the palms, soles, elbows and knees; brittle, uneven nails; dull, thinning hair; yellow-orange discoloration of the skin; and reduced sweat production. However, it may be difficult to distinguish from lymphedema.

Lipedema

This condition affects women, or men with a feminizing disorder. The edema is caused by the abnormal accumulation of fatty substances in the subcutaneous regions, typically between the pelvis and the ankle, with sparing of the feet. Although the pathophysiology of this disorder is uncertain, it does involve an excess of subcutaneous adipocytes with structural alterations in the small vascular structures within the skin. Indeed, regional abnormalities of the circulation may cause the initial accumulation of fat in the affected regions (59). The characteristic distribution, with sparing of the feet, should suggest the correct diagnosis. The absence of a Stemmer’s sign is an additional clue. Most often, lipedema arises within 1 to 2 years after the onset of puberty. In addition to the near lifelong history of heavy thighs and hips, affected patients often complain of painful swelling. In addition, there is commonly a propensity to bruising, perhaps a result of increased fragility of capillaries within the adipose tissue.
Malignant Lymphedema

In the United States, the leading cause of lymphedema of both upper and lower extremities is neoplastic disease and related therapies. Thus, in the differential diagnosis of new or worsening lymphedema, recurrence of cancer, leading to intrinsic or extrinsic obstruction of lymph flow, must be considered. Malignant lymphedema often develops rapidly and progresses relentlessly (60). In addition, pain, which is generally absent in benign lymphedema, may be present. The malignant form of lymphedema tends to begin centrally. Often, the tissue is quite firm from the outset, without the soft consistency seen in the early stages of benign lymphedema.

LYMPHEDEMA TREATMENT

General Therapeutic Measures

Lymphedema is a chronic condition that requires lifelong attention. Meticulous attention to control of edema may reduce the likelihood of disease progression and limit the incidence of soft-tissue infections (41). Aggressive implementation of decongestive lymphatic therapy is the mainstay of most therapeutic recommendations (61–63). This complex form of physical therapy integrates meticulous skin care, massage, exercise, and use of compressive elastic garments. Decongestive lymphatic therapy can acutely reduce limb volume as well as provide long-term benefits owing to the acceleration of lymph transport in the edematous limb and the dispersal of accumulated protein (63).

The specialized massage technique for these patients (manual lymphatic drainage or therapy) is intended to enhance lymphatic contractility and to augment and redirect lymph flow through the nonobstructed cutaneous lymphatics. Manual lymphatic drainage should not be confused with other forms of therapeutic massage that have no effect on lymphatic contractility. The mild tissue compression during manual lymphatic drainage produces better filling of the initial lymphatics and enhances transport capacity, through the cutaneous lymphatic dilatation and development of accessory lymph collectors (64).

During the acute approach to volume reduction, nonelastic, compressive wrappings should be applied after each session of manual lymphatic drainage and worn during exercise to prevent reaccumulation of fluid and to promote lymph flow during exertion. Complete decongestive physiotherapy, including manual lymphatic drainage, compression bandaging, garments and skin care, is an effective treatment modality for many patients with primary and secondary lymphedema (Figure 2). In a recent series of 299 patients, with an average follow-up of 9 months, there were average reductions of 59% in upper extremity volume, and 68% in lower extremity volume, with maintenance of 90% of this benefit during follow-up in compliant patients (65). In another, subsequent prospective analysis of therapeutic responses in chronic lymphedema, short-term decongestive lymphatic therapy, when coupled with focused patient instruction in long-term self-care, was documented to be efficacious, with sustainable long-term therapeutic responses (66).

The use of intermittent pneumatic compression with single or multichamber pumps removes excess fluid from the extremity and should be considered as an adjunctive approach (41). Pneumatic compression techniques, however, cannot clear edema fluid from the adjacent trunk. Consequently, as fluid shifts occur during pneumatic compression, the root of the limb must be decompressed with manual techniques. The use of any form of compressive therapy requires a sufficient arterial blood supply to the limb. In cases of limb ischemia, compressive therapy, which can compromise arterial blood flow and promote severe ischemia and necrosis, is contraindicated.

