Lymphedema: classification, diagnosis and therapy

Andrzej Szuba and Stanley G Rockson

Abstract: This review presents the diagnostic features, the pathophysiology and the available therapies for lymphedema. This disease is often able to be diagnosed by its characteristic clinical presentation, yet, in some cases, ancillary tests might be necessary to establish the diagnosis, particularly in the early stages of the disease and in edemas of mixed etiology. These diagnostic modalities are also useful in clinical studies.

Available modalities include isotopic lymphoscintigraphy, indirect and direct lymphography, magnetic resonance imaging, computed tomography and ultrasonography. Lymphedema may be primary or secondary to the presence of other diseases and/or to the consequences of surgery. Primary lymphedema may occur at any phase of life but it most commonly appears at puberty. Secondary lymphedema is encountered more often. The most prevalent worldwide cause of lymphedema is filariasis, which is particularly common in south-east Asia. In the USA, postsurgical lymphedema of the extremity prevails. Complications of chronic limb lymphedema include recurrent cellulitis and lymphangiosarcoma.

Most patients are treated conservatively, by means of various forms of compression therapy, including complex physical therapy, pneumatic pumps and compressive garments. Volume reducing surgery is performed rarely. Lymphatic microsurgery is still in an experimental stage, although a few centers consistently report favorable outcomes.

Key words: compressive therapy; lymphedema; lymphoscintigraphy; manual lymphatic drainage; microvascular surgery; pneumatic compression

Definition and description of different types of lymphedema

Lymphedema can be defined as the tissue fluid accumulation that arises as a consequence of impaired lymphatic drainage. This reduction of lymphatic flow can result from either congenital or acquired anomalies of lymphatic outflow. Although lymphedema usually affects one or more of the limbs, its effects can manifest in other organs. Whatever the pathogenesis, it is most often a chronic, unrelenting condition, posing long-term physical and psychological difficulties for the patient and a complex therapeutic challenge for the physician.

Hereditary lymphedema (Table 1), and heritable conditions associated with lymphedema, are rather rare: the reported frequency varies from single case reports to an estimate approximating 1:500 live births (Klinefelter’s syndrome). In contradistinction, there is a large, and growing, prevalence of acquired forms of lymphedema of the extremity. This is attributable almost exclusively to the large number of patients submitted for breast and pelvic cancer surgery and due, paradoxically, to the increasingly successful outcomes after oncologic therapy.

Diagnostic methods

In many cases of advanced sustained disease, a typical history and characteristic clinical presentation establish the diagnosis of lymphedema with near certainty. Nevertheless, additional tests are sometimes necessary to confirm the presence of impaired lymphatic flow and/or the typical pattern of abnormal fluid distribution within the tissues. The diagnosis is more difficult to ascertain in the early stages, particularly when edema is mild or intermittent.

Available tests include isotopic lymphoscintigraphy, indirect and direct lymphography, lymphatic capillaroscopy, magnetic resonance imaging (MRI), axial tomography and ultrasonography.

Direct lymphography is now rarely used: its use should be restricted to those patients who are potential candidates for lymphatic surgery. Lymphatic capillaroscopy is available only in specialized centers. In contrast, indirect lymphography, though not commonly employed, is quite a useful diagnostic modality.

Table 1  Hereditary lymphedema*.

<table>
<thead>
<tr>
<th>Chromosomal aneuploidy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner syndrome</td>
<td></td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td></td>
</tr>
<tr>
<td>Trisomy 21</td>
<td></td>
</tr>
<tr>
<td>Trisomy 13</td>
<td></td>
</tr>
<tr>
<td>Trisomy 18</td>
<td></td>
</tr>
<tr>
<td>Triploidy</td>
<td></td>
</tr>
</tbody>
</table>

| Dysmorphogenic–genetic disturbances    |       |
| Klippel–Trenaunay–Weber syndrome       |       |
| Noonan syndrome                       |       |
| Noon–Milroy hereditary lymphedema      |       |
| Meige lymphedema                       |       |
| Neurofibromatosis type I (von Recklinghausen) |   |
| Dichiathasis lymphedema                |       |
| Lymphedema–hypoparathyroidism syndrome |       |

*Adapted from Greenlee. 1

Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA
Address for correspondence: Stanley G Rockson, Division of Cardiovascular Medicine, Falk Cardiovascular Research Center, Stanford, CA 94305, USA.

