tein and fluid also occurs in the lymph nodes, but some controversy exists about the net direction of both of these.

Blood-lymph interrelationships

In regions with only continuous capillaries, apart from protein which is normally lysed in the tissues and which may be up to about a third of that which leaves the blood vessels (vide infra), the remaining protein which leaves them is returned via the lymphatic system. If this does not function properly considerable oedema results. A relatively small amount of fluid is also returned, but this amount is still very important in avoiding tissue oedema[2,3,23].

In regions where there are many fenestrated capillaries, it is becoming increasingly probable that there is a considerable circulation of plasma proteins, through the tissues, which re-enter the blood via the fenestrae on the venous side of the circulation[2,3,4,12]. It appears, however, that the lymphatics in this situation still are vital for the avoidance of oedema[24]. The amount of protein they remove may only amount to about 10–30%, but because this is in a concentrated form the mean concentration in the tissues is considerably reduced, and with it the colloidal osmotic pressures and tissue hydrostatic pressures. It appears that this reduction is essential for the avoidance of a mean positive tissue pressure and oedema.

Evolution

Primitive chordates have continuously lined great vessels, but the endothelial cells gradually become further and further apart in the smaller vessels, until even the basement membranes of the vessels may partly disappear and the tissue spaces are directly continuous with the blood vessels[2,3]. The higher animals have more continuous endothelial vascular linings, until in the elasmobranch the venous intercellular junctions in the body wall can still be opened by muscular movements, but in the viscera fenestrated capillaries appear, allowing macromolecular uptake there. In the teleosts the increased blood hydrostatic pressure no longer allows any blood vascular intercellular junctions to be openable, but also necessitates a raised plasma protein concentration. A separate lymphatic system now develops, which is filled by variations in the solid tissue pressure, but which propels the lymph and discharges it into the blood by means of the contractions of muscle in its walls. Thus, aside from part of the raised protein circulation through the tissues in fenestrated regions, protein is now returned to the blood via a separate system of pumps – the initial lymphatics, the segments in the collecting lymphatics and the lymph hearts, when these exist.

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Active Contractility of the Lymphangion and Coordination of Lymphangion Chains

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A 'lymph drainage capable of compensation' (FÖLDI[1]) is always based on the functional interplay between differentiated lymph drainage mechanisms, and specially effective importance is shown to be attached to the vasomotoric lymph drainage[2]. The initial lymphatics do not show any active contractions because of lack of muscle in their walls. The lack of that autorhythm of course does not mean the lacking of contractility. First information about open junctions in the lymphatic capillaries is given by CASLEY-SMITH and FLOREY[3]. My collaborator SCHIPP[4] observed in the peripheric lymph vessels intraendothelial filaments, which could be interpreted in the sense of a contractility of the endothelium. SCHIPP and SCHÄFER[5] found no open junctions inspite of experimental lymphostasis. LEAK[6] postulated in his studies on the permeability of lymphatic capillaries, that these small vessels are able to open and close the interendothelial cell joints by active contraction an relaxation of the endothelium. The larger musculous lymphatic vessels have a pronounced autorhythm. From the morphological point of view, the lymphatic vessel is characterized by its segmentation; it consists of valve segments with central muscle collars and directed multiple innervation of the smooth muscles. Physiologically the valve segment, we called it lymphangion[7], is an autochthonous efficiency element with its typical action potential[8]. The in vivo experiments of SMITH[9] and our own in vitro experiments demonstrated that the single

