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LETTER TO THE EDITOR

INCREASED INITIAL LYMPHATIC UPTAKE IN HIGH-FLOW HIGH-PROTEIN OEDEMA: AN ADDITIONAL SAFETY FACTOR AGAINST TISSUE OEDEMA

Recently, Taylor (1) published a useful and timely review of the alteration of lymphatic transport as one of the safety factors in oedema. He emphasized what has been known for some years, largely as a result of work by himself and colleagues, *viz*: that lymphatic transport capacity is greatly increased in high protein oedema states caused by damage to blood capillaries as compared with an equal low protein oedema state caused by acute elevation of venous pressure. (It is evident that these oedema syndromes are high-flow oedemas, unlike low-flow ones caused by a reduced lymphatic transport capacity, i.e., primary and secondary lymphedemas.) Whereas Taylor did not specify that oedema associated with increased lymph transport were high protein oedemas, it is apparent that this is the case from the typical condition cited namely "chronic elevations of capillary pressure or damaged capillary endothelium" (1, p. 119).

Thus, in addition to the traditional three safety factors against oedema (increased tissue hydrostatic pressure, reduced tissue colloidal osmotic pressure, and increased lymphatic transport), there is in high-flow high-protein oedemas, a fourth factor namely: increased lymphatic transport capacity. While this fourth factor is certainly acting once such oedema is grossly evident, it is still uncertain how large a role it plays when the oedema is only minimal. Taylor terms this (or these) factors "EDLF" or "edema-dependent lymphatic factors"; but the acronym "EDLF" may cause confusion when "oedema" is spelled in the English or German style. Perhaps "VDLF" is more suitable with "V" standing for tissue volume.

Taylor then provides seven possible explanations of this phenomenon (1, p. 120-121). One of these: "reduced tissue resistance," seems improbable because it would occur equally in both low- and high-protein oedemas. The next "altered tissue compliance" also seems unlikely although it is possible that this phenomenon is altered by excess proteins accumulating in the tissues. His final four other explanations refer to a variety of mechanisms which may increase "lymphatic pumping." Undoubtedly, all of these entities may increase pumping by the collecting lymphatics, but it is generally accepted that initial lymphatics do not pump actively (2). Initial lymphatic emptying may be more complete—so that they are marginally more efficient, but it is improbable that collecting lymphatics exert a suctioning effect at the level of the initial lymphatics (2). These influences, if present, are unlikely to affect the uptake of tissue fluid into the initial lymphatics. Yet this must be the primary mechanism for this safety factor to operate.

We are left then with Taylor's third explanation: "the lymphatics respond to the greater amount of protein in the

tissues by increasing their pumping ability" (1, p. 120)—for the reasons outlined above, this explanation must refer to the initial lymphatics not the lymphatic collectors. For this proposal, there is indeed experimental corroboration (3).

The peritoneal surfaces of the diaphragm provide an excellent site for physiological studies of the initial lymphatics, with the peritoneal cavity acting as a tissue space. Not only does initial lymphatic uptake vary with the hydrostatic pressure in the peritoneal cavity (especially at high positive pressures) but it also varies with the protein content of peritoneal fluid (3). Similar variations of initial lymphatic uptake with the protein concentration of tissue fluid are also implicit in the results of Courtice and Steinbeck (4,5) using this site (3). McKay et al (6) did not corroborate these findings, but they used a tissue pressure of +20cm H_2O; at this high pressure the effects of varying tissue protein concentration are known to be overwhelmed (3).

Although tissue hydrostatic pressure also affects initial lymphatic filling, especially at positive tissue pressures, these results tend to corroborate (3) that the colloidal osmotic pressure hypothesis is also correct (2). Irrespective of any disagreement about the forces promoting initial lymphatic uptake, these experiments substantiate that this uptake is markedly enhanced as the protein content of the tissue fluid increases. This physiological explanation verifies one of Taylor's proposals for increased lymphatic transport capacity with high-flow, high-protein oedemas.

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Dr. Taylor Replies:

I was delighted that John Casley-Smith responded to my recent paper (*Lymphology* 23:111-123, 1990), for my original intent was to stimulate discussion of the well known fact that lymph flows are much higher when the capillary endothelium is damaged in an organ as compared to that occurring when only venous outflow pressure is increased. I attempted to explain this phenomena by evaluating factors which affected either lymphatic filling or lymphatic pumping ability. *Fig. 1* is a cartoon of the lymphatic flow system showing the capillary, its endothelial cells, and a very diagrammatic overall lymphatic system that includes initial and large lymphatics. The lymphatics could remove more capillary filtrate if they fill more easily which occurs when the resistance to fluid flow within the interstitium decreases (shown as R_T) which occurs in edema as tissue spaces expand. The lymphatics can also remove more capillary filtration if the gradient for lymphatic filling is higher. If the tissue compliance increases, then the fluid entering the tissues from the capillaries does not elevate tissue pressure to levels that are transmitted into the lymphatics causing the lymphatic

