Lymphology 24 (1991) 100-104

EDITORIAL

THE ENIGMA OF LYMPHEDEMA – A SEARCH FOR ANSWERS

Until recently, lymphology (study of the lymphatic system) has been identified primarily with lymphedema and its most advanced form, elephantiasis. No one will argue that lymphedema is an important clinical problem as it affects about 250 million people worldwide. But we must understand that lymphedema is only one of many pathological conditions that affects the lymphatic system and should be considered within the context of the whole system.

Infections, cancer, transplants and implanted biomaterials cause lymphocytes in lymphoid organs to react, which alerts the lymphatic system. Furthermore, lymphoproliferative diseases also develop primarily within that system. There is, then, a strong need to find a common definition of the lymphatic system and of lymphology, derived from the current base of knowledge, to help in the search for one and more efficient diagnostic and therapeutic methods. The lymphatic system comprises tissue, interstitial space containing tissue fluid, lymph, lymph nodes and also the spleen, bone marrow and lymphocytes (the migrating lymphatic "messengers"). These anatomical entities are functionally interdependent; to separate them when interpreting clinical phenomena is not tenable.

Bacteria, viruses and fungi that invade tissues travel through the lymphatic vessels to the nearest lymph nodes where they are destroyed. Dying tissue cells or their debris also are carried away by the lymph vessels. Lymphocytes and other immunologically important cells migrate from blood to the interstitial space and then to the lymph vessels. Lymphocytes recognize and fight foreign invaders. A variety of cell hormones, called interleukins, are found in tissue fluid and in lymph fluid. These hormones stimulate or inhibit the proliferation of cells in tissue and lymph nodes. Like the heart, lymph vessels rhythmically contract, transporting fluid containing these important regulatory proteins or immune cells. Without lymphatic contraction, no other force can adequately propel the lymph through the vessel network.

These basic facts about the lymph system must be understood by clinicians and patients so that proper treatment can be instituted and cooperation between patients and doctors can be established. This appreciation is especially important when treating obstructed lymphatics.

The International Society of Lymphology (ISL) is seeking answers to several fundamental questions: Why does lymphedema develop after excision of lymph vessels and nodes in some patients but not in all? Are there special predisposing factors in the development of lymph stasis such as previous infections, impaired contractility of lymph vessels, or excessive lymph formation? Why, several months after the removal of lymph nodes and lymphatics in the axilla or groin, do the distal lymphatics tend to obliterate? Is this a latent inflammatory process caused by the lack of transport of microbes and cellular inflammatory products? How may trapped lymphocytes and their hormonal products influence proliferation of fibroblasts and, subsequently, the formation of firm, fibrotic skin? Why do so many patients with lymph stasis develop recurrent infectious dermatitis? Which prophylactically administered antibiotic drug is most effective in preventing recurrent lymphangitis and dermatitis?

Another group of studies concerns the diagnosis of lymphedema. Extremity edemas resemble one another, regardless of etiology. But, if the cause is different, the treatment should be different. How, then, do we discrimi-

nate between the systemic predilection for edemas in the extremities and the "primary" lymphedema? How do we measure the contractile capacity of lymph vessels in patients with lymphedema?

With the treatment of lymphedema, we look for answers to such questions, as "How is the tissue fluid removed during massage of the limb? Does removal occur via lymph vessels, blood capillaries, or through tissue 'spaces'?" The ISL also is studying the kinetics of the healing of lympho-venous anastomoses. Why do they close after time? The ISL is also devoting tremendous efforts toward solving such lymphatic issues as *in vivo* reaction of lymphoid tissue to cancer, transplants, and biomaterials.

Nevertheless, all the above-mentioned studies have a common denominator: How does the lymphatic system work? Finding the answer is a primary goal of the ISL. Only through the integrated efforts of all researchers, clinicians and our patients, who understand that the lymphatic system is a composite of functionally linked interstitial space, lymphatic vessels, lymph and lymphoid organs, will we begin to gather the necessary clues for solving a wider range of particularly difficult clinical problems.

Some results already have been achieved. We've eliminated elephantiasis in the developed countries through the use of a proper antibiotic therapy policy. Mechanical massage of edematous limbs is providing comfort and a better life to thousands of patients. Lympho-venous surgical anastomosis often prevents the progression and helps in the regression of lymphedema in a large number of patients. Anti-inflammatory drugs are being widely used and, soon, their effectiveness will be known.

Progress may be slow but it is evident. The ISL serves to accelerate this progress.

Waldemar Olszewski, M.D., Ph.D.
President, International Society of Lymphology
Warsaw, POLAND

Reprinted with modification from the National Lymphedema Network Newsletter 2:1,2,5, 1990.

On Lymphedema "Enigmas"

The following letter and Dr. Olszewski's reply were recently received in the Editor's office. Professors Földi and Clodius are former Presidents of the ISL.

