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The Fine Structure and Functioning of Tissue Channels and Lymphatics

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Summary

The fine structures of the tissue channels and the lymphatics are described. The two systems form part of the whole blood vascular-tissue channel-lymphatic complex. The fine functioning of this is very dependant on the structures of its individual components. In brief, the tissue-lymphatic system is a leaky swamp through which material flows due to the vagiaries of adjacent pressure changes. It enters the lymphatics via holes in their walls: it is retained in them when the holes are closed.

Tissue Channels

It is necessary to start a consideration of the lymphatic system in the tissues. Indeed it might be better to start at the blood capillaries. This is because the capillaries-tissue-lymphatic complex really forms an entire system; each part affects each other part.

The interstitial matrix is largely composed of mucopolysaccharides (13, 21, 25) which have most of the tissue water adsorbed to them (19, 20). The water which is actually free in the tissues is remarkably little, except of course in oedema. It appears to be present in the tissue channels. These are quite narrow (approx. 100 nm) and sparse (approx. 1 per um^2), and relatively short (Figs. 1, 2)/(10, 12). While most channels form a "fine circulation", passing from the arterial side of capillaries towards their venous sides, some pass to the initial lymphatics (15); these are often termed "prelymphatics". In some regions, however, the systems of channels are very long indeed, e.g. in the brain and retina they connect the deep portions of these tissues with the true lymphatics in the neck (11). While it is often said that these tissues do not have lymphatics, the prelymphatic pathways form a system of non-endothelialised channels (and potential channels) which perform this function, which

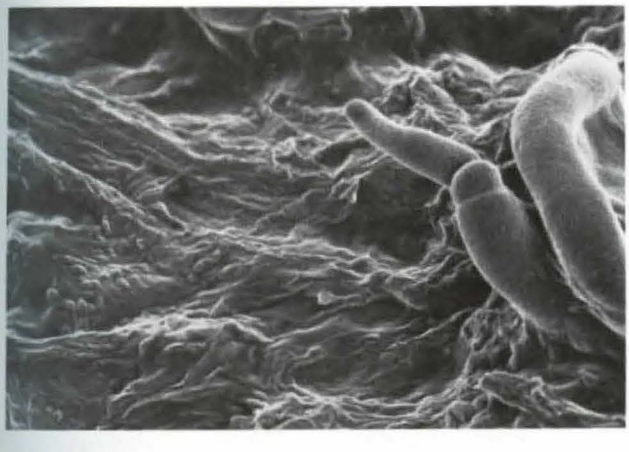

Fig. 1 Many tissue channels are shown, filled with plastic, in this scanning electron micrograph of rat ileum. Some are shown passing between the capillaries.
350 x (from Casley-Smith and Vincent, 1978).

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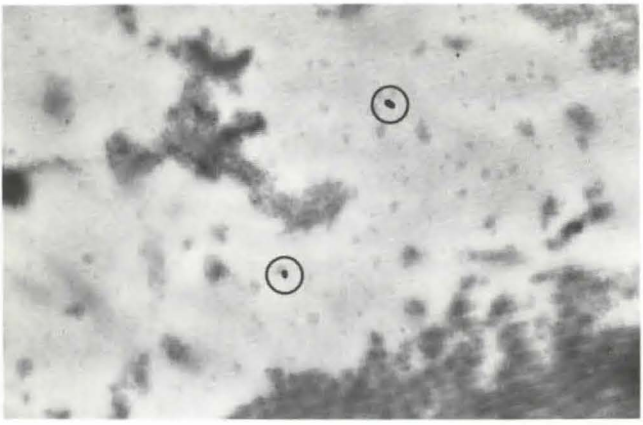

Fig. 2 Tissue channels, filled with ferri-ferrocyanide precipitate (circles), in normal skin. 18.000 x (from Casley-Smith et al., 1979).

empty into the true lymphatics, and which cause the same changes to be seen in the tissues they drain as are seen in tissues drained by true lymphatics when lymphostasis occurs. During lymphoedema the channels increase very greatly in size and numbers (12), as they due in other oedemas; in fact the hydraulic conductivity increases up to 100,000 times (Fig. 3)/(19, 20)!

The Initital Lymphatics

These are the most peripheral elements of the lymphatic system. Here material is taken up. They have a structure very similar to that of venous blood capillaries, with a few vital differences (Fig. 4)/(reviewed: 2, 3, 5, 26).

