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LYMPHEDEMA

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Discussion Leaders

DEFINITION AND CLASSIFICATION OF LYMPHEDEMA

Lymphologists generally consider "elephantiasis" an extreme form of lymphedema characterized by thickened skin (dermatosclerosis). Edema is often severe, and in advanced cases produces a contracted, fibrotic, rock-hard limb.

In contrast, parasitologists consider "lymphedema" a smooth-contoured pitting edema which disappears on elevation and is covered by thin, shiny skin of normal texture. "Elephantiasis" consists of thickened skin with slight or no pitting edema and clinically evident excess tissue fibrosis, or even the latter alone. Thus parasitologists designate less severe conditions as elephantiasis including involvement of deeper tissues. As little or no clinical edema may be present even with advanced fibrosis and large volumes of encapsulated fluid, the term "lymphostatic disorder" is useful to encompass all those conditions labelled "lymphedema" and "elephantiasis".

Foldi ("Lymphangiology", ed. M. Foldi and J.R. Casley-Smith, Schattauer, Stuttgart, and N.Y. (1983), p. 196) defines "lymphedema" as a high-protein edema caused by reduced "lymph transport capacity" with insufficient "tissue proteolytic activity" in the face of a normal lymphatic load. Lymphedema is thus a "low output failure" of the lymphatic system as distinguished from a "high output failure", where the lymphatic load is elevated and despite accelerated lymph flow and perhaps increased tissue proteolysis, edema fluid accumulates. When inflammation (even from excess tissue protein secondary to lymphedema) is superimposed, an increased "lymphatic load" is added to an already compromised transport capacity of the lymphatic system with worsening of clinical edema.

Lymphedema is a progressive condition characterized by four main components: excess tissue protein and edema, chronic inflammation, and fibrosis. Early, the edematous component predominates and later, the excess fibrosis. Excess tissue protein promotes edema and probably mediates chronic inflammation, causing further fibrosis. Fibrous tissue contracts particularly around remaining lymphatic vessels, and macrophages become filled with debris, reducing their phagocytic and proteolytic capacities. In later stages, neovascularization and fat deposition may predominate. Complications include: fibrotic occlusion of lymphatics and nodes with cessation of lymph flow; lympho-cutaneous fistulae; elephantine changes of hyperkeratosis and papillomata (either from longstanding simple lymphedema or more likely from secondary infections or immune mechanisms) and rarely angiosarcoma.

Stages of lymphedema include a subclinical (latent) phase, during which ongoing pathologic changes such as excess fluid and fibrosis (usually concentrated around the lymphatics) are not clinically detectable. The "pitting" quality depends on intensity of fibrosis. While limb edema occurs predominantly in the dermis and subcutaneous compartment rather than below the deep fascia, fibrosis involves both compartments.

In regard to terminology for associated inflammatory conditions, the term "erysipelas" is inappropriate to designate other than the classic dermal infection caused by hemolytic streptococci (occasionally staphylococci). Such inflammations may not be infectious in origin but

rather traceable to immunologic or traumatic causes. The terms "pseudoerysipelas" and "cellulitis" add to confusion. "Lymphangitis" (inflammation of the lymphatic vessels and adjacent tissues) and "secondary acute inflammation" are both useful terms, "acute" as distinct from the chronic inflammation due to excess tissue fluid protein.

CLASSIFICATION OF CHRONIC LYMPHEDEMA (LYMPHOSTATIC DISORDERS)

A system of classification of lymphedema applicable worldwide should be designed analogous to the New York Heart Association classification of heart disease including 1) etiologic, 2) anatomic, and pathophysiologic, 3) clinical and histopathologic, 4) functional-therapeutic (disability-related) to define precisely the disorder, plan optimal treatments, and compare effects of different treatments.

Etiologic diagnosis (e.g. ibid. p. 672) is usually possible in secondary lymphedema. Recognition of malignancy is essential as its treatment takes priority.