© Arnold 1998

1358-863X(98)VM225RA
Isotopic lymphoscintigraphy

Isotopic lymphoscintigraphy is a reliable and reproducible method for confirming the diagnosis of lymphedema.\textsuperscript{2-4} The radiolabelled macromolecular tracer (\textsuperscript{99m}Tc-antimony sulfide colloid or \textsuperscript{99m}Tc-rhenium sulfate, among others) is injected intra- or subdermally within one of the interdigital spaces of the affected limb. The lymphatic transport of the macromolecule is tracked with a gamma camera. The rate of tracer disappearance from the injection site and the accumulation of counts within the lymph node are both quantifiable. Various stress tests have been recommended to produce reliable quantitative results.\textsuperscript{2,3,5} Although various routes of administration may be utilized, subdermal injection has been recommended for optimal evaluation of the epifascial lymphatic transport.\textsuperscript{3} This may add useful information towards the evaluation of edema; according to Bräutigam et al, only evaluation of both epifascial and subfascial lymphatic compartments will permit an accurate assessment of lymphatic transport in the lower extremities.\textsuperscript{3} Lymphoscintigraphy enables the adequate assessment of lymphatic function and the visualization of major lymphatic trunks and lymph nodes. Typical abnormalities observed in lymphedema include dermal backflow, absent or delayed transport of tracer, cross-over filling with retrograde backflow, and either absent or delayed visualization of the lymph nodes.\textsuperscript{2,4,6}

Lymphoscintigraphy is probably the best of the readily available methods for the functional evaluation of the lymphatic system. Nevertheless, the technique does require standardization for the type and amount of injected tracer, for the site of injection (intradermal or subdermal), and for the stress protocol used.\textsuperscript{7}

Magnetic resonance imaging

The technique of MRI can be useful in the differential diagnosis of limb edema. In lymphedema, the images reveal a characteristic distribution of edema within the epifascial compartment, disclosing a honeycomb pattern along with thickening of the skin. In venous edema, both the epi- and subfascial compartments are affected, while in lipedema, there is fat accumulation without fluid.\textsuperscript{8-11} Magnetic resonance imaging is also helpful in the identification of lymph nodes, enlarged lymphatic trunks, and in the differentiation of the various causes of lymphatic obstruction in secondary lymphedema. The anatomic information derived from MRI may complement the functional assessment provided by lymphoscintigraphy. At times, these complementary sources of information are necessary to establish the diagnosis and to make the requisite therapeutic decisions.\textsuperscript{6}

Magnetic resonance images of the lymphatic system can be enhanced with newer contrast media, like preparations of iron oxide. These have already been shown to have promising applications in animal studies.\textsuperscript{12,13} The initial human studies with iron colloid have demonstrated the safety of this agent in normal volunteers.\textsuperscript{14}

Computed tomography

Computed tomography (CT) also has a diagnostic use in the evaluation of the swollen limb.\textsuperscript{15} The CT technique provides an anatomic definition of edema localization (subfascial versus epifascial), and can identify skin thickening as well as the characteristic honeycomb pattern of the subcutaneous tissue in lymphedema. Computed tomogra-

phy scans may be used to monitor responses to therapy in lymphedema through serial measurements of the cross-sectional area and tissue density in the tissue compartments of interest.\textsuperscript{16}

Indirect lymphangiography

Indirect lymphangiography utilizes water-soluble, iodinated contrast media that are infused intradermally and enter the lymphatics. Pictures of the lymphatics are obtained using mammography films or xeroradiography.\textsuperscript{3,17} This technique is particularly useful in visualizing local skin lymphatics and lymphatic trunks. Using this method, four types of lymphatic pathology in lymphedema have been described, based upon the visualized patterns of initial and peripheral lymphatics.\textsuperscript{3,18}

In addition to its investigative applications, indirect lymphangiography maybe useful in the assessment of lymphatic anatomy prior to reconstructive surgery, as well as in the assessment of lymphatic anatomy in patients with localized changes,\textsuperscript{19} and, more generally, as an aid in the diagnosis of the more complex presentations of lymphedema.\textsuperscript{3}

Contrast lymphography

Contrast lymphography is accomplished through the direct injection of iodine-based, lipid-soluble contrast media into subcutaneous lymphatics, which are first identified by the subcutaneous injection of the dye, patent blue, and subsequently cannulated. The technique was first performed by Servelle\textsuperscript{20} and later refined and standardized by Kinmonth.\textsuperscript{21,22} Contrast lymphography is useful for the visualization of the lymphatic anatomy and is used prior to reconstructive lymphatic surgery. However, its use has declined recently and been superseded by lymphoscintigraphy as the primary diagnostic tool for the assessment of lymphatic function. In addition, the technique of contrast lymphography poses distinct technical difficulties and may, in fact, induce exacerbation of lymphatic malfunction through accumulation and pooling of the oil-based contrast media.

Ultrasound examination

Ultrasound examination is utilized as a complementary tool for the non-invasive evaluation of the swollen extremity. In patients with lymphedema, thickening of the cutaneous, epifascial and subfascial compartments has been ultrasonographically observed. This contrasts with MRI observations, where the subfascial compartment was felt to be unaffected.\textsuperscript{8,10} High frequency ultrasound (20 MHz) reveals characteristic patterns of cutaneous fluid localization in various types of edema. In lymphedema, there is a distinctively uniform pattern of distribution.\textsuperscript{23} This imaging technique has applications both in differential diagnosis and in therapeutic monitoring, although further refinement may become necessary to better characterize the spectrum of subcutaneous fibrosis that can be encountered in lymphedematous skin.

