

DISTINGUISHING LYMPHATICS FROM BLOOD VESSELS IN NORMAL AND DISEASED SKIN

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ABSTRACT

If it were true that lymphatics are essential for the removal of macromolecules and in this way the oncotic and hydrostatic pressures within the interstitium are determined; if it were true that lymphatics are the principal pathway for the exit of antigen and of macrophages and hence, important for cell mediated immunity, then on both accounts the lymphatics are of great significance. There must be some anxiety that none of this can be confirmed and that some tissues such as the brain and the eye do not need lymphatic vessels as such. We must also note that in many diseases the lymphatic system seems to be severely disrupted, and yet it is difficult to show that the tissues are severely compromised. One wonders to what extent blood vessels or any other system, such as the mononuclear phagocytic system, can take over the role of the lymphatic. To answer these questions one needs to be able to identify the lymph clearance system as distinct from the blood supply system. Although this is easy in health, it becomes very difficult in disease.

ANATOMICAL DISTRIBUTION

While it is often said that the lymphatics follow the arterial system very closely, this is not actually true of the initial lymphatic. Blood supply is usually nearer the tissue requiring nutrition than

is the lymphatic system. In the skin the lymphatic system lies mostly deep to the capillaries that supply the epidermis, and they lie on the periphery of the fat lobules, which have a rich capillary blood supply. In pathology such as wounds or granulomas, the blood supply tends to penetrate into the tissues further than the lymphatic and this may be because the condensation of matrix and the increased cell density of a wound edge or granuloma prevent the penetration of lymphatic vessels, whereas blood vessels with their pulsatile and high pressure system are able to penetrate more deeply. It is a fact that the more distorted the anatomy from pathology, the more the lymphatics become separated from the blood vascular system. The question then has to be asked, how is lymph removed in pathology?

HOW IS LYMPH REMOVED IN PATHOLOGY?

Preferential pathway

It seems to be well established that there are preferential pathways for the clearance of lymph and cells. One such pathway is the elastin fibre as described by Hauck (1) in the mesentery. In normal healthy skin this also seems to be so, and we have shown that the distribution of elastin is ideal both for a pathway into the lymphatic system but also to transmit forces to the lymphatics

to aid them in their emptying (2,3). But again, the problem is that in pathology elastin is often destroyed. One of the original observers, Unna (4), pointed out that elastin seemed to be destroyed simply by oedema. Parish (5) has recently reemphasized the role of the neutrophil, and in our studies of leprosy we have noted that elastin is often removed from the lymphatic as it approaches a granuloma. Elastin is useful for identifying lymphatics in health but not in disease. If elastin is an important preferential pathway, does it matter that this pathway is so often destroyed in disease and does it contribute to the pathology? Alternatively, when elastin is destroyed, is it simply replaced by some other kind of pathway, as yet unidentified? My impression is that where elastin is destroyed, the connective tissue develops a more dense and inflexible matrix which may help to prevent the accumulation of macromolecules in the interstitium.

ANGIOGENESIS

Angiogenesis is a term that should encompass not only blood vessels but also lymphatics. We suppose that the newly developing blood vessel has to respond to heightened intravascular pressure and the oncotic effect of intravascular protein, as well as to intravascular coagulation products and platelets. The endothelium of the blood vessel thus requires a physical and biochemical capacity to equip it to deal with this internal environment. At the same time, exudation and the collection of macromolecules in the tissues produces a protein oedema, and collections of fluid become lined by endothelial cells, later to become lymphatics. The endothelium of the lymphatic does not have to acquire the equipment to deal with high intravascular pressure or coagulation and the platelet in its internal environment. I assume, therefore, that the appearance of endothelium as a rather attenuated structureless lining cell is determined by the fact that this is all its normal environment requires of it. It is conceivable, however,

that when the environment changes, then the endothelial cell has to change also. It is for this reason that in pathology the endothelial cell of the lymphatic is less easy to distinguish from the endothelial cell of the blood vessel. Much that is described as vasculitis or phlebitis, in fact, lymphangitis. I know of no evidence which suggests that endothelium is not pluripotential and therefore it seems of limited value to continue to look for morphological characteristics which distinguish the lymphatic from the blood vessel in pathology. Our studies of other cells, such as the fibroblast in tissue culture, also lead us to suppose that cells carry with them into culture only for a limited time certain characteristics, and that a changing environment *in vivo* can induce a change in cells so that they behave differently when subsequently transferred to the tissue culture system. It has always surprised me that experts on the endothelial cell in tissue culture have placed so much emphasis on identifying characteristics, to the exclusion of and failure to study cells which have not the characteristics expected of them. Some very interesting cell systems have thus been ignored. With my colleague, Masuzawa (6,7), we suppose that endothelial cells in tissue culture which have none of the characteristics of healthy blood vessel endothelium, might prove to be of lymphatic origin, and the most likely feature of such a cell would be a large and attenuated cell with a relatively small nucleus spreading widely in tissue culture.

ANGIOLYMPHOID HYPERPLASIA

The final feature that I would like to comment on is angiolymphoid hyperplasia. It is conceivable that lymph 'nodes' develop at points of partial obstruction of the developing lymphatic system, and that is why they are seen especially in the flexures. In the lymph node, the relationships between the lymphatic channels and the blood vessels include lymphatico-venous shunts and the development of high endothelium in the

post-capillary venule. The presence of both these features determine the pathways taken by macromolecules and cells. A case can be made for the concept that the pathway taken by the lymphocyte or macrophage is the determining factor in immunological responses. The presentation of antigen to cells within the lymph node is important for a T cell response and if antigen is diverted into the vascular system without being presented to the lymphoid tissue, then cell mediated immunity is impaired. It is important to look at the role of obstruction to the lymphatics in the production of angio-lymphoid hyperplasia at any site in pathology since it may influence the direction of communication. The development of high endothelium with macrovesicular transport in the arachnoid villae of the brain or of the canal of Schlemm is associated with an absence of normal lymphatic drainage in the form of lymphatic vessels. If instead of concentrating on the differences between the lymphatic vessel and the blood vessel, we were to concentrate on the microcirculation of lymph clearance as opposed to the microcirculation of blood supply, and if we were therefore to concentrate on pathways rather than on vessels, the lymphologist

might make a greater contribution to the understanding of disease. We have studied the pathways using technetium colloid and also carbon inoculated into the skin. While the pathway for their clearance is well defined in health (8,9), it becomes less so in disease.

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