

## IMMUNE PROTEINS, CELL INTERACTIONS AND IMMUNOREGULATORY HORMONES: LYMPH VERSUS BLOOD

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The topic of our session has been formulated as a question, "Are Lymphatics Different From Blood Vessels?". Every participant should give an answer based on his own understanding of the phenomena developing in both systems. A fast answer to the posed question would be, "Of course, there are major differences." An imaginative eye would immediately envisage differences in topography, gross- and ultrastructure, lymph flowing slowly in lymphatics and blood fast in arteries and veins, lymph vessel contractility, different cellularity of both fluids. There are certainly evident anatomical differences between the lymph and blood vessels; however, analysis of diversities at the level of structure and hydraulic function, which has been the most common approach, would not be adequate to the richness of assignments of both systems. The main difference between the two rests in the functional role of blood and lymph vessels, their organization and structure being only secondary to the performed functions. Which are the functions making lymphatics so different from blood vessels? Let us have an evolutionary look at the matter.

The peripheral lymphatic system (initial lymphatics, collecting trunks, lymph nodes with their sinuses [also vessels] and recirculating lymphocytes)

evolved in consequence of a continuing development and specialization of the peripheral blood system. The lymphatic system took partly over some of the functions of the blood transport system such as regulation of water and macromolecular environment of cells in tissues, but also developed its own specificities such as peripheral (local) immune responsiveness and most probably, although not proved yet, transmission of chemical signals from tissue cells to the regulating centers. The stages of the process of differentiation of the blood and lymphatic system as compared in *Table 1*.

In the proposed scheme most emphasis has been put on the growing evidence that lymphatics are an integral part of the local immune defense system. With well-developed basement membrane not only protein extravasation but also recruitment of cells at the site of foreign antigen deposition became restricted. This probably prompted the development of organized accumulations of lymphoid tissue along the lymphatics-lymph nodes.

As I had stressed several times before (1,2) at our conferences, the lymphatic system should be understood as an integrated unit comprising the intercellular matrix and fluid, lymphatics, lymph, organized lymphoid tissue and lymphoid cells circulating through the lymphoid and non-lymphoid tissues. Analyzing

Table 1  
Phylogenetic Comparison of Blood and Lymph Vascular Systems

	Blood	Lymph
Primitive species	Low pressure. Largely unrestricted fluid movement between intra- and extravascular space.	Non-existent
Highly differentiated species	High pressure. Basement membrane around capillaries, restricted macromolecule and cell (leucocyte) extraluminal migration. Functions: supply of nutrients, elimination of metabolites, immediate local immune reaction, coagulation.	Low pressure. Functions: return of macromolecules, cellular metabolites and immune cells which emigrate from vascular compartment back to the bloodstream, delayed hypersensitivity, recirculation of lymphocytes, and appearance of lymph nodes.

simple phenomena developing in the lymphatics not taking into consideration physiology of the interstitium, humoral and cellular composition of lymph, and organization of lymph nodes may lead to erroneous conclusions. May I then analyze the differences between lymphatics and blood vessels along these lines of reasoning and present some pertinent observations.

Peripheral lymphatics in man reveal spontaneous rhythmic contractility of lymphangions. So far no phenomenon like this has been documented in blood vessels. Pressures generated in the lumen of contracting segments of lymphatics are the main force propelling lymph proximally (3) (*Fig. 1*). The mechanism of contractions is myogenic. In contrast to the limb venous system, contracting foot and calf muscles do not have any directional effect on lymph flow in the collectors. Lymph collectors are located in loose connective and adipose tissue along most of their course. During muscular contractions, lymphatics are not pressed against fixed structures or squeezed like veins but rather displaced. Mean pressures in lymph collectors reach with obstructed flow 35-40 mmHg and with free flow diastolic pressures range between 0 and 15 mmHg. There is no hydrostatic pressure component as under normal

conditions most parts of limb lymphatics are empty. This is another meaningful difference from the leg venous system.