Pathogenesis and clinical presentation

Lymphedema can be primary or secondary as a consequence of surgery and/or other diseases (Tables 1, 2 and 3).
been described, distribution. A pattern of autosomal dominant transmission has the age of 35 years. Of the third decade of life; and tarda, which begins after 2 years of birth; precox, the most common subtype, which occurs either at puberty or by the beginning congenital form) of lymphedema are much more common.

Three types of primary lymphedema have been recognized (Table 2).22–24 Congenital, which is present at birth or occur in the first 2 years of life; precox, which is most common (non-neonatal form) congenital form) of lymphedema. The precox form accounts for 77–94% of all primary forms. The term ‘Meige disease’ should be reserved for the specific familial form of lymphedema, with its recessive pattern of inheritance, which appears at puberty. Kinmonth found a familial occurrence in 16 of 95 non-congenital primary lymphedema patients22 and Smeltzer in 7 of 105. Lymphedema precox is much more common in female patients, with an approximate male:female ratio, 4.8:1. A less pronounced female preponderance has also been reported (female: male ratio, 4.8:1). The edema is usually unilateral and limited to the foot and calf in the majority of patients. The common initial appearance at puberty and preponderance of affected females has led to the hypothesis that estrogen may play a pathogenetic role in the development of lymphedema. Kinmonth has classified the onset of disease after 35 years of age as lymphedema tarda. He found 12 such patients among his 107 cases of primary lymphedema.22

The introduction of lymphography has resulted in a further refinement of the diagnostic classification schema (Table 3), although some authorities have questioned the validity of this approach.22 Wolfe and Kinmonth have proposed prognostic and clinical correlates to the different lymphangiographic patterns of the disease. Distal hypoplasia or aplasia of the leg lymphatics was present in 31.9% of patients, and predominantly correlated with the presence of bilateral, peripheral leg lymphedema. This pattern is usually slowly progressive, if at all, after the first year. It affects predominantly women and rarely requires surgery. A familial occurrence was also more frequent (22%). Isolated proximal obstructive hypoplasia was seen in 21% of the patients. Clinically, the whole limb was usually affected (82%), edema tended to increase without interruption and, in this series, often required surgery (32%). Distal hypoplasia affects women and men equally. The presence of concurrent distal and proximal lymphatic occlusion accounted for 32.3% of patients. Megalymphatics and bilateral hyperplasia was observed in 14.4% of cases, and men were more often affected than women (male:female ratio, 3:2). Edema usually increased progressively and volume reducing surgery was often required in the involved extremity. Patients with megalymphatics usually had unilateral, whole leg edema and often presented with cutaneous angiomas or chylous reflux.

The appearance of primary lymphedema is usually spontaneous, although some patients relate its onset to ante-

### Table 2 Primary lymphedema (clinical classification).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency (% of all primary forms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital (onset &lt;2 years after birth)</td>
<td>6–12</td>
</tr>
<tr>
<td>Familial, autosomal dominant (Nonne–Milroy disease)</td>
<td></td>
</tr>
<tr>
<td>Familial, non-dominant inheritance</td>
<td></td>
</tr>
<tr>
<td>Sporadic (most common congenital form)</td>
<td></td>
</tr>
<tr>
<td>Lymphedema precox (onset between 2–35 years)</td>
<td>77–94</td>
</tr>
<tr>
<td>Familial, autosomal recessive (Meige disease)</td>
<td></td>
</tr>
<tr>
<td>Sporadic (83–94% of all lymphedema precox)</td>
<td></td>
</tr>
<tr>
<td>Lymphedema tarda (onset after 35 years of age)</td>
<td>11</td>
</tr>
</tbody>
</table>

### Table 3 Lymphangiographic classification of primary lymphedema.22

A. Congenital primary lymphedema

1) Congenital aplasia or hypoplasia of peripheral lymphatics (edema present at, or appearing within, 2 years of birth).

2) Congenital abnormalities of the abdominal or thoracic lymph trunks.

3) Congenital valvular incompetence (always associated with megalymphatics and often with chylous reflux).

B. Acquired primary lymphedema

1) Intraluminal or intramural lymphangio-obstructive edema.
   a) Distal: acquired obliteration of distal lymphatics, cause unknown.
   b) Proximal: acquired obliteration of the lymphatics in the proximal part of the limb, usually associated with distal dilation, cause unknown.
   c) Combined: acquired obliteration of all the lymphatics of the limb.

2) Obstruction of the lymph nodes by hilar fibrosis; may coexist with lymphangio-obstructive edema, and acquired valvular incompetence may follow.

### Primary lymphedema

Three types of primary lymphedema have been recognized (Table 2):22–24 congenital, which is present at birth or recognized within 2 years of birth; precox, the most common subtype, which occurs either at puberty or by the beginning of the third decade of life; and tarda, which begins after the age of 35 years. Congenital lymphedema may have a familial distribution. A pattern of autosomal dominant transmission has been described,25–27 but alternative patterns of inheritance have been observed also.28,29 Nevertheless, sporadic cases of lymphedema are much more common.30–32 The various forms of primary lymphedema show an association with heritable chromosomal abnormalities, like Turner syndrome,33–35 yellow nail syndrome,36–38 and others (Table 2).
cedent injury.\textsuperscript{32} Initially, the swelling is typically puffy and intermittent. Later, the involved structures become indurated and fibrosed.\textsuperscript{12,13} The extent of the swelling is usually demarcated within the first year\textsuperscript{30,32} but in some patients there may be a continual increase in girth.