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[7] H. MISLIN, Experientia *17*, 19 (1961).
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lymphangion is able to contract independently, but at the same time it plays a key role in the activation and coordination of lymphangion chains because of its extensive distention. In order to measure the dependence of the pulse rate on the pressure, flow-through canulae were put into the isolated lymphangion chains[2]. Pulsating segments of vessels normally show typical inherent frequencies with a characteristic amplitude of the vessel and in relation to the present angiotonus (f 8–55 min). With increasing internal pressure of 2–25 cm H_2O, the frequency of the lymphangions increases proportionally and reaches a temperature-dependent frequency maximum. In pressure experiments at 12 cm H_2O the maximal frequency of the active pulse was 55/min (short term). Long persisting and continually regular pulse is normally found at the mesenterial lymphangion at an internal pressure of 4 cm H_2O. In connection with the specific condition of the single angions, the active pulse is often released by an internal pressure between 4 and 8 cm H_2O or between 10 and 12 cm H_2O (f 15–25/min). In flowthrough experiments, and by employing the discharge drop counting method, the volume per min is doubled if the pressure increases from 8 to 10 cm H_2O and increases 3-fold at an increase from 10 to 12 cm H_2O. These investigations were carried out on the intestinal lymphangions of the guinea-pig, which proved the importance of the active contractions for the transport of lymph; they were completed by pressure measurements at lymphatic vessels of the intestine of rats after occlusion of the vessels carried out by WALDECK[10a]. Inside an in situ occluded lymphatic vessel, an increase of pressure from 15 to 40 cm H_2O has been registered within 10–20 min. The mean value was about 27 cm H_2O. The increase of frequency taking place continuously with the increase of pressure could reach up to 65/min in the in situ experiments.

In relation to the mean pressure, the pressure amplitudes varied as well. Even as the in case of the isolated single angion, they are small, if the pressure is low; they increase with increasing pressure to about 15 cm H_2O ($^1/_2$–$^2/_3$ of the diameter of the angion), then they decrease rapidly with still increasing pressure. With further increase in pressure, the volume per min as well as the volume per pulse decreases. Because of the small mass of muscle of the lymphangions, the isotonic as well as the isometric maximum curves run near the repose-distention-curve, as is known from the heart. WALDECK[10b] determined the work of the pressure volume of a segment of a lymphatic vessel in direct dependence on the pressure by multiplying the volume of the lymphpulse with the respective pressure. Starting at zero, he found the curve reaches its maximum at about 10–15 cm H_2O and then decreases rapidly with further increase in pressure. According to our experiments with isolated lymphangions, it is obvious that the high pressures found by WALDECK in occluded lymphatic vessels were caused by addition of the pressure in the single lymphangions. At isovolumetric contractions, the isolated chains of the lymphagions create pressures up to 2 cm H_2O. The final pressure is defined by the number of contractile unities and their capability to produce pressure. Physiologically the lymphangion chains can be compared with the multiple lymphatic hearts of the gymnophions, which, as is well known, produce an intermittent rhythm. With lymphatic fistulas in non-anesthetized, freely moving sheep HALL, MORRIS and WOOLEY[11] carried out long-term experiment with lymph canula, where lateral as well as final pressures could be measured. The decisive result of those fistula experiments was the proof of an autonomic intermittent rhythm of the lymph flow. The measured pulse frequencies were between 1 and 30/min, the pressures so caused were between 1 and 25 mm Hg. These experiments also show a good or relation between the volumes of the lymph flow and the contractions of the lymphangion chains. In theoretical investigations, REDDY[12] and REDDY et al.[13] have confirmed the theory of coordination of lymphangion chains. They expressed intralymphatic pressure of the terminal lymphatics (P_{tl}) in terms of the tissue pressure and wall hoop stress

$$P_{tl} = T + h/a\,(\sigma_{hoop}) \qquad [1]$$

where T is the tissue pressure, h is the wall thickness, a is the radius of the vessel and σ_{hoop} is the hoop stress which is a function of the modulus of elasticity, the instantaneous radius, and the unstressed radius of the vessel. Similarly the authors expressed the intralymphangion pressure (P_{ly}) in terms of the external pressure, the hoop stress and the stress due to active muscular contractions:

$$P_{ly} = P_{ext} + h/a\,(\sigma_{hoop} + \sigma_{act}) \qquad [2]$$

where σ_{act} is the stress developed due to active contractility in the walls of the lymphangion, and P_{ext} is the external pressure on the lymphangion. The stress developed due to active contractility σ_{act} depends on the time as well as distention of the lymphangion. We showed with our experiments on the isolated lymphangion chains that each active contraction lasts for a given period of time which is followed by a period of refraction. During the refractory period, a lymphangion does not contract even if the wall of the angion is dilated beyond the threshold. Together with HALL et al.[11] we concluded that the force amplitude developed due to an active contraction is dependent on the di-

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stention of the lymphangion wall just before the onset of the contraction, findings which are consistent with Starling's law of the heart.