The endothelial intercellular junctions are the single most important feature of the initial lymphatics. While, just as in the blood capillaries, there are many tight and close regions in these unions between the cells, the lymphatics are distinguished by having some 1–6% of the total junctional length open – with gaps of 0.1 to several μm (16a). These lengths increase to up to 50% if the tissues are very active, during oedema, or following even mild injury. These openings are occassioned by the relative lack of adhesion devices between the cells, by the tenuous basement membranes of the vessels, by the fibrils attached to their exteriors, and by the inflow of fluid through them. It has been frequently shown that it is

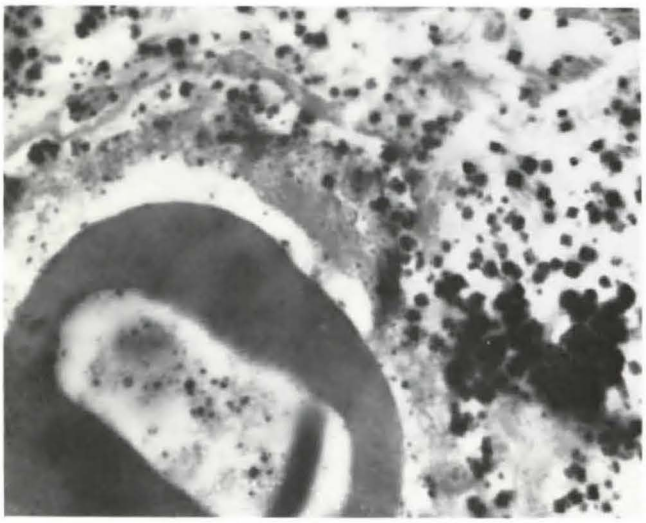

Fig. 3 Acute lymphoedema in the same region as for Fig. 2. The channels are very greatly increased both in numbers and dimensions. 18.000x. (From Casley-Smith et al., 1979).

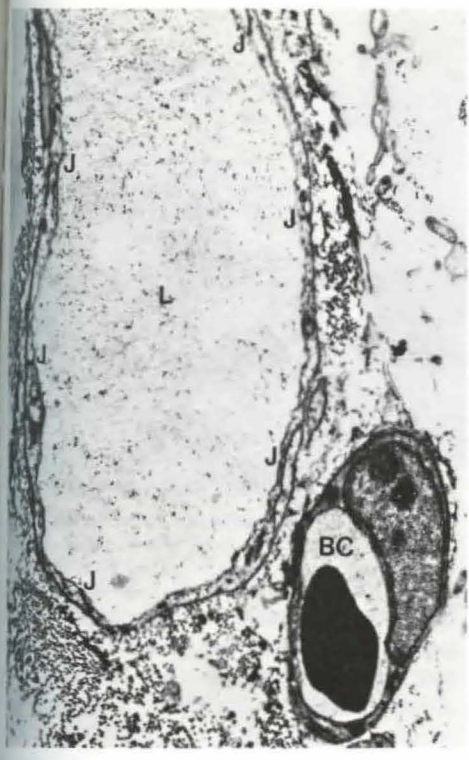

Fig. 4 An initial lymphatic (L) in normal mouse ear. A blood capillary (BC) is shown for comparison. There are many junctions (J) in the lymphatic endothelium. 4,000 x (from Casley-Smith, 1977a, as are the remainder of the Figs.).

via the open junctions that fluid, and macromolecules etc. carried by it, enter the initial lymphatics. Even relatively few open junctions can easily account for this passage, because of their great hydraulic conductivity (17)

In fact the junctions are only open during the filling-phase of the lymphatic cycle (Fig. 5). They close during the intermediate-phase (when the vessels are lying filled, but quiescent). During the emptying-phase, the raised total tissue pressure will be transmitted almost *in toto* to the lymph (and is greater than the tissue hydrostatic pressure). Hence the junctions are then held closed against the surrounding tissues (Fig. 6). It is important to note, however, that they are only "closed" to macromolecules: they are still quite permeable to small ones (Fig. 7).

There are fibrils attached to the outside of parts of the endothelial cells, connecting them with the interstitial tissue (27). Thus when the tissues are oedematous the fibrils act as guy-ropes – holding the vessels open against the raised total tissue pressure, and helping to open the junctions; if the injury is so severe that the tissues are disrupted their attachment to the fibrils fails and the vessels collapse (as occurs with hyaluronidase – 1).