Although lymphangiography is now rarely used because of the risk of exacerbating the lymphedema, it remains a useful tool for the identification of patients who might benefit from reconstructive lymphatic surgery and it should be performed if reconstructive surgery is contemplated.

**Secondary lymphedema**

Secondary lymphedema develops as a consequence of disruption or obstruction of the lymphatic pathways by surgery or other disease processes (Table 4). Secondary lymphedema is much more common than the primary form. Its global incidence can be ascribed, predominantly, to filariasis, which accounts for over 90 million afflicted individuals.\textsuperscript{43} Nevertheless, there is a growing number of lymphedema cases that are arising as a consequence of neoplastic disease, both through direct lymphatic invasion and, iatrogenically, through treatment of the neoplasm.

**Iatrogenic lymphedema**

Disruption of the lymphatic pathways may be caused by surgery and/or radiation therapy, which produce fibrosis. Surgical disruption of the lymphatic pathways may be intentional (lymph node dissection for cancer surgery) or accidental (e.g. during iliofemoral revascularization). In western society, the most common examples of secondary lymphedema would be the arm edema in women after axillary lymph node dissection for breast cancer, and lymphedema of the leg after inguinal and pelvic lymph node dissection for pelvic neoplasms.

Edema of the arm after axillary lymph node dissection is probably the most common cause of lymphedema in the USA. The incidence of edema after mastectomy varies substantially among different published series, from 5.5% to 80%.\textsuperscript{44} In a large series of more than 4000 women who were surgically treated for breast cancer, Schunemann observed arm lymphedema in 27% of the patients.\textsuperscript{45} He demonstrated that both the extent of breast surgery and the subsequent use of radiation correlated with a likelihood of postmastectomy edema. Furthermore, it was conjectured that changes in surgical technique and the prevalence of radiation therapy may have accounted for the reduced incidence of lymphedema (from 38% to 18%) in his series. Others have also described a correlation with radiation,\textsuperscript{44,46,47} surgical technique\textsuperscript{46,47} and obesity.\textsuperscript{44,46,48}

The prevalence of arm swelling after breast cancer surgery may be underestimated because milder degrees of arm edema might readily be overlooked. In a careful prospective study of 360 patients undergoing breast cancer therapy, arm lymphedema was found in 42%.\textsuperscript{49}

Edema of the leg is comparably common after a pelvic or genital cancer operation, particularly when there has been inguinal/pelvic lymph node dissection and/or irradiation. The reported frequency varies between 1.2% and 47%.\textsuperscript{50–53} Pelvic irradiation correlates with an increase in the frequency of leg lymphedema.\textsuperscript{54}

Lymphedema has also been observed following other surgical techniques, like ilio-femoral bypass surgery,\textsuperscript{55} which can produce traumatic or fibrotic disruption of the major lymphatics.

**Traumatic lymphedema**

Injury of the lymphatic channels can lead to obstruction and the development of lymphedema.\textsuperscript{56} Curiously, some patients with primary lymphedema report injury as an initiating event.\textsuperscript{32}

**Post-infectious lymphedema**

Allen, in his series of 300 patients with lymphedema,\textsuperscript{31} found primary inflammatory lymphedema in 41 cases (13.7%), and described single or recurrent attacks of streptococcal cellulitis or lymphangitis, which resulted in swelling of the limb. These attacks have a sudden onset and are accompanied with high grade fever, chills and general malaise. The involved extremity is swollen, hot, tender and erythematous, and the proximal lymph nodes are swollen and tender. After resolution, which requires 4 to 14 days, the edema of the limb persists and worsens after subsequent attacks. Smith\textsuperscript{37} reported that 43 of the 80 patients in his series of secondary lymphedema had swelling as a consequence of infection. In 21 of these cases it was ascribable to recurrent cellulitis and lymphangitis, and in 14, active trichophytosis. Affected patients were usually between 30 and 59 years old, with near gender balance. The authors’ own experience is similar to Kinmonth’s\textsuperscript{52} and indicates that primary inflammatory edema, as described by Allen,\textsuperscript{31} is now rather rare. This change in the etiologic mechanism may be attributed to the widespread use of potent antibiotics, but secondary recurrent lymphangitis and cellulitis, which punctuate and aggravate the course of pre-existing lymphedema, remain difficult to control.

