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REVIEW IN LYMPHOLOGY

The Interaction between Intracapillary and Tissue Forces in the Overall Regulation of Interstitial Fluid Volume

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Summary

This article is an attempt to integrate recent work on the regulation of interstitial volume with past work from this laboratory and others. A simple mathematical approach indicates how extremely sensitive interstitial fluid pressure and lymph flow are to small changes in interstitial fluid volume and how these two tissue factors coupled with tissue protein washout interact to maintain the tissues in a nonedematous state.

The purpose of this review is to discuss the recent developments from this and other laboratories concerning the manner in which the tissue and intracapillary forces, i.e., tissue hydrostatic pressure (P_T), tissue colloidal osmotic pressure (π_T), capillary pressure (P_C) and plasma colloidal osmotic pressure (π_C), are related to the volume and solute flows across the capillary and lymphatic walls. For the past five years we have investigated these forces and their contribution to the overall regulation of interstitial fluid volume. This article integrates the recent work from this laboratory with the current work in the field of interstitial fluid dynamics, specifically with the experimental findings related to changes in tissue pressure, lymph flow, and tissue protein concentration during the formation of tissue edema. The article describes the negative interstitial fluid pressure concept; establishes both experimentally and theoretically that the concentration of protein in lymphatic fluid most probably equals that of tissue fluid; and describes how tissue forces and flows interact to maintain the tissues in a relatively "dry" state.

Figure 1 schematically represents a capillary, an initial lymphatic (sometimes referred to in the literature as terminal lymphatic or lymphatic capillary), and a tissue space. A positive $J_{v,c}$ represents net volume flow out of the capillary into the tissue, and a positive $J_{v,L}$ represents net volume filling of the initial lymphatic. The following basic equations are used to describe the flows and forces represented in Figure 1.

$$J_{v,c} = K_{f,c} \; (\Delta P_C - \sigma_C \Delta\pi_C) \quad \text{.... (1)}$$

$$J_{v,L} = K_{f,L} \; (\Delta P_L - \sigma_L \Delta\pi_L) \quad \text{.... (2)}$$

$$\frac{dV_T}{dt} = J_{v,c} - J_{v,L} \quad \text{.... (3)}$$

or

$$V_T = \int_o^t (J_{v,c} - J_{v,L})\, dt + V_{T,o}$$

$$J_{v,L}' = f(J_{v,L}) \quad \text{.... (4)}$$

$J_{v,c}$ is the net volume flow across the capillary (ml/min-100 gm of tissue)
$J_{v,L}$ is the net volume flow into the initial lymphatic (ml/min-100 gm)

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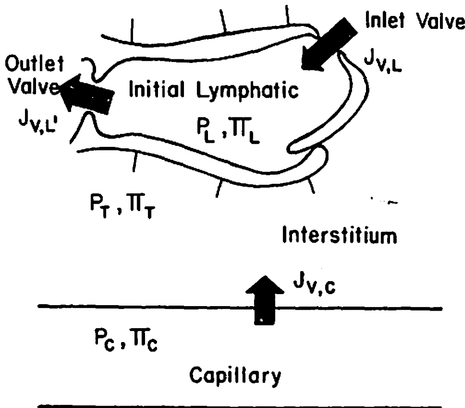

Fig. 1. Schematic representation of an initial lymphatic, interstitium and capillary. P_i refers to hydrostatic pressures and π_i refers to the colloidal osmotic pressure of the plasma proteins. $J_{v,c}$ is the net volume flow across the capillary, $J_{v,L}$ is the net volume flow into the initial lymphatic during the filling phase and $J_{v,L}$' is the lymphatic flow away from the initial lymphatic.

V_T is the interstitial fluid volume (ml/100 gm)

ΔP_c is the capillary pressure (P_c) minus interstitial fluid pressure (P_T) (mm. Hg)

σ_c is the reflection coefficient of protein for the capillary membrane. (We have used only a single σ_c [for all plasma proteins rather than individual σ_c's for each plasma protein) $\sigma_c = 1$ if the capillary is impermeable to protein and $\sigma_c] = 0$ if the membrane offers no restriction to the flow of the protein.

$\Delta\pi_c$ = colloidal osmotic pressure of plasma (π_p) minus colloidal osmotic pressure of the tissue (π_T), (mm. Hg)

$K_{f,c}$ is the filtration coefficient of the capillary membrane (ml/min - 100 gm - mm. Hg)

$K_{f,L}$ is the filtration coefficient of the initial lymphatics in the filling phase (ml/min - 100 gm - mm. Hg)

ΔP_L is the interstitial fluid pressure (P_T) minus lymphatic hydrostatic pressure (P_L) (mm. Hg)

σ_L is the reflection coefficient of plasma proteins for the initial lymphatic wall

$\Delta\pi_L$ is colloidal osmotic pressure of the tissue (π_T) minus colloidal osmotic pressure of the lymphatic (π_L) (mm. Hg)

$J_{v,L}$' is lymph flow away from the initial lymphatic (ml/min-100 gm)

$V_{T,o}$ is the normal extracellular fluid volume of the tissues (ml/100 gm)

These equations have been used by many investigators since *Starling* (49) and are introduced here in order to discuss each tissue force and flow and their relative contributions to interstitial fluid volume regulation.

