Hypothesis: The causes and management of lower limb lymphedema in the Western population are different from those in the developing world.

Objective: To look at the differential diagnosis, methods of investigation, and available treatments for lower limb lymphedema in the West.

Data Source: A PubMed search was conducted for the years 1980-2002 with the keyword “lymphedema.” English language and human subject abstracts only were analyzed, and only those articles dealing with lower limb lymphedema were further reviewed. Other articles were extracted from cross-referencing.

Results: Four hundred twenty-five review articles pertaining to lymphedema were initially examined. This review summarizes the findings of relevant articles along with our own practice regarding the management of lymphedema.

Conclusions: The common differential diagnosis in Western patients with lower limb swelling is secondary lymphedema, venous disease, lipedema, and adverse reaction to ipsilateral limb surgery. Lymphedema can be confirmed by a lymphoscintigram, computed tomography, magnetic resonance imaging, or ultrasound. The lymphatic anatomy is demonstrated with lymphoscintigraphy, which is particularly indicated if surgical intervention is being considered. The treatment of choice for lymphedema is multidisciplinary. In the first instance, combined physical therapy should be commenced (complete decongestive therapy), with surgery reserved for a small number of cases.

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LYMPHEDEMA IS the swelling of a body part due to an abnormality in the locoregional lymphatic drainage. This results in an increase in interstitial volume secondary to the accumulation of tissue (lymphatic) fluid. It is most common in the lower limb (80% of cases) but can also occur in the arms, face, trunk, and external genitalia.1

Lymphedema is an important differential diagnosis in lower limb swelling, with various investigation and treatment options available. In this review, we look at the common causes of lower limb swelling and their clinical features, the investigations used to exclude nonlymphedematous causes, and the current treatment of lymphedema in the Western population. Filariasis, the most common cause worldwide, and the management of postmastectomy lymphedema are not discussed although the general principles apply to both of these conditions.

METHODS

A PubMed search was conducted for the years 1980-2002, using the keyword “lymphedema.” All abstracts were studied and only articles dealing with lower limb lymphedema were further scrutinized. Other articles were extracted by cross-referencing.

RESULTS

DIFFERENTIAL DIAGNOSIS

A swollen leg may be due to local or systemic causes. Systemic causes include congestive cardiac failure, renal failure, hypoalbuminemia, and protein-losing nephropathy. Local causes include primary and secondary lymphedema,2-8 lipedema,2,4,5,9-12 deep vein thrombosis (DVT) and chronic venous disease,2,5,7,8 postoperative complications following ipsilateral, surgery,1,13-17 cellulitis,18 Baker cyst13,18 and cyclical19 and idiopathic edema.5,7 In children, lower limb swelling is seen in association with arthritis but the underlying mechanism for this association is unknown.20

Primary Lymphedema

This is caused by a congenital abnormality or dysfunction in the lymphatic sys-
Lymphedema is common in the developed world secondary to infection with the parasitic nematode *Wuchereria bancrofti* (otherwise known as filariasis), making this the most common cause of lymphedema worldwide. The most common of these is the praecox variety. Primary lymphedema is more common in females, especially lymphedema praecox, where the onset is particularly common around menarche. Symptoms may be linked to a minor trauma, suggesting that the abnormal lymphatics have coped under normal circumstances but are unable to cope with an increase in tissue fluid.

Alternatively, primary lymphedema can be classified according to the abnormality found in the lymphatics. Thus, it may be aplastic, hypoplastic, or hyperplastic. These terms suggest an abnormality in the development of the lymphatic system. While this is true for congenital lymphedema, cases of later-onset primary lymphedema might be due to an acquired abnormality. It is difficult to prove whether the abnormal lymphatics seen when these patients were investigated had existed in the same state since birth. Browse and Stewart have made a case for a new classification system that disregards of these terms.25