Filariasis is the most common cause of lymphedema in the world. It is estimated that up to 90 million people are infected.\textsuperscript{43,55} Most of the symptomatic patients have lymphedema; in a recent study from India, this incidence exceeded 85%.\textsuperscript{59} Filaritic lymphedema can affect up to 11% of the population in endemic areas,\textsuperscript{60,61} which are located in tropical zones throughout the world. *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* are the organisms respon-

---

**Table 4** Secondary lymphedema.

<table>
<thead>
<tr>
<th>Blockade at the level of the lymph node</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional lymph node dissection</td>
</tr>
<tr>
<td>Axillary (post-mastectomy lymphedema)</td>
</tr>
<tr>
<td>Pelvic and para-aortic (leg and groin lymphedema)</td>
</tr>
<tr>
<td>Neck (head and neck lymphedema)</td>
</tr>
<tr>
<td>Neoplastic disease</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Cervical cancer</td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Melanoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disruption or obliteration of lymphatic channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery, e.g. ilio-femoral bypass</td>
</tr>
<tr>
<td>Direct injury, e.g trauma of the medial aspect of the thigh</td>
</tr>
<tr>
<td>Radiation-induced fibrosis</td>
</tr>
<tr>
<td>Neoplastic infiltration of lymphatic channels</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Filariasis</td>
</tr>
<tr>
<td>Recurrent infection, e.g. erysipelas</td>
</tr>
</tbody>
</table>

sible for human filariasis. Many other species of Wuchereria and Brugia have been described in animals, with the potential to "cross-infect humans.58 Various pathologic mechanisms may become involved in the lymphatic destruction in this disease: direct toxic effects of the worm, the host’s immune response58 and superimposed bacterial infection62,63 have all been proposed. The parasite is transmitted by a mosquito vector which carries the infective larvae. The acute clinical manifestations of filariasis include episodic attacks of adenolymphangitis, with fever. In most of the cases, lymphedema of the lower extremity develops and progresses after these recurrent attacks of adenolymphangitis.58–60

Neoplastic disease
Neoplastic obliteration of the lymphatic vessels, lymph nodes (metastases) and lymphatic ducts (external compression or carcinomatous lymphangitis) is a major cause of secondary lymphedema. The most frequent causes are breast cancer in lymphedema of the arm, and prostate cancer in disease of the leg.77

Other causes of secondary lymphedema
Isolated cases of lymphedema in patients with arthritis are quite numerous.64–70 Lymphedema can accompany both rheumatoid64,69 and psoriatic arthritis.70 The upper extremity is more likely to be affected,65,66,68,70 but lower extremity involvement has been described.67,69 The pathogenesis is conjectured to be either lymphatic obstruction or lymphangitis.

Lymphatic abnormalities are also observed in other types of chronic edema, such as chronic venous insufficiency71–73 and lipedema.74

Complications
Chronic lymphedema is often complicated by recurrent lymphangitis/cellulitis and in the long-standing disease, numerous neoplastic complications have been described.

Lymphangitis/cellulitis
Accumulated fluid and proteins serve as a perfect culture medium for bacterial growth. Impaired lymphatic drainage impedes the local immune response, which, in turn, promotes bacterial and fungal invasion.57 The infection further impairs lymphatic drainage and the aggravation of the edema usually persists after the infection resolves. With recurrent infections, there is progressive damage of the lymphatic capillaries.57 The different types of lymphedema display a variable propensity towards the development of cellulitis. In primary lymphedema, the reported infection rate varies from 13%61 to 31%.62 Milroy, on the other hand, did not describe any attacks of cellulitis in the congenital lymphedema family under his scrutiny.57 In secondary lymphedema, infection has been reported in 41% of breast cancer patients,63 the most common cause being infection by Streptococcus.31,71,78 Infection by Streptococcus group G, C and S. sanguis,78 group B beta-hemolytic79 and enterococcus80 have been reported, as has cryptococcal cellulitis.80 Brook and Frazier found various aerobic and anaerobic organisms and suggested a polymicrobial etiology for cellulitis.81 In a recently reported series of cellulitis complicating lymphedema, Staphylococcus and Micrococcus species were more often identified as the infective agents.82

In general, it is difficult to identify the infectious factor in lymphedema patients with cellulitis. Blood cultures,78 skin biopsy cultures83 and needle aspirates81 are rarely positive.

The clinical picture may vary from acute attacks of a rapidly progressive infection (high fever, chills and general malaise, with localized edema, erythema and characteristic changes of peau d’orange) to a subclinical course with, at best, subtle skin changes and normal body temperature. Recurrent attacks of cellulitis damage existing cutaneous lymphatics, worsen skin changes and further aggravate existing edema. Acute attacks of cellulitis usually resolve quickly after antibiotic therapy but tend to reoccur, becoming more resistant to antibiotic therapy when they do. Prophylaxis against cellulitis includes meticulous skin care, avoidance of minor trauma and the prophylactic use of antibiotics.82,84

Various treatment regimens for lymphedema may also prevent the recurrence of cellulitis. This has been reported for heat therapy,85 coumarin administration,86 manual lymphatic therapy87 and following microsurgery.88 Others ascribe the observed reduction in the frequency of cellulitis to meticulous skin care during pneumatic compression therapy rather than to the compression itself.89

Malignant tumors
In rare cases, chronic lymphedema may be complicated by the development of malignant tumors within the involved limb. In 1948, Stewart and Treves90 described six cases of angiosarcoma in the edematous arms of breast cancer-treated women. Since that first report, over 400 cases have been described in the literature.91–93 Malignant tumors of the lymphedematous extremity can evolve from lymphedema of any etiology: postsurgical, traumatic, filarial and primary,94 but the phenomenon is most often observed in postmastectomy edema of the arm, with a described frequency of 0.45%.95 The latency period between surgery and the development of the new malignancy may vary from 4 to 44 years.91 In one series of 48 patients with sarcomas related to breast cancer therapy,91 lymphangiosarcomata were observed in 46% of the cases and non-lymphangiosarcomata in 54%.