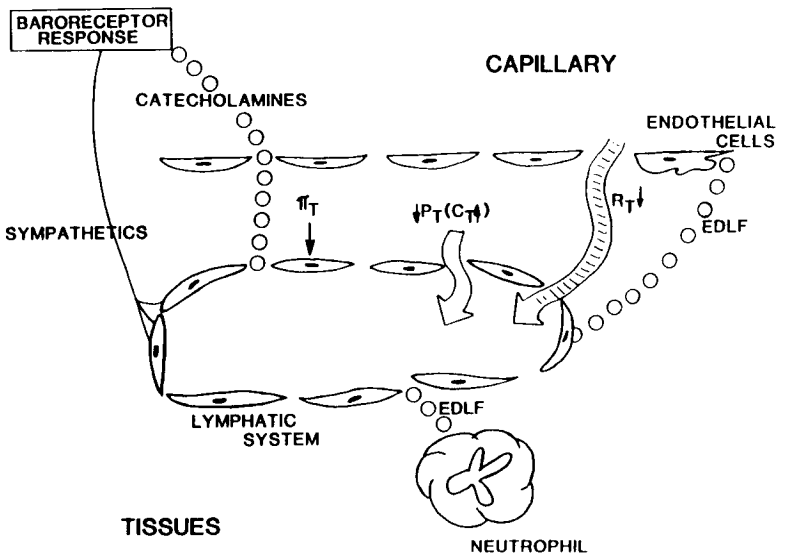

Fig. 1. Possible mechanisms responsible for producing a greater lymph flow with damaged capillary endothelium. $R_T\downarrow$ indicates a decreased tissue resistance and an increased lymphatic filling. $\downarrow P_T(C_T\uparrow)$ indicates an increased tissue compliance which allows P_T to be lower for a given tissue volume, π_T is tissue colloid osmotic pressure, and EDLF refers to edema dependent lymphatic factors.

filling pressure (tissue fluid pressure minus lymphatic fluid pressure) to be higher than that associated with only venous pressure elevation. R. Drake and J. Benoit suggested to me that the presence of edema may cause the lymphatic vessels to behave like pipes and lymph flow is determined by the difference in initial lymphatic pressure and some downstream intralymphatic pressure. This process requires that the lymphatic valves be either incompetent, or not closed, except in regions where the lymphatics drain into the venous system. If these conditions exist, i.e., decreased tissue resistance, increased tissue compliance or continuous lymph flow unimpeded by valves, then the increased lymph flow seen with damaged capillary endothelium would not necessarily be related to factors that effect lymphatic smooth muscle mechanisms.

But, like John, I also surmised that the increased lymph flow had to somehow rely on mechanisms that would increase the pumping ability of the lymphatics and indirectly affect lymphatic filling as shown in the cartoon. The lymphatic pumping ability could be augmented by the high concentrations of tissue proteins associated with damaged capillaries in some unknown fashion as Dr. Casley-Smith points out in his letter. In addition, the release of edema dependent lymphatic factors (EDLF) from damaged endothelial cells, neutrophils, or the lymphatic endothelium could increase the effectiveness of lymphatic pumping mechanisms and the nervous system could also increase lymphatic pumping ability either by direct innervation or indirectly through the release of catecholamines as shown in *Fig. 1.*

To evaluate these concepts further, let us consider the following two sets of data: The data shown in *Fig. 2* were generated by R. Drake, G. Laine, and J. Gabel (*J. Appl. Physiol.* 58:70-76, 1988), who measured lymph flow from a lymphatic draining a dog lung after elevating the lymphatic outflow pressures. Note two things: 1) the decrease in lymphatic flow begins at very low outflow pressures and has decreased to 5% of its original flow

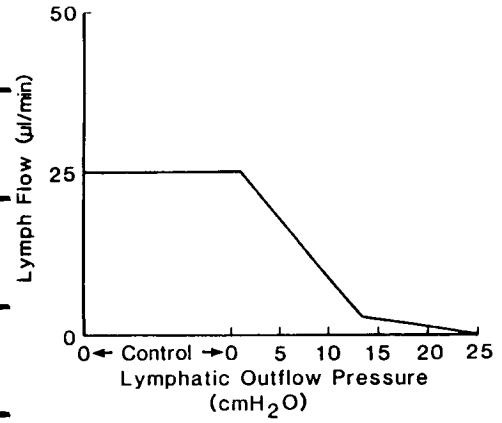

Fig. 2. Effect of increasing lymphatic outflow pressures on lymph flow. (Published with permission of Saunders Publishing Co., reprinted from Taylor, Rehder, Hyatt, and Parker, et al., In: Clinical Pulmonary Physiology, *pp. 180, 1989).*