In a recent issue of the *National Lymphedema Network Newsletter* (here reprinted as an Editorial), Professor Olszewski raises several "enigmas" that are misleading and demand clarification. First, Dr. Olszewski considers it puzzling that lymphedema occurs after radical lymph node dissection in some patients but not in all. But, this paradox is not really all that unexpected. Lymphedema is a clinical condition in which there is low flow failure of the lymphatic system or, in effect, where the maximum lymph flow or transport capacity has become less than that needed for the removal of a normal load of surplus tissue protein and water. If the lymphatic transport capacity has not been reduced by radical operation and/or irradiation below that needed to handle the normal interstitial protein and water load, then lymphedema doesn't develop. Scar formation (acting as a barrier to lymph flow), aging and "fatigue" of contractile propulsive elements in lymph trunks compensating for those vessels excised or blocked may further restrict lymph transport after these therapeutic (and destructive) procedures, and eventually end the latent stage (i.e., subclinical lymphedema) with the development of overt or gross lymphedema. The premorbid structural state (i.e., before operation or irradiation) of the peripheral lymphatics among individuals varies considerably, influences the potential activation of collateral lymphatic flow, and thereby also determines whether or not lymphedema develops. An additional factor may be the capacity of interstitial macrophages to catabolize trapped tissue proteins, a phenomenon which also demonstrates wide individual variation.

Second, Professor Olszewski wonders why after regional nodal and lymphatic excision do distal lymphatics become obliterated

and opines that this phenomenon may represent the end result of a latent inflammatory process secondary to failure to transport tissue microbes and cellular inflammatory byproducts. But this hypothesis is vague and unnecessary. In this situation, lymphatics obliterate because lymph fluid stagnates behind the obstruction and, rich in clotting factors, simply coagulates like plasma.

Third, Professor Olszewski ponders why so many patients with lymph stasis develop recurrent infectious dermatitis. But, it is well known that lymph stasis is accompanied by an immunodeficiency in the stagnant drainage area, a circumstance favoring opportunistic infection.

Fourth, Professor Olszewski is perplexed by the mechanism of removal of interstitial fluid and lymph during massage of a lymphedematous limb, and further he questions whether surplus tissue fluid is removed via lymph vessels, blood capillaries, or through tissue spaces. Yet, isotope lymphography (lymphangioscintigraphy) has clearly demonstrated that lymphangion motor activity (i.e., truncal wall contraction) is augmented by the special massage method designated as "manual lymph drainage." In other words, remaining lymph vessels remove excess tissue-lymph fluid.

Finally, Professor Olszewski suggests that elephantiasis has been eliminated in the developed countries and that lymph-venous surgical anastomoses have prevented progression and led to regression of lymphedema in a large number of patients. Taken in its most favorable light, these statements are gross exaggerations. *Fig. 1A* shows a young European man with prominent elephantiasis despite having undergone earlier a lymph-venous shunt in a surgical clinic which has pioneered in this operation. After combined decongestive physiotherapy (manual lymph drainage, bandages, calisthenics, skin care) (1) his left leg has been dramatically improved (*Fig. 1B*).

L. Clodius, Zurich, Switzerland
M. Földi, Hinterzarten, Germany

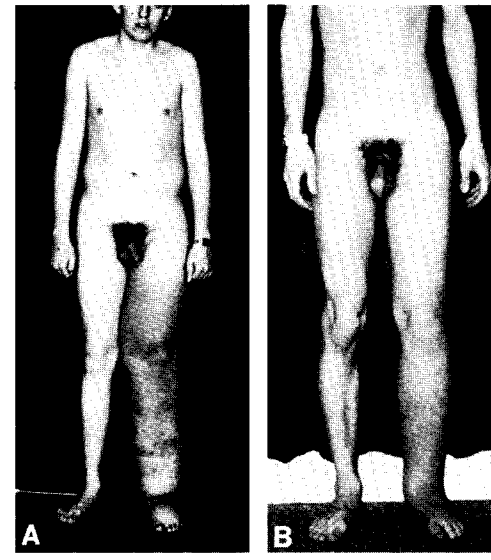

*Fig. 1. Despite having undergone a lymphovenous shunt several years earlier, this young man presented with prominent elephantiasis (**A**). After intensive decongestive physiotherapy, his lower extremity lymphedema was markedly improved (**B**).*

REFERENCE:

1. Földi, E, M Földi, L Clodius: The lympedema chaos: A lancet. Ann. Plastic Surg. 22 (1989), 505-515.

Dr. Olszewski Replies:

I am pleased that my article has generated much interest among eminent lymphologists. Only presentation of conflicting views and criticism can challenge old and new ideas and elevate the field of lymphology into a modern scientific discipline.