Lymphangiosarcoma usually presents as a multicentric lesion with bluish nodules, sclerotic plaques or bullous changes.96 The neoplasm is usually very aggressive in its growth pattern, and 5-year survival rates vary from 5%92 to 29%.91

Other malignant tumors that appear with increased frequency in the lymphedematous limb include Kaposi`s sarcoma, squamous cell carcinoma, malignant lymphoma and melanoma.97

Treatment
Lymphedema is a chronic condition which requires lifelong treatment. Far from being incurable, the disease now has many treatment options that have demonstrable efficacy for the reduction of edema volume and the prevention of fluid accumulation. On the other hand, if the treatment regimen is abandoned, continuous accumulation of edema will ensue, exacerbated by recurrent infection, with resultant massive edema, grossly impaired limb function, psychoso-
cial disability and life-threatening infectious or malignant complications.

Medical therapy

Complex physical therapy

Complex physical therapy (complex decongestive therapy, combined physiotherapy) is a physiotherapeutic approach to lymphedema that is designed to improve lymphatic drainage. The therapeutic intervention includes manual lymphatic drainage, exercise, fitting with non-elastic wrappings and compressive garments, together with meticulous skin care. This ambulatory treatment is performed on a daily basis for 1 to 6 weeks. At each session, manual lymphatic drainage (MLD) is performed after skin cleansing and lubrication. Manual lymphatic drainage is a specific massage technique, based upon principles described by Winivarter and Vodder, and Foldi.99 The intent is to enhance and redirect lymph flow through intact skin lymphatics and to redirect this flow to other regions with a preserved lymphatic circulation. According to Foldi et al, who, with 2500 patients per year have arguably the greatest accrued experience,99 MLD should be applied first to the contralateral quadrant of the trunk. This enhances lymphatic contractility and stimulates lymph flow through lymphatic watersheds. Subsequently, massage is applied to the root of the limb, followed by therapy to the more distal parts. The particular massage technique of MLD is very gentle and is, in fact, sometimes compared to the touch of a cat’s paw. Non-stretching compressive wrappings should be applied after each session of MLD and worn during exercise, to prevent the reaccumulation of fluid and to promote lymph flow during exertion. Bandages are not removed until the subsequent treatment session.99,100 This approach is popular in Europe and Australia and has been demonstrated to be both safe and effective. It is recommended for all stages of the various types of lymphedema.

These therapies are becoming more popular in the USA.108 In one series of 399 patients with benign lymphedema (not caused by neoplastic lymphatic blockage), volume reduction was achieved in 95% (including >50% volume reduction in 56% of the patients) immediately after completion of the therapy. After 3 years of follow-up (in 177 patients), the effects of the therapy were sustained in 54% of the patients.109 Other reports have shown similar efficacy.7,98,100,102,103

Intermittent pneumatic compression

Intermittent pneumatic compression with single or multi-chamber pumps does effectively remove excess fluid from the extremity and can be used as a primary or adjunctive therapy for lymphedema.89,104–110 Most studies have commented only on the early effects of this therapy, but long-term results, after sequential intermittent pneumatic compression therapy, have been reported in one study of 49 treated lymphedema patients. Mean follow-up was 25 months. Of 36 patients, 26 fully maintained the benefits of the therapy and 10 patients had a partially sustained result. No worsening of the edema or other complications were reported.89 Some studies suggest an advantage of multi-chamber pumps over unicompartmental devices,111 while others have shown no difference.107 Although complications of compressive therapy have not, generally, been reported, there have been warnings that the generated pressures might damage skin lymphatics112,113 and that the residual proteins, which remain after forceful fluid displacement, can induce secondary inflammation and accelerate fibrosclerotic changes. In addition, a ring of fibrous tissue can form, over time, above the sleeve of the pneumatic pump, thereby further compromising lymphatic outflow.98,114 Recently Boris observed an increased incidence of genital edema in patients when using the pneumatic pump therapy for leg lymphedema.115 Pneumatic compression with lower pressures (40 mmHg) can also be effective, and may pose a lower risk for complications.116 The use of any form of compressive therapy does require 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,117 is contraindicated. Isolated cases of induced or aggravated lymphangitis,118 and of peroneal nerve palsy119 have also been reported as complications of sequential pneumatic compression.