The fast intrinsic transport of lymph not only prevents accumulation of excess tissue fluid, it also helps in rapid transportation of foreign antigens away from the tissue to the lymph nodes, where they become inactivated and eliminated.

Another difference between blood and lymph vessels concerns the composition of their contents--proteins and cells. The concentration of proteins in lymph is lower than in serum; there are also different proportions of individual proteins in both compartments (4). This is due to a restricted transport of serum proteins across the capillary wall and further to the tissue space and lymph. In effect, proteins with high molecular weight are represented in lymph at lower levels than those with small molecules (*Fig. 2*). Moreover, the biological activity of some proteins may vary depending on whether they are present in blood vessels or tissue space. For example, the hemolytic activity of C3 complement component in lymph is around 10% whereas its protein concentration is 25% of that of serum (5). This indicates that either during the passage through the capillary wall C3 protein loses some of

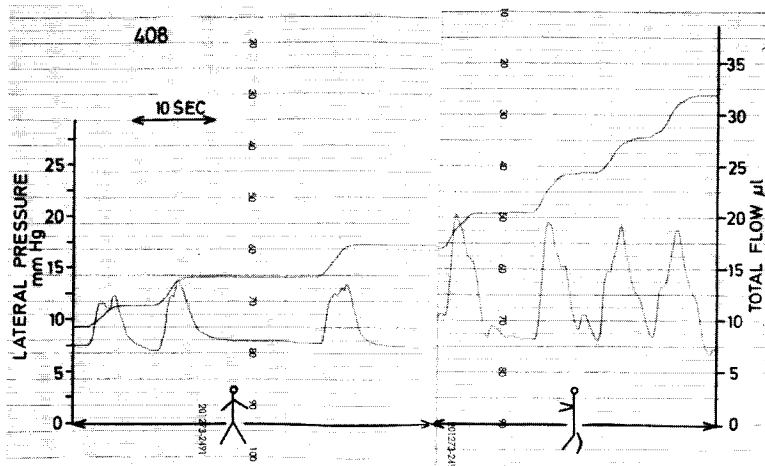


Fig. 1. Lymph pressure and flow recordings in superficial lymph vessels of lower leg in a normal man.

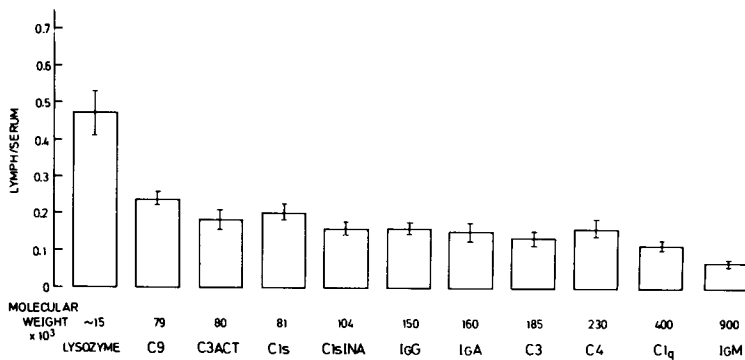


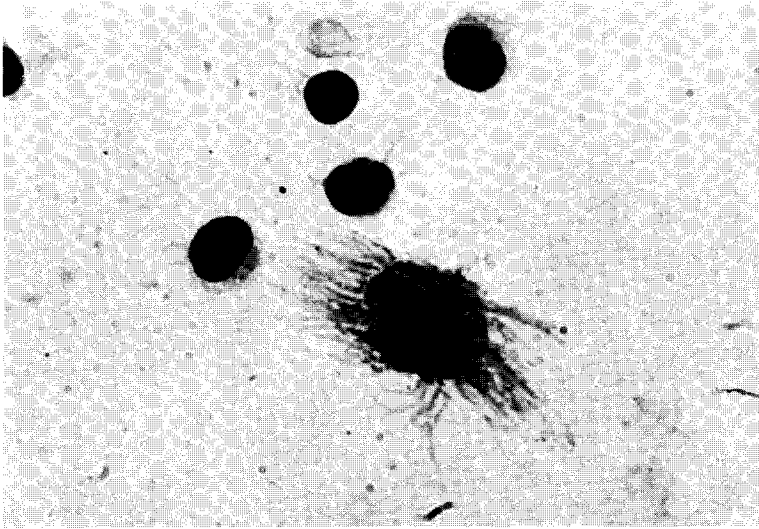
Fig. 2. Concentration of proteins with various molecular weight in prenodal lymph from human leg.