Anatomical and pathophysiologic classification is important for certain forms of therapy, such as choosing the proper type and site of operation (e.g. ibid p. 196), but specific classification systems remain controversial. If, however, a simple anatomical subclassification is added to the pathophysiologic (e.g. "proximal" or "distal" or "combined" when describing blocked lymphatic trunks), agreement can be reached. Anatomical diagnosis usually involves direct lymphography, indirect lymphography, or lymphoscintigraphy. For primary lymphedema, in vivo microcirculatory studies suggest four Types (I to IV) for subclassification (Partsch and Bollinger, in "The Initial Lymphatics", ed. A. Bollinger, H. Partsch and J.H.N. Wolfe, Georg Thieme, Stuttgart and N.Y. (1985) pp. 218-219).

Pathophysiological (functional) evaluation is now possible using a variety of techniques (see Special Examinations). No single technique uniformly provides an exact classification, but a combination of several including lymphoscintigraphy usually provides an accurate anatomical and pathophysiologic diagnosis.

Clinical and histopathological classification of the severity of lymphedema is needed to evaluate different forms of treatment. Brunner's classification is generally useful with subclassifications of each grade by "mild", "moderate" and "severe", recognizing that different grades may apply to different regions of the same limb: Grade I: pits on pressure: is largely or completely reduced by elevation; clinically no or slight fibrosis; Grade II: edema no longer pits and is not reduced by elevation; clinically moderate to severe fibrosis. Elephantiasis: may occur in Grade II and should be considered a severe form of lymphedema. Marked damage to deeper tissues may be present without skin alterations.

Lymphedemas (lymphostatic disorders) exist in other regions of the body (e.g. face, intestines, liver, and brain), but no classifications currently exist such as whether or not there is extensive fibrosis. Grades I and II with substeps for severity including degree of fibrosis as for classification of limb lymphedema can be applied to develop prognostic indicators and evaluate therapeutic approaches.

Functional-therapeutic (disability) status can be classified on a scale of 1-5 (1 noticeable and 5 incapacitating) using the World Health Organization's scheme ("W.H.O. International Classification of Impairments, Disabilities, and Handicaps" W.H.O. Geneva, 1980, especially pp. 157-205). This classification measures the significance of the disease for a particular individual and alterations by various treatments and includes: pain; difficulties in dressing oneself and buying ready-made clothes; activities in the home and workplace; poor cosmetic or social acceptance; psychologic depression, etc.

DIAGNOSIS OF CHRONIC LYMPHEDEMA

Clinical diagnosis of chronic lymphedema is attainable in the vast majority of cases and in many parts of the world is the only method available: case history, inspection, palpation, and eliminating other causes of edema, both general and local. Stemmer's sign (thickening of the skin on the dorsal aspects of the toes or fingers—caused initially by edema but later by fibrosis) and the characteristic clinical picture differentiate lymphedema from venous edemas, lipedema, and idiopathic cyclic edema. Acute traumatic lymphedema is difficult to distinguish clinically from hematoma and is seldom correctly diagnosed.

Malignancy should be excluded either by clinical features or by special examinations of lymph nodes, lymphoscintigraphy, computed tomography, and in selected cases, lymphography.

Special examinations are available to confirm clinical judgment and provide more information about etiology and site of obstruction. Some procedures are not available where most patients

with lymphedema reside. Overall, lymphoscintigraphy yields the greatest information with the least risk. Specific tests are needed to determine patency of lymphovenous anastomoses.

The danger of direct lymphography was the subject of considerable discussion. Some considered the procedure injurious and seldom indicated. Others reported few or no complications. For lymph node detail, some maintained that lymphography gave much better definition of structure (e.g. to exclude malignancy) but others considered lymphoscintigraphy or computed tomography nearly as good. For microsurgery, lymphography is valuable, but visual dyes are also helpful. One eminent microsurgeon, however, stated, "If you demonstrate a functioning lymphatic by lymphography, that may be the last time it does function".

While better commercially available contrast media are needed, indirect lymphography provides useful information about initial lymphatics, collectors, trunks, and lymph nodes, although the latter was disputed. Questions were raised about injury from the new media and the high non-physiologic injection pressures. In addition, injected media may pass directly into blood vessels.

Computed tomography provides static images but does not evaluate lymphatic function. Dermal and subcutaneous thickening and excess fat and fluid may be visualized to distinguish lymphedema from venous edema except in chronic venous insufficiency; deep vein thrombosis produces substantial edema in the subfascial but little in the extrafascial compartment (c.f. lymphedema). The procedure is costly and not generally available. Ultrasound and xerography offer comparable information about the state of the skin and subcutaneous tissues. Some discussants doubted whether any of these procedures are useful.