Primary hypoplastic lymphedema can be further subdivided into proximal and distal hypoplasia. The most common form of primary lymphedema is distal hypoplasia. It is milder, often bilateral, and symptoms are confined to below the knee.26 Not surprisingly, proximal disease causes more severe symptoms, with whole-limb swelling. Patients with primary hyperplastic lymphedema have an increased number and size of lymphatics. It is unusual in that it has a male preponderance and is more often familial.26 An association with other congenital abnormalities is sometimes seen.26 The thoracic duct may be absent or abnormal in such patients.26

Secondary Lymphedema

This is edema due to a reduction in lymph flow by an acquired cause. The causes of secondary lymphedema include trauma, recurrent infection, and malignancy, including metastatic disease. In the developed world, the most common cause of secondary lymphedema is malignancy (including that resulting from cancer treatment). Lymphedema is common in the developing world secondary to infection with the parasitic nematode *Wuchereria bancrofti* (otherwise known as filariasis), making this the most common cause of lymphedema worldwide.

It is unusual for surgery alone to cause lymphedema, as lymphatics have excellent regenerative capabilities. Some series have shown significant lymphatic damage in more than 60% of patients undergoing varicose vein surgery.20 Lymphedema is unusual after varicose vein surgery but patients should be examined preoperatively, as vein stripping can significantly exacerbate mild lymphedema. Patients with venous disease have been shown to have impaired lymphatic drainage.

Even after radical lymph node excision for malignancy, lymphedema does not always ensue. When it does occur, it is often a late complication. The reasons for this late development are uncertain, but gradual failure of distal lymphatics, which have to “pump” lymph at a greater pressure through damaged proximal ducts, has been postulated. The transected lymphatics will regenerate after node clearance procedures. If combined with radiotherapy, however, the risk of lymphedema is higher, as fibrous scarring reduces regrowth of ducts.32

Recurrent cellulitis can complicate venous disease of the lower limb, exacerbating swelling in venous hypertension and making venous ulcers harder to treat because lymph exudes through ulcers. The common causes of lymphedema are shown in Figure 1.

**Figure 1. Causes of lymphedema.**

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comes thicker (hyperkeratosis) and rougher (papillomatosis) and skin turgor is increased\(^3\) (Fig\. 2). In severe cases, the skin can break down, with lymph exuding through any skin breaks. This compromises healing and leads to an increased risk of infection. Recurrent infections, cellulitis, and lymphangitis are common. This unfortunately can lead to further deterioration in lymphatic drainage, ending in a vicious cycle of infection and worsening edema.

Lymphangiosarcoma is a rare late complication of lymphedema.\(^3\) This was originally described in the lymphedematous arms of patients following radical mastectomy (Stewart Treves syndrome\(^3\)) but has also been described in patients with Milroy disease.\(^3\) It appears to be an earlier complication following radical mastectomy than in those with congenital lymphedema (average, 10 vs 38 years postdiagnosis).\(^3\) Treatment is primarily radiotherapy, with surgery reserved for patients with discrete, nonmetastatic disease.

**Lipedema**

The clinical features of lipedema (also known as lipomatosis of the leg) include early age of onset, female exclusivity, and positive family history in some patients.\(^1\) The clinical signs include elastic symmetrical enlargement of both legs with sparing of the feet,\(^3\) so called "riding breech thighs" and "stove pipe legs,"\(^3\) hypothermia of the skin, a negative Stemmer sign, and pantalar positioning alterations.\(^1\) Weight loss does not affect leg appearance.\(^3\)

**DVT and Chronic Venous Disease**

Deep vein thrombosis results in obstruction to venous flow, occurring mainly in the soleal plexus. The clinical picture is thus one of a swollen, warm, tender calf. The resulting edema is pitting in nature and is usually much softer than in established lymphedema. Often, there are underlying risk factors, such as recent surgery or immobility, malignancy, a preceding long flight, or thrombophilia. The diagnosis is confirmed with duplex scanning or venography. Treatment is with anticoagulation.\(^4\)