With [1] REDDY observed that a rise in the interstitial fluid pressure causes the intraluminal pressure of the terminal lymphatics to increase. Therefore, if the pressure in the terminal lymphatics is larger than the pressure in the lymphangion adjacent to the terminal lymphatics, then fluid flows from the terminal lymphatics into the lymphangion adjacent to the terminal lymphatics. From [2] it can be seen that the lymphangion pressure increases with the inflow due to the contribution of the hoop stress in this terms. If, now, the dilation of the lymphangion wall reaches its threshold, an active contraction in the lymphangion is initiated so as to propel the lymph into the lymphangion in front of it. It is clear that the outflow from the lymphangion causes the lumen size to decrease. During the recovery phase of the active contraction, the contribution of active contractility stress terms is zero. In their note on the mechanisms of lymph flow through the terminal lymphatics, REDDY, KROUSKOP and NELL JR.[13] offer an explicit explanation of these mechanisms: 'The negative pressure is responsible for the lymph absorption by the terminal lymphatics. If the threshold strain required to initiate an active contraction in the lymphangion adjacent to the initial lymphatics is zero or just above zero, then this lymphangion acts as a pump regulated by the tissue pressure'. This suction effect of the terminal lymphatics is very unlikely, as is shown by actual measurements of intralymphatic pressure given by ZWEIFACH and explained by CASLEY-SMITH[14], who proposes an alternative explanation for terminal lymphatic filling. However, even with this, variations in tissue pressure will affect the filling of the terminal lymphatics. Thus, the rest of the explanation of REDDY et al. will hold.

The duration of a contraction and the duration of the refractory period can be altered by several pharmacological agents: MISLIN[15], TIRONE et al.[16].

This theory suggests that the lymph absorption is dependent on the pressure gradient between the interstitial pressure and the pressure in the lymphangion adjacent to the initial lymphatics and can be in agreement with the conception of CASLEY-SMITH.

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Diseases of Lymphostasis

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Definition

Lymphoedema of the extremities is the only sequela of chronic stagnation of lymph on which interest is focused. It is, however, a well established fact that lymphostasis will induce not only extracellular oedema, but an intracellular too, i.e. it causes parenchymal cell lesions. A whole series of lymphostatic syndromes; 'diseases of lymphostasis' have been identified.

'Diseases of lymphostasis' may appear in any organ drained by lymphatics, independently of whether the lymph capillaries lie inside the parenchyma organs with short prelymphatics (e.g. dermis, gut) or outside (organs with long or very long prelymphatics, e.g. liver). They are characterized by typical functional and pathological alterations. 'Diseases of lymphostasis' form a new chapter in medicine. Although most of them are described up to now as experimental syndromes and still await clinical application, it is possible to outline our knowledge of this new field.

Experimental lymphostatic syndromes

Experimental 'diseases of lymphostasis' are induced surgically. The usual methods are: a) By ligating or resecting all lymph vessels and lymph nodes found, or by an intralymphatic injection of phlogogenic substances, thus provoking lymphangitis and lymph-vessel thrombosis, an acute or subacute lymphatic disease may be induced which will be terminated by lymphatico-lymphatic and/or lymphatico-venous anastomoses. b) To induce chronic forms of lymphostatic diseases, not only lymphatics must be resected but also a strip of connective tissue, even the adventitia of blood vessels, too. Such techniques have been devized, by CLODIUS (extremities) and LIE (liver), in order to delay regenerative processes. Repeated intralymphatic injections of sclerosing substances may be helpful too.

Pathomechanism

As a result of lymphostasis, the plasma proteins accumulate in the interstitium; this leads to an increase in interstitial colloid-osmotic pressure and to lymphoedema. Intracellular oedema and cell damage will soon follow due to the increase of interstitial pressure, disturbed cell nutrition and transport of metabolites. Stagnation impairs the 'vehicle function' of proteins; hormones and vitamins bound to plasma proteins participate in their extravascular circulation as well as