'Prelymphatic': a question of terminology?

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There is some confusion in the literature about the term 'prelymphatic'; in part due to different interpretations of the evidence, and in part because of semantic difficulties. What follows are some reflections on the results obtained so far, and a comment about nomenclature.

Most workers today regard the interstitial tissue as a two-phase system. They consider that the more solid gel-phase contains effectively no free water - although large amounts of bound water are present. The fluid sol-phase is usually far less in volume, and contains the free water with minimal amounts of the mucopolysaccharides. No doubt there are areas of gradation from one state to the other, where the two phases meet.

For may years, it was thought that the sol-phase was in the form of many isolated, small (50 nm, or so), vacuoles lying in the gel-phase (Chase, 1959). However, high voltage electron microscopy of thick sections has shown that, in fact, they form irregular, randomly arranged and interconnected channels (Casley-Smith and Vincent, 1978). The sizes and numbers of these can be estimated by filling them with a precipitated tracer, which has a high charge-density and, hence, is retained in the sol-phase rather than also entering the gel-phase (Browning, 1979; Browning and Casley-Smith, 1980; Casley-Smith and Vincent, 1978, 1980; Casley-Smith et al., 1979). It has been found that the numbers and dimensions thus estimated agree well with those found by macro-physiological methods; both show very similar enormous increases after injury, or in edema. They appear to be concentrated in the neighborhood of the blood vessels - as might be expected from the increased fluid flow in these regions. Their numbers and dimensions seem to have a negative-feedback, i.e. are self-regulating, by virtue of the conflicting effects of high flow-rates in the larger channels eroding their walls - but larger channels also tending to have slower flow-rates because they allow quicker equilibration. Other calculations, based on these data, also agree well with macro-physiological results (Casley-Smith, 1976a).

These 'tissue channels' seem to form a 'fine circulatory system', transmitting the bulk-flow of fluid through the tissues, and no doubt providing the major paths for diffusion - although one wonders if substances might also diffuse, perhaps with more difficulty, through the bound water of the gel-phase. Thus one envisages the channels as providing paths, from the arterial to the venous sides of the capillary systems. No doubt some of them also provide paths which terminate at the walls of the initial lymphatics - sometimes at endothelial intercellular junctions which are openable (Collan and Kalima, 1974). At times the term 'prelymphatic' is used for all the channels, at others just for those which terminate at the initial lymphatics.

The difficulty is that the system of tissue channels is so randomly arranged and interconnected; the individual segments are so short (a few μm, or less); their walls are probably not definite, but are formed by a gradual alteration from the gel- to the sol-phase (the extent of this gradation is unknown - it may be 1 nm; it may be 100 nm). Thus one can sympathize with, although not agree with, those who do not even wish to call them 'channels'. (I think, however, the words 'tissue channels' are justified: a channel is simply a path in which fluid flows - nothing is implied about its walls.) There is much more doubt about the propriety of labelling them all, or even those segments terminating at an initial lymphatic, as 'prelymphatics'. After all, most of the channels conduct fluid which is leaving, or returning to, the capillaries; those segments actually terminating at an initial lymphatic are often very short and relatively infrequent. I think, then, it is better just to call all these 'tissue channels', remembering that fluid passes in them from and to the blood capillaries, and to the initial lymphatics.

The situation is, however, different in a few regions. While most systems of tissue channels conduct fluid for only a few μm, in the brain, the eye, and perhaps in cortical bone, the tissue channels carry fluid for many cm from deep within these regions to the nearest true initial lymphatics. For the brain and eye, these latter are largely in the adventitia of the internal carotid artery, outside the skull (reviewed: Casley-Smith, 1976b; Földi, 1969, 1972, 1977; Földi et al., 1968a). These systems of non-endothelialized spaces - and potential spaces - lie in the basement membrane regions of the smaller vessels and the adventitia of the arteries. They act very similarly to the true initial lymphatics (although no doubt not concentrating the lymph). If the true initial lymphatics which drain them are occluded, both the regions drained by these and those drained by the long system of tissue channels display the changes of lymphedema (reviewed: Casley-Smith et al., 1978, 1979; Földi, 1969, 1972, 1977; Földi et al., 1968b). These systems, which perform such a special role, seem to deserve a special name. For them, 'prelymphatic system' seems justified.

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Comments

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Transport of macromolecules across the microvessel wall and their return to the blood stream via the lymph is by now a generally accepted mechanism. In fact, the question has been posed by Zweifach, whether or not under physiological conditions the lymph represents the major return path, not only for protein, but also for water. This flux, water and protein, which will eventually become the lymph, has to cross the extravascular space and the possibility that, in this process, a system of low resistance channels is used is a most intriguing idea.

Two apparently independent candidate systems of pathways have here been described: a pathway along the tissue fibers and a pathway along the conducting channels. It would be interesting if a relationship between these two, the fiber network path and the conducting channel system path, existed. Such a correlation would go a long way towards 'explaining' the origin of the heterogeneity in proteoglycan distribution which creates the channels.

We know that hyaluronic acid and the associated proteoglycans are in principle free to diffuse through the tissue space even though they are severely constrained. Unless, therefore, the heterogeneity which is seen is a (perhaps a very slowly relaxing) transient one, the phase separation, i.e. the concentration distribution which is found, must have arisen voluntarily either due to incompatibility of the macromolecular components or because of a pre-existing, pre-imposed heterogeneity formed by the fibrous network system in the tissue space. It would, indeed, be considerably easier to account for the occurrence and stability of the conducting channel system if it were correlated to the fiber system. Two points should be checked however: are the channels really seen under physiological, i.e. non-edematous conditions? are the channel contents of a higher protein concentration than the surrounding gel?

An important point to note is that drainage of the channel contents into the lymphatic system will be down a pressure gradient, even though this can be extremely slight. It would be hard to imagine that the pressure in the channel is lower than that at the mouth of a terminal lymphatic.

On the semantic score, I think that the use of the terms 'bound' and 'free' water is much more misleading and reprehensible than 'prelymphatic'. The water in the gel is as free, on the molecular level, as the water in the sol. There are stronger frictional constraints on convected transport, but this is all. Diffusional freedom is hardly impaired. I do agree, however, that the term 'prelymphatic' is better used only where the channels are essentially unique extensions of the terminal lymphatic vessels. In instances where the channels merely represent connected regions of lower proteoglycan content they are better attributed, also by name, to the connective tissue space.

Final remarks

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Critical remarks center essentially on two areas: the terminology employed and experimental interpretation and conditions. The term 'prelymphatic tissue channels' was not created by us and first used by Casley-Smith. We prefer also the term 'low resistance pathway' (see also Clough and Smaje, J. Physiol. (283 (1978)). But the topographical term 'prelymphatic channels' does not anticipate anything and is open from a morphological view. The term can always be specified. Important seems the fact that new findings obtained by different methods in different tissue and animals suggest the existence of preformed structures in the extravascular space which are not identical with the true lymphatic system. However, identification of the electronmicroscopical and vitalmicroscopical findings is yet to be made. The vitalmicroscopic studies show the direct connection of the channel-like structures with the true lymphatics. This cannot be the effect of an edematous swelling or damage of the tissue. Consequently, the interpretation must be, that the beginning of the fluid drainage system is more peripheral than with the true lymphatics. The beginning would be localized in the surroundings of groups of tissue cells, defined as drainage unit. The investigations were carefully performed and the tissue was protected against unphysiological conditions as far as possible.