The prescription of compressive garments is a necessary adjunct to all other forms of lymphedema therapy. Relatively inelastic sleeves and underwear that transmit high-grade compression (40 to 80 mm Hg) will prevent reaccumulation of fluid after successful decongestive treatments. Garments must be fitted properly and replaced when they lose their elasticity (every 3 to 6 months).

Other treatments are under investigation. Low-level laser therapy may be effective in postmastectomy lymphedema; in a series of 10 patients, subjective improvement was accompanied by objective documentation of improved bioimpedance and reduced extracellular and intracellular fluid accumulation (67). In addition, some promising responses have been reported after local hyperthermia (68) and the intra-arterial injection of autologous lymphocytes (69). In the latter approach, it is postulated that regression of edema is linked to the expression of L-selectin, a lymphocyte-specific adhesion molecule (69).

Pharmacotherapy and Diet

The reported benefit of coumarin (5,6-benzo-[a]-pyrone) in lymphedema (70) is ascribed to its stimulatory effect upon cutaneous macrophages and, thereby, upon local proteolysis. Coumarin also stimulates other cellular elements of the immune system and may promote protein reabsorption. Efficacy has been demonstrated in lymphedema of the arms and legs (70), as well as in filarial elephantiasis (71). A meta-analysis of 50 clinical trials suggests that these slow-acting compounds can provide a mean decrease in edema volume of about 55% (72). However, coumarin administered orally may cause idiosyncratic hepatitis. Topical coumarins are under investigation; none is available for clinical use in the United States.
States. There are scant, but provocative, data concerning the therapeutic benefit of augmenting dietary flavonoids (73). These naturally-occurring compounds, particularly the rutin derivatives, are thought to benefit lymphedema through protective effects on vascular endothelium and general improvement in the microcirculation. In addition, there is one report that suggests that dietary restriction of long-chain triglycerides provides some relief of edema in these patients (74).

**Surgical Therapy**

Invasive approaches may be necessary in patients with unacceptable subcutaneous adipose hypertrophy and fibrosis (75–77). Two main surgical approaches have been utilized. In excisional procedures, part or all of the lymphedematous epifascial tissue is removed, whereas microsurgical interventions involve the creation of lymphaticolymphatic, lymphaticovenous-lymphatic, lymphaticovenous, or lymph node-venous anastomoses (78). Although lymphaticovenous anastomosis (79,80) and transplantation of lymph collectors have been advocated (81–83) for chronic lymphedema, the long-term results of such interventions have not been uniformly encouraging (81,84). Debulking surgical procedures are designed to remove redundant skin and subcutaneous tissue (85), often with wide excision and split skin grafting (86). The procedures do not improve lymphatic drainage. Other surgical techniques include treatment with transfer of an omental pedicle (87) or interposition of a vascular pedicle flap to serve as a lymphatic wick (88). Surgical approaches, however, may cause further damage to cutaneous lymphatics and may lead to skin necrosis, papillomatosis, ulceration, fistula formation, and edema exacerbation (75,89). Additional surgical risks include sensorineural damage, hypertrophic scarring, ulceration, graft necrosis, and exophytic keratosis. Nevertheless, partial excision may be indicated for cases of advanced fibrosis or frank elephantiasis.

Suction techniques may also be used to remove excess subcutaneous tissue. Surgical liposuction of chronic postmastectomy lymphedema has been reported to produce excellent results, with sustained reduction of excess volume (89,90). In one series, an average long-term reduction of edema volume of 106% (in some patients, there is actually surgical overcorrection so that, when compared with the normal limb, the therapeutic response is actually >100%) was observed in 28 patients with an average edema volume of 1,845 mL (89). Liposuction with long-term decongestive compression therapy re-
duces edema volume more successfully than does compression therapy alone. However, the volume reduction will not be successful unless compression therapy is maintained after the surgical intervention (91).

ACKNOWLEDGMENT
The assistance of Dr. Andrzej Szuba in the preparation of the figures is gratefully acknowledged.

REFERENCES