Compressive garments

The utilization of compressive garments is adjunctive to the other forms of lymphedema therapy. Relatively non-distensible elastic sleeves and stockings that transmit high grade compression (up to 80 mmHg) (graduated compression garments) will prevent reaccumulation of fluid after successful decongestive treatments. In order to provide the requisite degree of compression, the garments should be carefully chosen on the basis of meticulous limb measurements. Such garments lose their compressive capabilities after 3 to 6 months and must be replaced. For many patients with mild lymphedema, grade II compression (30–40 mmHg) will suffice. Although higher grades of compression are often desirable and recommended,120 these are much less well tolerated by patients.

Inelastic compression devices such as CircAid® (CircAid®Medical Products Inc., USA) and LegAssist™ (Compression Specialists BSAC, Inc., USA) have recently been introduced to permit better long-term maintenance of limb volume in patients with chronic edema. These devices, constructed of Velcro strips, can be easily fitted to the extremity. The CircAid device has been shown to be more effective than elastic stockings in the maintenance therapy of chronic venous insufficiency.121 It may be useful in the maintenance therapy of lymphedema as well.

Another compressive device, called the Reid sleeve, is constructed from a specially designed foam and utilizes adjustable bands to provide a wide-range of gradient pressures. The degree of available compression ranges from 20 to 40 mmHg. The sleeve is designed to be worn overnight and is easily self-applied. Preliminary results demonstrate a significant volume reduction (32%) in patients with lymphedema after 4 weeks of therapy.122 Randomized trials are under way to compare the therapeutic effects of the Reid sleeve to those which result from intermittent pneumatic compression.

Heat therapy

Application of local hyperthermia to the lymphedematous limb has been described as a safe, successful therapy in China.123–125 Liu and Olaszewski85 described regression of
the inflammatory changes in lymphedematous skin following heat therapy. A significant reduction in limb volume was also observed. The treatment was applied for 30 to 45 min/day over 15 days.85,124 With the utilization of a microwave oven as the heat source, the subcutaneous tissue temperature rises to 39–40°C. The published results are promising and the method is simple.

Other physical therapy options
Balzarini and coworkers116 have published results of an investigation on postmastectomy arm edema, in which ultrasound therapy for chronic edema was compared with the use of pneumatic compression. They achieved a similar degree of volume reduction in both groups, but there was a greater degree of subjectively perceived tissue softening in the ultrasound-treated group.

Autologous lymphocyte injection
Intra-arterial autologous lymphocyte injection is another proposed therapy for lymphedema. The first observation came from Katoh et al.,126 who observed reduction of lymphedema in five of seven cancer patients who were treated with autologous lymphocyte injections. Three subsequent cases reports from the same group127–129 described five additional patients (out of seven) who also benefited from this therapy. The appearance of novel proteins in the lymphedematous fluid was observed following the lymphocyte injections, and it has been suggested that this therapy enhances proteolysis of extracellular proteins.128 Recently, Nagata et al reported treatment results in 13 patients. All of the patients benefited from the therapy, with a mean edema reduction of 63%; in nine patients, the benefit persisted during 3 months of follow-up.130 In an experimental canine model, it has been demonstrated that reduction of lymphedema is accompanied by a reduction in skin collagen and total protein content together with an increase in acidic proteinase activity.131

Pharmacotherapy and diet
Pharmacotherapy is being reported as adjunctive or primary therapy for various types of lymphedema. Coumarin (5,6-benzo-[a]-pyrone) has been observed to provide a significant, albeit slow, reduction in various types of lymphedema, both in human86,132,133 and animal studies.134 Coumarin can control proteolysis by increasing the neutral protease activity of macrophages at the site of injury. The drug also has stimulatory effects on other cells of the immune system: it increases the T helper/T suppressor ratio and stimulates NK cells. Coumarin can also suppress the production of the superoxide anion and hydrogen peroxide by the monocytes135,136 thereby enhancing protein reabsorption. Nevertheless, Knight et al could not confirm the stimulatory effect of the coumarins on the macrophages’ proteinase activity in vitro.137 Flavonoids have been also reported to have beneficial effects in patients with lymphedema.138 However, these drugs do not enjoy common therapeutic application, even in large lymphedema treatment centers.139 Furthermore, in their consensus document, the International Society of Lymphology did not endorse coumarin or other benzopyrones as substitutes for complex physical therapy.7 On the other hand, sulodexide has been recommended as an effective prophylactic measure for the prevention of postmastectomy lymphedema.140

In filariatic lymphedema, medical treatment of the filariasis must accompany the general measures that are directed towards the lymphedema itself. Effective medications include diethylcarbamazine citrate and the macrolide antibiotic, ivermectin. Both agents are used for treatment and for prophylaxis (e.g. the DEC-mediated salt in endemic areas). Ivermectin has the advantage of a single dose daily treatment regime and fewer side effects.58 Zinc supplementation has been found to correct both the lymphedema and the nail changes associated with yellow nail syndrome.141 Sori et al reported that dietary modification, by restricting the intake of the long-chain triglycerides, proved to be beneficial in two patients with idiopathic lower limb lymphedema.142

Surgical therapy
Surgical therapy for lymphedema is generally entertained when medical therapy fails. There are two main surgical approaches: (1) excisional procedures, where part or all of the lymphedematous epifascial tissue is removed, and (2) microsurgical interventions, for the creation of lymphatico-lymphatic, lymphatico-veno-lymphatic, lymphatico-venous and lymph node-venous anastomoses. Other surgical techniques include treatment with transferred omental pedicle and myocutaneous flap interposition.