its activity or tissue fluid contains inhibitors of C3. The latter seems more likely (6). With the low level of immune proteins in tissue fluid and lymph, the question arises as to whether it will suffice to inactivate bacteria and viruses penetrating our integuments. The problem is solved when foreign antigens evoke inflammatory reaction with enhanced capillary permeability and protein concentration in tissue fluid may reach serum levels. However, in tumor tissues no inflammatory reaction is initiated and local immune resources do not suffice to inhibit neoplastic proliferation.

Recent observations (7) indicate that human lymph drained from skin contains

interleukin 1/epidermal thymocyte activating factor (IL1/ETAF), a lymphokine which has so far not been detected in serum. This might be an example supporting the notion that lymph transfers regulatory factors produced by parenchymal non-lymphoid cells (in this case keratinocytes) to the regulatory centers (lymph nodes).

Lymph cells found in lymphatics differ from those of blood vessels phenotypically and functionally (8). The capillary wall acts as a filter for blood cells which are about to extravasate. The mechanism of this process in the non-lymphoid tissues remains largely unknown. Moreover, some subsets of leu-



*Fig. 3. Two main cellular components of normal human lymph: Langerhans cell and lymphocytes.*

cocytes which leave the blood circulation might undergo phenotypical changes in the tissue space. They are then retrieved from lymph with a totally changed appearance and surface antigen expression (e.g. Langerhans cells) (*Fig. 3*). Lymph has a higher percentage of T cells than blood, specifically T4 helper/inducer cells and is lower in T8 cytotoxic/suppressor, B cells and monocytes. There are no granulocytes but approximately 6-8% of Langerhans cells, which only rarely can be found in blood. The lymph mononuclear cell population undergoes in culture spontaneous autotransformation which is not observed with blood cells. Its responsiveness to mitogens and allogeneic stimulatory activity is much higher than that of the blood mononuclear population.

Lymph is a fluid in which the morphological equivalents of immune cell cooperation can be found. Rosettes formed spontaneously between Langerhans cells and lymphocytes (predominantly T4 cells) are a frequent finding in lymph cell smears, a phenomenon not encountered among blood cells (personal observations).

These are a few examples illustrating differences between blood and lymph

vessels, based on the results of our studies in humans. In general, it should be recognized that blood vessels serve as conduits for transport of humoral and cellular factors to the tissues, and blood itself behaves as a crude inert material which only by reaching tissue space and coming in contact with resident cells can display its functional properties. Under normal conditions, no active cellular or biochemical processes specifically involving immunity takes place in blood. For example, the presence of pure serum in lymphocyte culture medium almost totally inhibits cell responsiveness to PHA, and several lymphokines do not reveal their activity in whole serum until it is diluted so much as to attenuate the activity of specific inhibitors (unpublished observations). In contrast, lymph is a fluid in which active processes are continually taking place such as autotransformation of lymphocytes, rosette formation between Langerhans cells and lymphocytes, with active lymphokines.

In conclusion, lymph flowing in lymphatics is a well-informed messenger about all the events developing in tissues; blood flowing in blood vessels is mainly the supplier, its messenger function being gradually taken over in highly organized

species by the lymphatic system. This represents the key difference.

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