

EDITORIAL

WHAT IS LYMPHOLOGY IN 1991?*

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It is my great pleasure and honor to give an address on the current state of lymphology. This is the second time that I have been assigned this task, the first being in 1981 at the VIIIth Congress meeting in Montreal. Over the past 10 years, considerable progress has been made in both basic and clinical lymphology. I will try to summarize these events as well as project developments in the field in the coming years. The task is particularly arduous as my assessments and prospective vision may not be all inclusive. I apologize in advance therefore for omitting some issues which you in the audience may personally consider more germane.

From my previous presidential newsletters over the past two years to the ISL membership at large, I considered it important and tried to inform the medical community including patients what lymphology is all about. We need to recognize that the discipline is still not widely appreciated. I will define in descriptive fashion my own understanding, but you should feel free to modify, improve, or broaden this viewpoint. In brief, *lymphology is the medical discipline that deals with function of the lymphatic system in health and disease. The lymphatic system,*

itself, 1) is composed of functionally interrelated lymphoid tissue, lymph and lymphatic pathways; 2) operates to maintain a homeostatic environment of nonlymphoid elements in the organized tissues and secures their genetically restricted self especially in the tissues having direct contact with the external environment such as skin, gut, and lungs; 3) acts to integrate the neural and endocrine system.

In its entirety, therefore, the lymphatic system consists of the intercellular compartment including interstitial fluid, initial lymphatics and collectors with their circulating messenger elements of lymphocytes and macrophages as well as organized lymphatic organs such as lymph nodes, spleen, bone marrow, Peyer patches, Waldeyer ring, etc. Migrating cells perform varied functions. For example, they pass through the capillary membrane, transport a variety of protein moieties and polypeptides as immunoglobulins and cytokines while "surveying" the noncirculating parenchymatous cells. Moreover, other plasma proteins with diverse functions and properties also "leak" into the tissue spaces and circulate back to the bloodstream.

In basic lymphology, since my last plenary lecture in Montreal in 1981, the

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functional receptors of migrating lymphoid cells have been better defined, the role of endothelium in selecting and facilitating escape of these cellular elements has been established, the regulatory function of cytokines and cell proliferation have been demonstrated, and the process of adherence of lymphocytes to ground matrix molecular structure has undergone intense scrutiny. Further understanding of the nature and control factors of lymphatic contractility *in vitro* has also progressed, ultrastructure of initial lymphatics has been pursued, and more detailed chemical composition of lymph has been characterized. Whereas these are global "advances," I will now turn to specific accomplishments and expectations.

Morphology of the Lymphatic System

Sophisticated ultrastructural studies of the lymphatic microvasculature have delineated the portals of entry of tissue fluid into the initial lymphatics and better characterized the lymphatic endothelium. We still, however, need to distinguish more confidently blood from lymphatic endothelial cells, to provide better insight into the phylogeny of the lymphatic pathways, and the uniqueness of mechanisms regulating lymph kinetics and lymph propulsion. Consistent methods of histological staining or other reliable markers of lymph capillaries are still sorely needed. Moreover, more refined study of lymph nodal ultrastructure is also needed and specifically the spatial relationship among lymphocytes, dendritic, and stromal cells so as to better understand immune function.

Lymph Dynamics

Although many studies of lymph formation and flow continue in experimental animals, information in patients remains sparse. In lymph stasis, our group has provided lymph pressure-flow recordings in human leg lymphatics in healthy subjects and those with lymphedema. These tracings show great

variability normally of intralymphatic pressure patterns. In lymphedema patients, the main derangement is high intralymphatic hydrostatic pressure (100-250mmHg) generated by contraction of calf muscles, a phenomenon seen only in secondary lymphedema and not in control subjects.

Preliminary findings in inflamed tissues indicate that regional lymph flow is higher than theoretically expected, and it raises the question of whether alterations in tissue fluid elements can influence capillary filtration and lymph formation. Perhaps, local deposition of hemoglobin is a prime instigator of these microcirculatory phenomena.