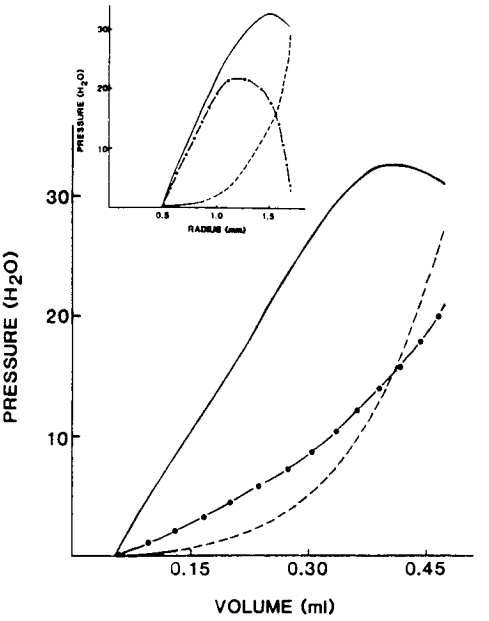

Fig. 3. Plot of pressure generation (cmH_2O) in a lymphangion as a function of volume (mls). Solid line is total pressure, dotted-dashed line is active pressure and dashed line shows passive pressure. The inset shows the same data, but pressure is plotted as a function of lymphangion radius (mm) (redrawn from T. Ohhashi, T. Azuma, and M. Sakaguchi, Am. J. Physiol. *239:H88-H95, 1980).*

at outflow pressures of 12-15cmH_2O. 2) It had also been shown in these studies that the lymphatic vessels used to collect the data shown in *Fig. 2* could produce stop-flow pressures of 25-30cmH_2O, yet lymph flow decreased to extremely low levels at 15cmH_2O outflow pressure. These data clearly show that any condition which alters lymphatic pressure either by decreasing the initial lymphatic pressure or elevating upstream pressure produces a tremendous effect on lymph flow regardless of the pumping capabilities of the lymphatic system. Therefore, the pressure gradient within the lymphatic system from initial to larger lymphatics is also a most important determinant of lymph flow.

Fig. 3 shows a pressure volume curve of a lymphangion from the elegant work of Ohhashi, Azuma and Sakaguchi (*Am. J. Physiol.* 239:H88-H95, 1980). In this study, the initial increase in the active component of pressure generation when lymphangion volume was increased (dashed-dotted lines) was due to an increased contractile force and a moderate increase in contraction rate. This initial portion of the active pressure phase was then followed by a steep increase in rate but an actual decrease in contractile force. These changes occurring in active tension are better appreciated when the upper insert in *Fig. 3* is considered. The pressure developed by the lymphangion is shown in this insert as a function of the radius. Note two things: 1) the total pressure generated (solid lines) increases until the lymphangion radius has increased to about 1.4mm, and then it decreases. 2) The active tension (dash-dotted line) increases to a maximum at about 1.2mm and then drastically decreases as the lymphangion radius increases. From this figure, one can hypothesize that any condition that alters the shape of the pressure--volume curve can greatly affect the lymphatic drainage system because the absolute magnitude of the lymph flow is ultimately determined by the length-tension characteristics of the lymphatic smooth muscle. For example, if the lymphatic volume was 0.15 and doubled to 0.30 upon filling, then the intralymphatic

pressure generated would increase from 10 to 25mmHg, providing a tremendous increase in the gradient to propel lymph out of this particular angion. Obviously, any compound (EDLF) or condition which increases the initial slope of the pressure-volume curve or the maximum pressure rise of the lymphangion will increase overall lymph flow for a given intralymphatic volume. Finally, although Casley-Smith argued against a decreased tissue resistance as a possible mechanism to explain the greater lymph flow associated with endothelial damage, it is clear from *Fig. 3* that a large lymphatic volume, which occurs in edema, will result in the generation of a greater actively generated intralymphatic pressure and consequently a greater pressure head to propel lymph away from the tissues. Presently, all mechanisms depicted in *Fig. 1* could be responsible for producing the very high lymph flows observed with damaged capillary endothelium. But, the most likely mechanisms responsible for this effect is an increased intralymphatic pressure gradient to propel lymph caused by a combination of the decreased tissue resistance and the greater effectiveness of the pumping ability of the lymphatics secondary to the release of an unknown edema dependent lymphatic factor by damaged endothelial cells.

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