Microsurgery
To be considered for a microsurgical procedure, the patient’s lymphatic ducts should be patent below the locus of blockage. Consequently, the procedure is usually performed either in patients with postsurgical lymphedema or in those with primary lymphedema who have proximal occlusion. Postinflammatory lymphedema and primary lymphedema with distal occlusion are not suitable for microsurgery. In some cases of advanced lymphedema (grade II, III), combined operations can be performed.

Recently Campisi et al reported the long-term outcome of 64 lymphedema patients who underwent interposition autologous lymphatico-venous-lymphatic anastomoses.143 Improvement in limb function and edema volume was observed in all patients and the regression endured for more than 5 years.

Baumeister performed autologous lymphatico-lymphatic grafting in 66 patients who had, predominantly, secondary upper and lower limb lymphedema. The mean reduction in volume after surgery was 60%. This quantitative improvement was maintained during a follow-up phase of 1 to 5 years.144 Although it has been suggested that bypass operations should be performed within the 2 years following lymphatic disruption,145 Baumeister has undertaken surgery on patients whose mastectomies occurred 1–20 years ago.

Lymphatico-venous anastomosis (LVA) for lymphedema has been performed in many centers, with varying success rates. In a series of 233 patients reported by Campisi, with 1 to 5 years’ follow-up, a very good response was seen in 71, a good response in 101, a fairly good response in 47, and no effect in 14 patients.146 Filippetti et al performed 25 modified LVA in 25 postmastectomy patients and during the 18 months’ follow-up, 55% of the patients had a desirable outcome.147 O’Brien et al performed LVA in 134 lymphedema patients, of which 90 were available for a mean follow-up of 4 years (52 had LVA, 38 LVA with surgical


Downloaded from http://vmj.sagepub.com by on June 3, 2010
The average volume reduction was 44%, and subjective improvement was seen in 73% of the patients. Notable, also, was a reduction in the incidence of recurrent cellulitis by 58%. However, other centers have not been able to readily duplicate these results. Gloviczki et al reported results of LVS in 18 lymphedema patients, in whom 14 successful lympho-venous anastomoses were performed. The mean follow-up was 36 months. Only one of seven patients with primary lymphedema and four of seven with secondary lymphedema showed significant improvement. 148

Olszewski has presented more than a decade of follow-up of lymphedema patients who have been treated with lymph node-venous (LNVS) anastomoses. In postsurgical lower limb lymphedema, 27 patients were operated on and good results were obtained in 80%. 22 patients died from recurrent cancer. Of the five surviving patients, four have experienced a sustained benefit for over 18 years. Out of the 20 patients with postinflammatory lymphedema who were treated with LNVS, only two showed permanent improvement. Ten patients were operated on for hyperplastic lymphedema. Seven patients had more than 10 years’ follow-up; of these, five showed permanent improvement and two patients showed no improvement. Two additional patients worsened in the absence of medical therapy despite application of conservative measures. In primary idiopathic lymphedema, no differences were observed between surgical and conservative treatment. 149

The entero-mesenteric bridge operation was designed for patients with primary lymphedema resulting from proximal (pelvic) occlusion. A small segment of ileum, with its intact mesentery, is sutured to a transacted femoral or inguinal lymph node, allowing a bypass of the occluded pelvic lymphatics. Hurst et al reported a salutary outcome after 2.5 to 7 years follow-up in six of eight of the surgical patients. 149

An omental flap with intact lymphatic vessels can also serve as a lymphatic bridge. The earliest attempts were not successful, despite an initial improvement, because of subsequent fibrosis of the omental pedicle. 150 Omental transfer has successfully ameliorated the acquired lymphedema of animal model systems. 134, 151 Recently, omental transfer with lymph nodal-venous anastomosis was used to treat 21 patients with chronic lymphedema. Good results were observed in 14 patients during the 3 to 24 months’ follow-up and the results were satisfactory in five patients. 152

A myocutaneous flap is occasionally used for the treatment of postmastectomy edema, 153 as well as for lower limb lymphedema. 154 However, no larger studies have been performed and long-term results with substantial numbers of patients are not available. 150

‘Debulking’ procedures

Surgical procedures, in which excesses of lymphedematous skin and subcutaneous tissue are excised, carry the potential to destroy existing cutaneous lymphatics and also carry the risks of papillomatosis, necrosis of the skin and exacerbation of the edema. Indications for partial excision include advanced, fibrosed lymphedema and elephantiasis. 42, 147, 155

Radical excision of skin, subcutaneous tissue and deep fascia was proposed by Charles in 1912 and, until recently, has been performed in a modified fashion. The procedure always leaves a significantly deformed limb and carries the risk of serious complications, including hypertrophic scar-