Nuclear magnetic resonance imaging accurately measures the amount of edema, distinguishing fat from fluid. However, it is costly, generally unavailable, and impractical for most lymphedemas. NMR and CT may be useful in lymphostatic disorders of deeper organs, where clinical and other non-invasive methods are limited. More research is needed into these conditions including the potential of NMR and CT to elucidate the process.

Fluorescent lymphography provides useful diagnostic information about the state of the initial lymphatics and precollectors, but the cost, complexity, and limited availability of the apparatus restrict its usefulness.

Quantitative indirect lymphoscintigraphy is considered by many the best way to evaluate lymphatic function. While dye studies provide similar information, quantitative lymphoscintigraphy is accurate and can be applied at any depth, not only in limbs. Anatomic and pathophysiologic classification of lymphedema can be carried out, but greater standardization is needed especially regarding variability of clearance tests and exercise responses.

Visualization with vital dye ("blue test") is a simple direct measure of lymphatic function, applicable to the superficial lymphatic system of the skin (or at operation, the viscera). Cosmetic problems and occasional morbidity were mentioned, but the value of dyes was acknowledged in acute post-traumatic lymphedemas and in lymphatic surgery.

Protein concentration of edema fluid estimated by refractometry on an aspirated specimen is useful even in the field but not widely practiced. Questions were raised about the accuracy of such determinations but others felt that in the edematous extremity the level closely approximates that in lymph. Lymphedema is not the only high-protein edema (c.f. the venous and other hydrostatic low-protein edemas) but treatment may be similar, e.g. benzopyrone drugs.

Tonometry, a measurement of the depth a standard plunger indents the skin under a standard force, is useful to monitor patients at risk during a latent stage (e.g. after mastectomy) and to follow results of therapy.

THE OPTIMAL TREATMENT OF LYMPHEDEMA

The ideal result from both the patient's and clinician's point of view is the ancient Greek concept of the "confident nude", i.e. someone whose condition is so improved that no external support is needed and who is confident that the condition will not return. Whether this ideal is attainable and if so, how, was the subject of much discussion. The goals of treatment and criteria for success or failure were enumerated as follows:

Success: the "confident nude", cosmetically and socially acceptable, restored function, restoration of movement and dexterity, freedom from pain, reduced limb volume, improved tonometry (softness), freedom from inflammation, freedom from threat of neoplasia, occupation and lifestyle resumed, rapid recovery, short stay in hospital, low cost in time and money, not exposed to danger, including iatrogenic, ac-

ceptable to patients, objective improvement in tests, simple, with low risk of failure and possible in developing countries.

Failure: harm has been done, unable to return to previous lifestyle, increased number or severity of inflammatory episodes or neoplasia, volume of limb not reduced or greater, deformity produced, mutilation or amputation, increased scarring and fibrosis, objective worsening of tests, improvement only temporary, feelings of depression and isolation, patient's family and aides remaining ignorant, patient disadvantage by costs or duration of treatment, reduced options for further treatment.

All methods of treatment rely on the skill of those providing the treatment and their choice and judgment in timing the specific treatment based on the anatomy and functional capacity, intelligence and compliance of the patient, and socioeconomic considerations. The surgeon should be experienced in performing a variety of operations, recognize the indications for them, and refer appropriately. The potential for worsening the condition through operation should be recognized. The ISL declined as a group to recommend certification of individuals treating lymphedema either operatively or non-operatively, but practitioners in this area should become more informed and aware of options.

Treatment modalities should be judged by long-term results. Various treatments have been proposed with enthusiasm based on short-term results in a few patients without long-term follow-up or sufficient reporting of poor outcomes. In the future the various classifications of lymphedema should be used in discussing results, and indications for different methods of treatment should be more precisely outlined. The "placebo effect" is well recognized, and simple bed rest and better hygiene alone can lead to improvement.

Geographical and socioeconomic variations were stressed. As satisfactory non-operative treatment is available in only a few countries in Europe and a few centers in the United States, and as experienced surgeons and physical therapists are few and far between, patients with lymphedema have restricted choices. The ISL should stress continuing education of physicians and allied health professionals and the tailoring of specific methods to local geographical and socioeconomic conditions.