The once considered passive behavior of blood endothelial cells in the process of transcapillary fluid and macromolecular exchange is no longer tenable. Endothelial derived relaxing factor (nitric oxide), endothelin and other hormones and cytokines are paracrine regulators of the interplay among microvascular endothelium, media smooth muscle, and other perivascular cell elements. Could there be "signals" emanating from parenchymal cells and directed at endothelium that influence transcapillary migration of liquids, cells, and plasma proteins?

There is still a strong need to know more about lymphatic contractility in inflamed tissues. This aspect is especially relevant for understanding the development of lymphedema in filarial infestation. In this condition, lymphatics are dilated, seem unable to contract with only partial obstruction of the truncal lumen. What factor(s) contribute to this lymphatic paralysis? Whereas there are studies on the role of neurotransmitters and vasomodulators on *in vitro* lymphatic contraction, investigations of drug effects on lymph formation and flow in intact hosts (human and experimental animal) are scarce.

Immunology of Lymph

(Re)circulation of lymphocytes is now commonly studied with great emphasis on

recognizing homing phenomena and relevant receptors. Blockage or stimulation of expression of these receptors may allow manipulation of lymphocyte trafficking. Our group recently detected that interleukin (IL)-1 and IL-6 in human lymph regulate proliferation of keratinocytes and skin fibroblasts. More studies on cytokines and filarial lymphatic dysfunction are planned with the expectation that the pharmacologic control of tissue overgrowth may be possible with administration of blocking cytokines.

Lymph Stasis

This subject matter is replete with anecdotal observations and more quantification is needed of its pathomechanisms and sequelae. Several important questions can be raised — does lymphedema appear only when nearly all lymphatic drainage of a limb or organ is obstructed? What happens to accumulated tissue protein when lymphatics are blocked and venous absorption apparently is impossible? Perhaps the issue of whether macromolecules such as tissue protein can be absorbed directly into venous capillaries needs to be reexamined. Clinical observations of patients with apparent total blockade of lymphatics and relatively slow progression of swelling cast doubt on the current understanding of protein absorption-transport from tissue spaces exclusively via lymphatics.

Furthermore, we did not find high tissue fluid and lymph protein concentrations in patients with lymphedema except with overt dermatitis and lymphangitis. Consistent objective data on local degradation of tissue proteins are still lacking. Another puzzling phenomenon observed both clinically and experimentally concerns dilated lymphatics without apparent edema. We described this phenomenon 20 years ago but this enigmatic observation awaits explanation and bears directly on forecasting appearance of lymphedema in the clinic.

One of the most challenging problems in peripheral lymphedema is hyper-

proliferation of skin keratinocytes and fibroblasts. The primary signals are unknown although the mediators are increasingly recognized and include the paracrine cytokines, IL-1, IL-6, fibroblasts, epidermal growth factor, and other growth substances. If this process could be controlled, the cellular mass of lymphedema limbs could be sharply decreased. This issue should be earmarked for intensive study by the World Health Organization (WHO).

Lymphatic Infections

Studies of lymph transport of bacteria and viruses are scarce. Environmental antigens are undoubtedly transported via lymphatics; however, no simple and consistent method for intralymphatic detection of microorganisms has been developed. Cytotoxic substances in skin lymph (e.g., high levels of lysozyme) suppress bacterial growth *in vitro*.

A fascinating question relates to the filarial adult worm which seemingly dwells undisturbed in peripheral lymphatics for many years. What is the adaptive mechanism by the parasite and why is lymph such a favorable environment for its survival? Answers to these questions may someday alleviate the suffering of millions worldwide.

Lymph, Lymphatics, and Tumors

Most knowledge on tumor cell growth originates from *in vitro* cultures in artificial media. *In vivo* tumor grows at least in its initial stages in the environment created by local tissue fluid. When we examined tumor cell proliferation in human lymph, the growth kinetics differed from that in fetal calf serum. Most tumor lines were inhibited by human lymph but some paradoxically grew better.