In a few regions these fibrils probably play this role normally, i.e. where the tissue hydrostatic pressure is positive, e.g. the kidney and testis; here the lymphatics probably function more as conduits, with fluid just pouring into and through them. In the remaining tissue it

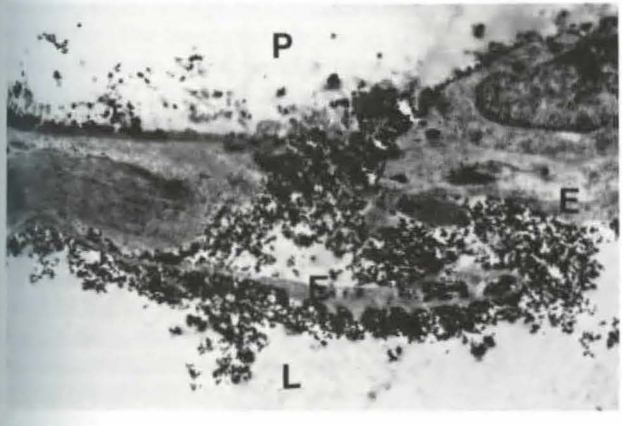

Fig. 5 A mouse diaphragm, fixed during the filling-phase (relaxation). Much carbon is passing from the peritoneal cavity (P) to the lymphatic lumen (L) via an open junction. 7,500 x.

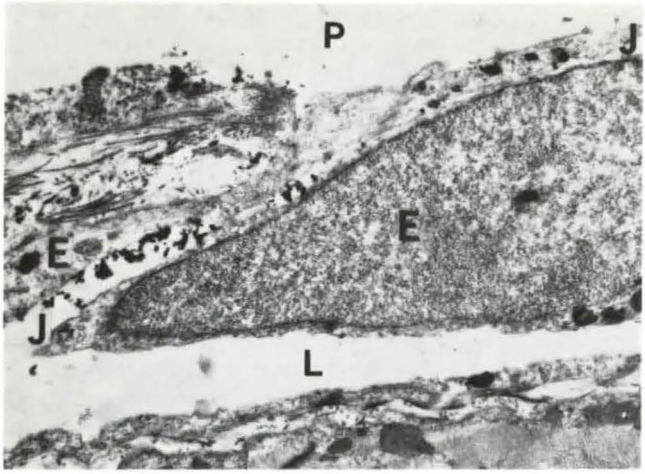

Fig. 6 As for Fig. 5 but fixed during the emptying-phase (contraction). A junction (JJ) is almost closed to macromolecules and carbon. 12.000 x.

is likely that total tissue pressure is less than in the lymphatics (reviewed: 3, 4, 5). Hence the vessels will be pushed out against the tissues.

Not only this, but it is likely that the tissue hydrostatic pressures are normally less than the intralymphatic pressure in the majority of regions. Thus it can be seen that the forces causing the filling of the vessels are not likely to be simply the hydrostatic pressure difference, as is so often assumed. True, such a difference has sometimes been measured (23), but only in immobile, oedematous tissue. Elsewhere, the intralymphatic pressures are usually measured to be about atmospheric (14, 23, 39), while those in the tissues are some cm of water less than this (14, reviewed: 3, 4, 5, 18, 19, 20). Since most measurements have indeed been made on immobile tissue, where the initial lymphatic pumps cannot function, it is likely that the normal initial lymphatic pressures are even less than those found.

Alternatives to a hydrostatic pressure gradient have been suggested, e.g. suction from the collecting lymphatics, and active vesicular transport. The former is negated by the fact that initial lymphatic pressures do not fall during the filling of the adjacent collecting segments and anyway are greater than tissue hydrostatic pressures (22, 28, 37, 38); the latter goes against both the structure of the endothelium (which is most unlike tissues specialized for active transport) and against all the evidence

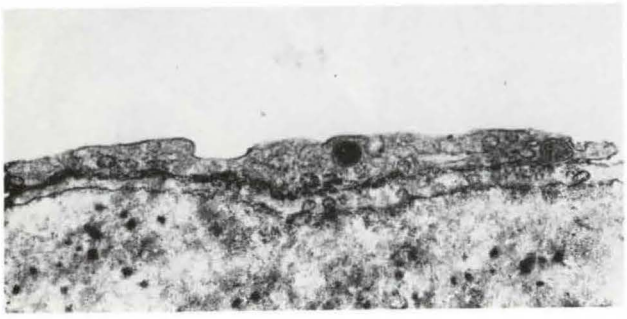

Fig. 7 A close junction in the diaphragm, with much ferri-ferrocyanide precipitate in it: showing permeability to small molecules. 35.000 x.