The letter of Drs. Clodius and Földi is certainly pertinent but it does not contain novel concepts nor are the ideas fully substantiated by rigorous analysis. For example, in explaining why lymphedema does or does not develop after ablative surgery, Clodius and Földi maintain that it depends on whether the tissue water and protein load exceed the trans-

port capacity of regional lymphatics. Whereas this explanation is reasonable, there are no corroborating data in patients and it is merely an opinion empirically extrapolated from animal experiments. Clodius and Földi envision lymph formation and transport strictly in mechanical terms as if the exchange microvasculature and lymph vessels were inert, passive, structures. But newer understanding and interpretation implicate up and down regulation of transcapillary transport by endothelium (e.g., EDRF, endothelin), dynamic shifts under the influence of mast cell byproducts, the effect(s) of local cytokines on microvascular transport and lymphatic contractility, angiogenic properties of various lymphokines and perhaps most important the destruction of lymph vessels by a chronic inflammatory process that is persistent in lymphedematous tissues. As for tissue macrophages acting as proteases to hydrolyze interstitial proteins thereby permitting lower molecular weight polypeptides to be absorbed directly by venous capillaries and reverse the obligatory oncotic force generated by lymphedema fluid, this concept remains a theory and needs more rigorous experimental documentation.

Although Clodius and Földi somewhat glibly assert that lymphatics downstream of lymphatic blockade obliterate because of lymph clotting, there is scanty evidence for this hypothesis. Whereas histopathology of these distal peripheral lymphatics sometimes shows intraluminal amorphous material, in most instances there is mononuclear accumulation in the lymphatic wall and subendothelial deposits of collagen and hyaline with progressive encroachment on the lymphatic lumen. Lymph fluid contains only 10% of the clotting factors present in plasma and the coagulum slowly forms, and is a loose gel. As with obstruction of a major regional vein where few distal peripheral veins ordinarily undergo thrombosis, distal lymph vessels seldom "clot" in the presence of residual flow and efficient fibrinolysis.

In discussing why patients with lymph stasis develop infectious dermatitis, Clodius and Földi postulate that the phenomenon is rooted in local immunodeficiency. Ironically, I have been working for more than 10 years on this aspect of lymphedema and have not (nor have others) found convincing evidence of "immunodeficiency." There is some indirect support for dysregulated immunoresponsiveness, but much greater substantiation is needed for such an ex cathedra proclamation. Even bacteriological studies of human lymph are suboptimal and culture techniques still need vast improvement.

In expostulating that tissue fluid removed during massage of the lymphedematous limb is solely by lymphatics, Clodius and Földi are somewhat inconsistent. On the one hand, they maintain that lymphatics are plugged with coagulum and on the other that lymphatics remain patent and massage facilitates lymphatic truncal contractile activity. But, lymph pressure recordings in humans in our laboratory suggest that much of the contractile motion is lost in obstructive lymphedema probably as a consequence of destroyed contractile elements. In most of these patients, edema seems to translocate from the distal part of the limb to the more proximal portion. Had auxiliary lymphatics taken over lymph transport, tissue fluid should not have accumulated in proximal tissues even where these parts have been massaged initially. Even if Clodius and Földi are correct that lymph vessels remove surplus tissue fluid, what is the biomechanism of lymph propulsion (e.g., "suction," pressure gradients, wall contraction)?

Finally, I still maintain that elephantiasis has been largely eradicated from developed countries. The combination of massage, compression, local hygiene, antibiotic drugs, and surgical lymph-venous anastomoses have together contributed to this decline. Whereas I congratulate Clodius and Földi on the patient illustrated, a single patient unsuccessfully managed by a lymph-venous shunt does not by itself deprecate the method of treatment. As a pioneer in the construction of lymph-venous shunts for treatment of lymphedema and hav-

ing performed more than several hundred of these operations with established criteria for their use, I stand by the value of this mode of therapy. Unquestionably, many centuries of experience with "decongestive therapy" has documented the usefulness of this non-operative approach. Nonetheless, the search for better and more efficient methods of treatment for lymphedema is still worthy of intense pursuit.

W. L. Olszewski

Editor Comment:

The lack of prospective clinical trials and the imperfect nature of current treatment modalities in the management of lymphatic insufficiency continues to generate heated disagreement as to the optimal therapeutic approach in patients with congenital and acquired lymphedema. Nonetheless, what is still sorely needed are valid measurements (not just hypotheses) in these patients of functional changes in the interstitium and matrix including the autocrine, paracrine, and endocrine effects of lymphokines, the receptors and control mechanisms of lymph propulsion including the regulatory role of arachidonic metabolites and adrenergic protagonists and antagonists, the specific stimulus for unyielding fibroplasia, the correctable deficiency behind spontaneous cellulitis and ultimately the stimuli behind lymphangiogenesis and how this phenomenon can be manipulated to circumvent the disastrous stasis consequences of lymphatic hypoplasia or that associated with disease processes (e.g., filariasis) or the end result of cancer treatment (i.e., radical dissection and irradiation).