One of the long-term sequelae of DVT is postphlebitic syndrome. Here, there is reflux in the deep venous system, or deep venous insufficiency, resulting in chronic swelling of the limb, lipodermatosclerosis, and varicose veins, and in severe cases, venous ulceration. On clinical grounds alone, this may be more difficult to differentiate from lymphedema, and further investigation, as outlined later in this article, may be required.\(^4\)

**Postoperative Swelling (Predominantly After Arterial Reconstruction)**

The incidence of peripheral edema following arterial reconstruction is high, especially if the procedure is a femoropopliteal bypass.\(^4\) If the swelling is significant (>4.5-cm increase in diameter), it is more likely to be due to thrombosis of the tibial or popliteal veins.\(^4\) Following arterial reconstruction, there may be impairment of lymphatic drainage or lymphatic disruption secondary to the surgical dissection in the thigh and popliteal region.\(^4\)

The swelling may persist for up to 3 months.

**INVESTIGATION OF LIMB SWELLING**

The main reason for investigating is not only to confirm the diagnosis but to exclude a potentially lethal condition, such as DVT. General examination is necessary to exclude medical causes, such as cardiac failure. Simple serum biochemical analysis should exclude hepatic or renal impairment, and analysis of the urine should exclude any protein-losing nephropathy.

**Clinical Examination**

The contralateral leg may be used to assess whether the affected leg is actually swollen. However, the disease may itself affect both sides, or the unaffected leg may previously have been larger than the diseased leg. The Leg-O-Meter (François Zuccarelli, MD, Hôpital St-Michel, Service de Chirurgie Vasculaire, Département de Phlébologie et d’Angiologie, Paris, France) is designed to measure the circumference of the ankle or calf.\(^4\) This has high interobserver reliability and is easy to use. It has been mainly used in assessing leg swelling related to venous disease and has so far not been validated in lymphedema. A normal tape measure will assess the swelling relative to the contralateral leg but this is not a reliable technique.

Water displacement volumetry, although not commonly used, measures leg volume\(^4\) and is more accurate than calculating the leg volume from circumferential measurements with a tape measure.\(^4\) In lymphedema,
the tissue tonicity (degree of tissue resistance to mechanical compression) is either higher or lower compared with the nonedematous leg. Measurement of tissue tonometry is more useful in assessing the response to treatment than in the initial assessment of disease. Biopressure measurement has been used successfully for the evaluation of swelling in patients with postmastectomy lymphedema but has not yet been evaluated for leg edema.57

Finally, Cesarone and coworkers48 developed the edema tester. This involves applying a plastic plate with either protrusions or holes over the swollen area, applying pressure, and measuring the marks made. It may allow the differentiation between primary and secondary lymphedema, although it is only recommended at present as a screening tool.

Radiologic Investigation

Lymphangiogram. Before lymphoscintigraphy became the gold standard, this was the main technique used for visualizing the lymphatics. It involves direct cannulation of the lymphatics through a skin incision and may lead to infection, local inflammation, and fibrosis. It is technically demanding, painful, and time-consuming, with an increased risk of hypersensitivity reactions and emboli.49 As a diagnostic tool, the technique has largely been abandoned. However, it is still useful if operative intervention (ie, bypass procedure) is to be undertaken.50

Lymphoscintigram. This technique was first introduced in 1953 and is now the gold standard for assessing the lymphatics. The radiolabeled protein used is usually technetium Tc 99m-labeled colloid, including antimony sulphur5,57,10,51 and albumin.15,18,52,53 It allows measurement of lymphatic function, lymph movement, lymph drainage, and response to treatment.51,54

To aid in the measurement of lymph flow, the patient should take an oral dose of heptaminol adenosine phosphate to increase lymphatic flow.55 The sensitivity of the lymphoscintigram is 73% to 97% and the specificity is 100%.4,56,57 A lymphoscintigram may be sufficient if any bypass procedure is intended but some patients may also require a contrast lymphangiogram to fully elucidate the lymphatic anatomy.50,58