Are there specific attractors of tumor cells to lymphatics or do they simply migrate like other cells in a sense mimicking lymphocyte trafficking? Perhaps if one could regulate tumor cell entry into initial lymphatics, their spread could be prevented.

The current clinical trials of tumor treatment by intravenous specific monoclonal antibodies has prompted us to examine the mechanism of capillary filtration in solid tumors. Some excellent studies along these lines have already appeared.

Lymphatic System and Transplantation

Studies on transport of alloantigen primed lymphoid cells remain a high priority. Another is repopulation of lymphoid organs after bone marrow transplantation, although most attention is directed toward recovery of hematopoietic tissue and much less on restoring function of lymph nodes, spleen, and thymus.

Imaging and Diagnosis of Lymph Stasis

Organ specific and whole body lymphangioscintigraphy may someday allow better diagnosis of lymphatic dysfunction in visceral organs as well as in the extremities. So, too, may indirect lymphography although these modalities depend on better insight into absorption and local concentration of tracers and other markers (both small and large molecules) instilled into the tissue spaces. A real consternation remains the lack of modern interest in the phylogeny of the lymphatic system.

Lymphedema Therapy

I do not wish to dwell on contemporary methods of treating lymphedema. This has been done on many occasions but I would like to raise several points.

First — little progress has been made over the last 10 years in therapeutic options.

Second — manual and machine massage is relatively effective. Nonetheless, an open question remains as to how edema fluid is mobilized. Is edema fluid transported via tissue spaces or by residual lymphatic collaterals to more proximal regions and does massage stimulate lymph vessel growth to bridge the site of obstruction? More lymphscintigraphic

studies are needed to place treatment options on a more rational basis.

Third — most surgical lymphatic-venous anastomoses performed in patients with lymphedema close with time. Yet, in dogs, a lymph-venous shunt between mesenteric lymphatics and the vena cava may remain patent for years. Why the difference? Is it possibly the stagnant “noxious elements” in lymphedema that are primarily responsible for damaging the lymphatics that facilitate shunt closure? Detailed ultrastructural studies on the healing process of these lymphatic-venous reconstructions would be of great value.

Fourth — microwave hyperthermia seems to be beneficial in postinflammatory and some postsurgical peripheral edemas. The cellular infiltrates in the dermis and subcutaneous tissues undergo regression and lymphatic “lakes” subside. Some of the inflammatory components of secondary lymphedema are also reduced. Broader use of this method needs to be coordinated with more studies on the mechanisms behind alleviation of these skin phenomena.

Fifth—prophylactic administration of antibiotics (e.g., penicillin) is thus far the best method to minimize recurrent lymphangitis and subsequent skin changes. Nonetheless, a blinded prospective control study should be designed. Similarly the use of non-steroidal anti-inflammatory (“anti-phlogiston”) drugs should be examined in controlled trials preferably under the auspices of WHO.

Finally, the methods of evaluating and treating peripheral lymphedema still require more uniform standardization. Clinical impressions rather than objective measurements still abound.

Closing Remarks

Ladies and Gentlemen— 10 years ago in Montreal, I showed my conception of a lymphologist. He had a big brain, big eyes, and in order to see more, he enthusiastically climbed a high ladder. The aim was to uncover the secrets of lymphology hidden behind the mountains directly beyond. What has this poor chap accomplished during these 10 years? He has come closer to the mountains, has put his head between the peaks so as to see the horizon more clearly. In the interim, he developed lymphedema! What has he discovered? Not much more than the classic teachings, i.e., basic tenets in lymphology have not appreciably changed over the last 10 years. Yet beside the book of Assellius and other lymphology primers lies

a trunk and a key which hopefully fits the lock. And in the trunk perhaps resides the mystery behind the genesis and interworkings of the enigmatic lymphatic system.

In conclusion, I cite the astronomer who after watching the 1991 solar eclipse remarked, "The sun is greater than we thought!" I suspect the lymphatic system is also much greater than we think!

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