With regard to specific operations, lymphnodo-venous anastomoses can be performed in about an hour whereas lymphatic transplants and microsurgical anastomoses require much more elaborate tools and skills. Generally, such therapies are not available to patients with filariasis, and even non-operative physical treatments appear impractical. Benzopyrones are reasonably cheap but have not yet been shown clinically effective.

There was extensive discussion about when treatment should commence. Most participants recommended that treatment of lymphostasis should be started as early as possible as prolonged delay produces a vicious cycle of greater tissue alterations. Patients at risk, for instance, after radical mastectomy or lymph node dissections in the axilla, groin, or neck, should be monitored periodically to detect lymphatic compromise before lymphedema is overt. Suitable investigative methods include tissue tonometry, microlymphography, and quantitative lymphoscintigraphy. On the other hand, a minority disagreed suggesting that a mild disorder is better left alone, and patient worrying might produce a psychological cripple ("living for the limb") and/or lead to treatments associated with iatrogenic morbidity.

All agreed that sound advice is as important as correct diagnosis, suitable surgery, or physical therapy. Regular exercise is uniformly beneficial. Early treatment is justified as long as it is unlikely to do harm.

Coexistent malignancy or filariasis in lymphedema should receive first priority in treatment, and removal of lymph nodes is discouraged.

Conservative physical therapy alone or in combination with other methods, e.g. surgery or drugs when appropriate, should be instituted first.

Some experienced practitioners claimed success in all grades of lymphedema (including Grade II with elephantiasis) and reported that some patients eventually abandon elastic supports.

Microsurgical procedures can, when successful, produce "confident nudes" promptly without need of elastic support. Selected cases generally did not include mild or far-advanced manifestations or those with venous or arterial disease or malignancy. Reduction operations were frequently combined with microsurgery, and conservative methods were used for several days before operation. Microsurgeons were disturbed by the length of time and required compliance for success of physical methods as well as the delay with attendant fibrosis, which might compromise the surgical outcome.

Compared with lympho-venous, lymphnodo-venous anastomoses are easier to perform and remain patent more often, but others pointed out

that nodes are atrophied in some lymphedemas. More long-term data are needed based on appropriate classifications and special examinations should be performed to confirm the patency of anastomoses.

Macrosurgical procedures such as ligation and resection are correct treatment for reflux of lymph with and without chyle. These techniques are well described in Kinmonth's text ("The Lymphatics. Surgery, Lymphography and Diseases of the Chyle and Lymph System". Arnold, London, 1972 and 1982). Many speakers questioned this approach in the absence of reflux. Bridging operations for sharply demarcated lymphedema and classical excisional operations particularly with full-thickness skin grafts have limited usefulness and may be harmful. A satisfactory trial of non-operative measures should be tried first.

Benzo-pyrone drug treatment. Several speakers commented on the efficacy, reliability, and safety of these agents not only in lymphedema including filariasis, but in other forms of chronic high-protein edema and in a variety of locations where excess fibrosis interferes with function. Some benzopyrones are cheap while others are relatively expensive.

Benzopyrones work slowly requiring months to years to reduce limb volume appreciably, but according to some, improved mobility and reduction in "pressure discomfort" and incidence of secondary acute inflammations are noted sooner. These drugs can be combined with physical methods or surgery. Some speakers questioned both the short- and long-term value of benzopyrones. More research is clearly needed including controlled clinical trials.

Corticosteroids by intralymphatic injection have been inadequately studied to treat fibrosis of lymph nodes and the lymphostatic sequelae.

Diuretics long-term are generally useless except for concomitant diseases or short-term when lymphedema is life-threatening.

Anti-filarial drugs are indicated to prevent reinfection and spread of the disease, but cannot be relied upon to reduce lymphedema, particularly the more severe grades including elephantiasis.

Antibiotics as long-term prophylaxis are of questionable benefit in secondary acute inflammation. The best approach is to provide patients with penicillin or a broad-spectrum antibiotic and instruct them to start a course as soon as inflammatory signs appear and seek prompt medical attention.

Non-bacterial inflammation (allergic or auto-immune in origin) in filariasis and post-mastectomy lymphedema may respond to antihistamines. Proper primary treatment of the lymphedema reduces such attacks and even the allergic or auto-immune states which stimulate them.