The amount of time that the lymphatics are visualized is equally important. If lymphatics are not imaged within the first hour after isotope injection, the diagnosis may be missed.4 In some patients, the 1-hour image may show normal lymphatics, while only delayed films (2-24 hours postinjection) may show the true abnormality.8,9 In one series, 32% of patients would have had normal lymphoscintigram results if only the 1-hour film had been considered. Other techniques that improve detection of lymphatic abnormality include condensate image processing using a modified Kleinhans score and time activity curves.5,59,60

Lymphoscintigraphy alone can exclude lymphedema as a cause of limb swelling in approximately one third of patients.5,57 A lymphoscintigammogram will also differentiate between lymphedema and edema of venous origin.6 A patient with venous leg ulcers, lymphscintigra-
in the cross-sectional muscle area and enlarged superficial veins. However, if calf swelling is not present following DVT, there will be no change in the muscle and so CT becomes an unreliable investigation.

Magnetic Resonance Imaging (MRI). Magnetic resonance imaging can differentiate among lymphedema, lipedema, and phlebedema. Features of lymphedema on MRI include circumferential edema, increased volume of subcutaneous tissue, and a honeycomb pattern above the fascia between the muscle and subcutis, with marked thickening of the dermis. It is, however, generally difficult to differentiate primary from secondary lymphedema using MRI. Magnetic resonance imaging will also show the typical features of angiosarcoma while evaluating the swollen limb.

Following reconstructive surgery, MRI shows the edema to be located around the entire circumference of the limb but restricted to the subcutaneous tissue, increasing the leg volume by a mean of 26% (range, 8%-45%). In DVT, there is edema of the leg muscles, particularly in the posterior compartments, with an increase in the leg volume of 23% (range, 15%-90%). In chronic lymphedema, there is an increase in leg volume of 40% (range, 27%-120%). Magnetic resonance imaging in lipedema will confirm that peripheral lymphatics are normal, soft tissue swelling consists solely of fat, and subcutaneous edema is absent.

TREATMENT

The main aims of treating patients with lymphedema are to prevent the progression of disease, to achieve mechanical reduction and maintenance of limb size, to alleviate the symptoms arising from lymphedema, and to prevent skin infection. Hence, treatment depends on the symptoms and the severity of the condition. The treatment can be divided into conservative, pharmacologic, and surgical.

Conservative

For the very mild cases, elevation of the affected limb coupled with skin care may be sufficient. The latter is particularly important to reduce the increased risk of cellulitis and lymphangitis.

Physical Treatment

This modality consists of compression, special exercise, massage, or a combination of the three to enhance lymphatic drainage. Compression with a custom-made elastic stocking (minimum pressure, 40 mm Hg) is an effective method, particularly in secondary lymphedema. In a study of 40 patients with primary and secondary lymphedema, only 1 limb from the secondary lymphedema group deteriorated after compression with elastic stocking therapy.

Multilayer bandaging is another form of compression and has been shown to be effective in both upper and lower limb lymphedema. This form of compression consists of an inner layer of tubular stockinette followed by foam and padding to protect the joint flexures and to even out the contours of the limb so that the pressure is evenly distributed. Compression is provided by an outer layer of at least 2 short-stretch extensible bandages. Treatment using this technique in 90 female patients with either upper or lower limb lymphedema was significantly more effective than hosiery alone. In lipedema, no difference was made by compressive stockings.

Another form of compression and massage comes from pneumatic pumps. These pumps allow the development of high pressure up to 150 mm Hg. These pumps can reduce the limb girth measurements by 37% to 68.6%. Following treatment, however, patients should continue to wear a compression stocking because there is a high risk of recurrence. In a study using external pump compression, a significant number of patients developed genital edema. The pumps may not be suitable for use in patients with coexisting renal failure or congestive heart failure. Patients should ideally also be free of metastasis in the limb to prevent the risk of spreading the malignancy. One study reported that the use of a pneumatic pump showed a greater effect in women, although why this should be so is difficult to explain.