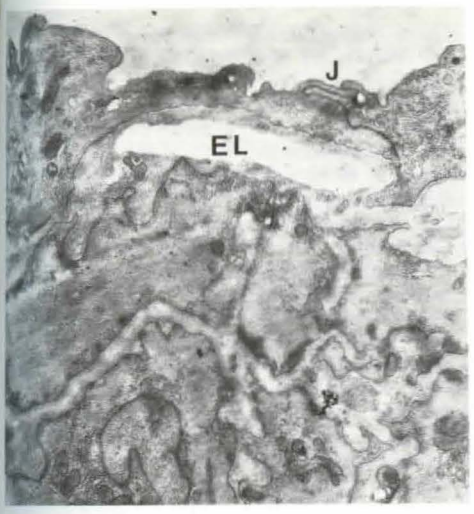

Fig. 8 **Thoracic duct, showing some of the muscle** in its wall and a closed junction (J) in its endothelium. The elastic lamina (EL) is visible. 7.000 x.

in favor of the open junctions as the path into the vessel. One other possibility is that the lymph might be more concentrated than the tissue fluid and cause fluid to enter by a colloidal osmotic pressure difference.

There has been considerable controversy about whether lymph is more concentrated than tissue fluid. The arguements and counter-arguements are too long and complex to go into here (reviewed: 3, 4, 5, 6, 7, 17). In general it appears that it is not possible to sample tissue fluid,save in the most general sense, and certainly not from just adjacent to an initial lymphatic; similarly lymph has not been sampled from other than a large collecting lymphatic – in a normally functioning tissue. The lymph which has so far been sampled from initial lymphatics has been from tissue which has been immobile for periods of up to 30 minutes or more (34, 35).

Certainly lymph from a large collector has a concentration similar to that obtained from a generalized sample of tissue fluid, but this could simply be due to equilibration across the wall of the vessels once they leave the region (the remote collectors). While *Hargens and Zweifach* (22) showed that the concentration of lymph increased as it ascended the collecting lymphatics (due to ultrafiltration), *Nicolaysen* et al. (29) found that it was constant from the initial lymphatics to the central ends of the adjacent collectors (i.e. in the same tissue). However these latter measurements were taken randomly over the whole of the initial lymphatic cycles and it is very likely (4, 5) that the mean of these will equal the concentration in the adjacent collectors – which are subjected to similar pressures. When the concentrations in the initial lymphatics were compared with those in the adjacent tissue channels, the former were some 3 times the latter. It was also found that the lymph concentrations varied considerable during the cycle – being diluted during filling and concentrated during emptying (4, 6).

If this concentration difference does exist, it is quite possible for a large effective colloidal osmotic pressure to be exerted even over a pore much larger than the protein molecules, as has been shown in vitro (8, 9). Also, proteins are carried up their own concentration gradient by the flow of fluid caused by this (8). This rather surprising finding has received theoretical explanation (30, 31, 40). Of course the inflowing fluid will dilute the lymph, which is reconcentrated during the next emptying-phase by ultrafiltration of fluid via the "closed" junctions (both those normally close and the openable ones). Much of this fluid passes to the tissues and thence to the blood. A mathematical model (17) shows that it is quite physical possible and will possess the property of negative-feedback (homeostasis).

The Collecting Lymphatics

The collecting lymphatics, while they are basically tubes connecting the initial lymphatics with the blood, are still quite complex and have quite an influence on the functioning of the system (reviewed: 2, 3, 5, 16, 17, 33, 28). As one passes centrally, the junctions become less and less frequently openable, until all are closed (Fig. 8). Also, the walls become thicker and thicker. Hence the permeability of the walls to large molecules diminishes, although they are still quite permeable to small ones (16, 18, 24, 33, 36).

The thicker walls basically consist of contractile smooth muscle, which helps to pump the lymph along – aided by varying total tissue pressures caused by respiration, contraction of adjacent muscles, etc. The intra-lymphatic valves direct the flow. The intrinsic contractility is autoregulated, allowing for variations in input (28, 32, 37, 38) – i.e. more homeostasis.

Finally, it is important to note that there are many more connections between the collecting lymphatics and the blood than just the thoracic duct. It appears that lympho-venous anastomoses occur in many places (18), allowing much lymph to enter the blood "unobserved". In addition, it appears that in the lymph nodes both small and large molecules pass from lymph to blood, or vice versa – depending on local pressure and concentration gradients.

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