CRITERIA FOR ADEQUATE CONSERVATIVE PHYSICAL TREATMENT

Views were divergent on the best type of physical therapy. Heat (including ovens, hot packs, and alternating current) and compression in a mercury pressure gradient have been advocated but no formal recommendations were made. Five basic principles of therapy apply:

1. The patient must be given sound advice tailored to his/her disease, intelligence, and lifestyle. Scrupulous attention should be paid to skin hygiene with soap and water, prompt treatment of minor cuts, abrasions, insect bites or fungal infections, and avoidance of extremes of climate. Exercise, elevation of the part, and weight reduction are important along with psychological support.
2. External bandaging limits edema progression and prevents fluid from reaccumulating in "emptied" tissues. Thereafter, a well-fitted inelastic sleeve or bandage is recommended because as tissue pressure varies with limb movement, fluid transport through tissue spaces is facilitated. In addition, both help to fill initial lymphatics and pump collecting lymphatics. Occasionally such bandaging can be abandoned after successful physical therapy. In general, bandaging is not applicable to extremely hot climates or muddy surroundings.
3. Some form of external pressure is essential. Masseurs should preferentially empty more central portions of the limb and later the distal portions. In this way lymph is milked centrally and across lymphatic watersheds. Pneumatic and other mechanical devices are also effective, particularly with extensions to compress the axilla or groin and adjacent truncal regions. Unfortunately, such regions are often drained by the same obstructed nodes which caused the edema, leading to movement of fluid from one poorly drained area to another. The bulk of evidence including statistical details, alterations in lymph transport capacity, and amounts of tissue protein favors these manual methods.

   Better mechanical devices are needed. Lymphedema occurs, however, largely because of complete or partial blockage, and even

though lymph can sometimes be forced through obstructed nodes and tissue spaces, collaterals must be developed. It is important to empty the nodes on the contralateral side of the body as well as the ipsilateral groin or axilla so that lymph has somewhere to go. Manual massage accomplishes this task better than a machine but the two modalities combined represent a reasonable compromise between cost and efficiency.

4. Suitable exercises, either isotonic or isometric, with the limb bandaged or in an elastic sleeve, should be carried out regularly.
5. Elevation of the affected part is useful but less so than in venous edema.

FINAL RECOMMENDATIONS

1. The term "lymphostatic disorder" should be used in place of or in conjunction with the term "lymphedema" to avoid confusion. Clinical and histopathologic classification should include Grades I and II expanded by the adjectives "mild", "moderate", and "severe". The term "elephantiasis" correctly refers to gross alterations of extremity skin.
2. Other classifications (etiological, anatomical, and pathophysiological and by disability) are also important. The W.H.O. classification of disability is recommended.
3. The term "erysipelas" should be abandoned as a generic term for "secondary acute inflammations" (the latter term should be used instead). "Erysipelas" specifically refers to spreading infection from hemolytic streptococci.
4. Lymphedema is usually satisfactorily diagnosed by clinical methods. Special examinations at times are helpful including indirect lymphography and quantitative lymphoscintigraphy. Direct lymphography and phlebography are required only under special circumstances.
5. Excision of regional lymph nodes is discouraged unless there is a good reason (e.g. for prognosis in breast cancer) because edema worsens when lymphatics are further interrupted.
6. Lymphedema is a progressive condition, and preferably non-operative treatment should be instituted soon after the diagnosis is made.
7. As a damaged lymphatic system is susceptible to further injury, invasive diagnostic or therapeutic maneuvers should be used with caution and performed by properly trained personnel.
8. An adequate course of non-operative physical therapy should precede other forms of treatment of lymphedema.
9. Clinical trials and surgical procedures should conform to the classification schemes outlined above and require long-term follow-up to assess results.
10. Benzopyrone therapy should be considered along with other non-operative and operative treatment for lymphedema. The ultimate value of these drugs should conform to the recommendations in 9.
11. Diuretics are not recommended long-term for treatment of lymphedema except for an accompanying disorder.
12. Secondary or superimposed acute inflammation must be treated promptly and effectively.
13. Anti-filarial drugs should be given in lymphedema due to filariasis to minimize reinfection and spread of the disease both in the affected individual and to others. These medications may also reduce lymphedema in the milder grades.