Usually a combination of these methods is employed to achieve optimal benefit. Some authors have called this approach either combined or complex physical therapy (CPT), while others have called it complete decongestive therapy. They have been demonstrated to significantly reduce the amount of edema and microlymphatic hypertension, paralleled with a considerable decrease in the mean circumference of the ankle and foot. Following the initial stages of CPT, it is important for these patients to continue to wear their compression garments to prevent any relapse. The effect of physical treatment is to produce focal lymphatic damage to the endothelial lining of the lymphatics as well as that of lymphatic pools. This leads to translocation of fluid from the interstitium into the lymphatic lumen. Some patients with leg edema may benefit from raised leg exercise but this has not been shown to be of any benefit when the cause of leg swelling is due to lymphedema.

Heat Therapy

Heat therapy has produced some benefits, which can be achieved by hot water immersion, microwave, and electromagnetic irradiation. Microwave heat therapy has been
combined with compression hosiery, hot water immersion, and benzopyrones to reduce leg volume and improve skin tonometry. This method of treatment has not led to complications, to our knowledge, during or after treatment.

The mechanism of action of thermal treatment is not fully known. One group suggested that heat by means of electromagnetic radiation produced its effect by increasing the venous return rather than by improving lymphatic flow. However, one criticism of this study is that the subjects were normal rather than patients with lymphedema, and heat may produce different effects in the 2 groups. Histologically, the skin after heat treatment for lymphedema shows a near resolution of perivascular cellular infiltration, disappearance of the so-called lymph lakes, and dilatation of blood capillaries. This decrease in the dermal inflammatory process associated with alteration of extracellular matrix may explain the reduction of lymphedema seen after heat treatment.

**Pharmacologic Treatment**

**Micronized Purified Flavonoid Fraction.** This is an effective drug in decreasing venous stasis and has also been shown to be beneficial in idiopathic cyclic edema, chronic venous insufficiency, and postmastectomy lymphedema. It exerts its action by reducing the capillary permeability and the inflammatory component typical of this condition. Trials of this drug are awaited for lower limb lymphedema.

**Benzopyrones.** This group of drugs has also been shown to be effective in the treatment of lymphedema by reducing edema fluid, increasing softness of the limbs, and decreasing elevated skin temperature. More importantly, there were markedly fewer instances of secondary infection, and there was improvement in the symptoms, such as reduction in the bursting pain and feeling of hardness, tightness, heaviness, swelling, and an increase in mobility. Adverse effects, such as nausea and diarrhea, were uncommon and had disappeared by 1 month of treatment. These findings were supported by other groups using a combination of benzopyrones in addition to microwave heat therapy and compression treatment.

Benzopyrones alone can provide adequate reduction in the symptoms and signs as well as a decrease in instances of secondary infection. However, the effect was slower when compared with that of physical therapy. The reported advantages of benzopyrones included low toxicity, oral or topical application, and the lack of need for compression therapy, which is particularly helpful for patients who do not tolerate high-pressure treatment. The combination of benzopyrones, whether in a topical or oral preparation, and CPT is significantly better than CPT alone.

Benzopyrones work by increasing the number of macrophages, thus enhancing proteolysis and resulting in removal of protein and thereby edema. In addition, the stimulus that excess protein provides for inflammatory and fibrotic process is removed and its presence as a good culture medium for bacterial growth is also eliminated. Benzopyrones, however, are not licensed for use in the United Kingdom, Australia, or France due to reports of hepatotoxicity.

**Surgical Treatment**

The importance of accurate preoperative evaluation cannot be overemphasized. Before any surgery, patients should be admitted for a few days to allow leg elevation and compression to optimize the leg for surgery. Following surgery, it is important for the patient to wear some form of stocking to prevent recurrence. This is especially true of patients undergoing debulking procedures. The treatment can be divided into debulking operations, bypass procedures, and prophylactic surgery.

**Debulking Procedures.** One method, which has been described but is not widely popular and is not a debulking procedure according to the widely accepted definition, is the subcutaneous drainage of lymphedema fluid by means of multiperforated silicon tubes linked to a chamber by a 1-way valve. This chamber is in turn connected to the venous system via the long saphenous vein in much the same way as a peritoneovenous shunt. In a study of 10 patients with moderate to severe lymphedema, there was a mean reduction of 70% in peripheral edema. One problem with such a device is limited long-term patency because it is liable to block owing to the high protein content of edema fluid. This may explain the lack of popularity of this method.

A well-tested method, the Charles procedure, is the radical excision of subcutaneous tissue together with primary or staged skin grafting. This involves removal of the skin, subcutaneous tissue, and deep fascia en-bloc. Some surgeons prefer primary skin grafting with either the skin from the excised tissue or from a nonaffected area. Others favor a delayed approach to skin grafting. Both the 1-stage and the 2-stage procedures reported good results in terms of function, contour, and reduction in the incidence of secondary cellulitis. There was no difference in results between congenital and acquired lymphedema but men were shown to have less improvement than women. Skin and subcutaneous excision alone or in combination with liposuction improves symptoms but leads to foot edema. Servelle described a technique where the entire affected limb undergoes a 2-stage reduction (first, the medial aspect and later, the lateral aspect of the limb). This has been termed total superficial lymphangectomy and is probably a modification of the Homan procedure. This is in contrast to the Charles procedure, where only the affected part of the limb is treated and the cosmetic outcome is mediocre.

The main complication of the above debulking procedure is infection and necrosis of the skin graft, which can lead to poor cosmetic and functional results. A successful surgical outcome is shown in **Figure 4** and a complication is shown in **Figure 5**. Liposuction has been
used in a limited number of patients, with up to a 23% reduction in volume\(^1\) and with cellulitis as the main complication.

**Bypass Procedures.** Bypass procedures are only performed in selected cases; this is reflected in the literature by small patient numbers in the series reported. These microsurgical procedures are reserved for patients in whom intensive combined medical therapy has not produced clinical improvement. Lymphatic-venous anastomosis can only be performed in the presence of a competent venous system and intact lymphatic structures, such as patent regional lymphatics and lymph nodes.\(^{101}\)

Nielubowicz and Olszewski\(^ {102}\) first attempted lymphovenous anastomosis in the treatment of lymphedema. Unfortunately, this early technique was noted to occlude owing to venous thrombosis at the anastomotic surface or to reendothelialization over the cut anastomotic surface of the lymph node.\(^{103}\) With refinement in the technique, direct end-to-side lymphatic-venous anastomosis can be performed.\(^{103}\) This technique avoids venous reflux into the lymphatics, seen with the end-to-end technique, and thus decreases the risk of venous thrombosis. Also, by using a secondary tributary of the main vein as the site of anastomosis, the risk of anastomotic stricture is avoided. For the smaller pediatric patients, lymphatic capsule-venous anastomosis is possible.\(^{103}\)

In another series of 15 patients who underwent lymphovenous bypass, there was a reduction of more than 5 cm in leg diameter in 9 (70%) of 13 patients followed up for an average of 6 months,\(^ {104}\) while Struick and coworkers\(^ {105}\) reported that 5 of 8 patients operated on demon-
We have reviewed the literature on the diagnosis and management of lower limb lymphedema in the Western world during the last 20 years. We have summarized the available modes of investigation, with indicators to the differential diagnosis. The mainstay of treatment is nonoperative, with CPT being the treatment of choice. Pharmacologic therapy in the form of benzopyrones seems to have been successful but is not available on license in many countries. Many surgical procedures are available, but clinical trial numbers are still small and further evaluation is required. Surgical intervention should be reserved for the highly refractory cases only (Figure 6).

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