Volume Flow Across the Capillary ($J_{v,c}$)

Filtration Coefficient ($K_{f,c}$)

The filtration coefficient (or hydraulic conductance) is a constant for a given membrane-solvent system, and relates net fluid filtration to the pressure head across a membrane

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Filtration coefficients have been measured in several isolated tissues by changing capillary pressure and analyzing the transient weight change of the tissue. *Pappenheimer's* classical study of the hind limb preparation yielded a $K_{f,c}$ of .015 ml/min - 100 gm - mm. Hg for that tissue (38). Similar isolated techniques have yielded $K_{f,c}$'s (ml/min - 100 gm - mm. Hg) of .11 - .37 for intestine (27, 13), .32 for heart muscle (58), and .03 - .26 for pulmonary tissue (19, 52, 15). Recent evaluations of the methods used to estimate $K_{f,c}$ in isolated perfused tissues reveal that the measured value may either under or overestimate the true $K_{f,c}$ by an order of magnitude (14, 44).

Heterogeneity of capillary porosity is not only apparent when comparing different organs, but it is also evident when comparing capillaries within a given tissue since the porosity of the arterial end of a capillary has been demonstrated to be much less than the porosity of the venular end. Therefore, the mean measured $K_{f,c}$ reflects several Kf's in parallel, i.e., $K_{f,c} = K_{f,arterial} + K_{f,venous}$.

Also, there is a possibility of changing capillary porosity under certain experimental and physiological conditions. The "stretched pore" concept was developed by *Mayerson* to explain an increase in capillary permeability to larger molecules at high capillary pressures (48); the same observations have been made in lung tissue by *Pietra and Fishman* who demonstrated an increase in capillary leakiness to hemoglobin as pulmonary capillary pressures were increased from normal to 30 mm Hg (42). The tight junctions between endothelial cells seem to be pushed further and further apart with increasing intracapillary pressure. Any tendency of the capillary wall to become leaky, such as caused by the "stretched pore" phenomenon, results in a large increase in $K_{f,c}$ since flow in large channels is proportional to the fourth power of the radius. For purposes of discussion, we will simply refer to some average $K_{f,c}$ which when multiplied by an average pressure head across the capillary wall results in volume movement into the tissues.

Capillary Pressure (P_c)

Landis' and Pappenheimer's (30) excellent review of the exchange vessels has fully described the physical and physiological principles of the forces and flows that occur across the capillary wall. Basically, the average hydrostatic pressure head minus the effective average osmotic pressure causes a slight volume flow into the tissues, but, under normal conditions, this is exactly counter-balanced by equal outflow from the interstitium via the lymphatics.

Capillary pressure has been measured both directly and indirectly by many investigators and has ranged from 10 to 30 mm Hg in the same tissue (hind limb). Since most capillaries are continually opening and closing, the capillary pressure varies considerably from moment to moment. Also, since the capillary wall is not homogeneous with respect to porosity from arterial to venous ends, then the functional mean capillary pressure that moves fluid across the capillary is determined by both the pressure drop occurring along the length of the capillary and the porosities of the different capillary systems. *Wiederhielm* (61) has demonstrated that the filtration coefficient at the arterial end is one-sixth that of the venular filtration coefficient. If the pressure drop occurs mainly at the arterial end of the capillary, then less filtration will occur for a given pressure head than if the drop occurs at the venular end of the capillaries. Also, the capillaries are continually opening and closing such that the average capillary may be closed to the arterial side of the circulation as much as 80 per cent of the time.

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Thus, the time integrated average capillary pressure might be very near to the venular pressure.

Interstitial Fluid Pressure (P_T)

In the latter 1930's *Burch* (3), *McMasters* (35), and *Wells* (60) developed methods believed to measure the hydrostatic pressure in tissues. A small needle was inserted into the tissue, and the pressure was measured either after a small amount of fluid was injected into the tissue or during a constant continuous microinfusion into the tissue spaces. Tissue pressures were found to be +.5 to +6 mm Hg in a variety of tissues by using the above methods. During severe edema formation, tissue pressure was increased to 20 mm Hg in muscle. These early investigators concluded that tissue pressure in subcutaneous tissue was not changed by small fluid movements into the tissue and that no significant rise in tissue pressure was observed with the needle technique until gross edema was present in the tissue.

Recent investigations from *Guyton*'s (20) and *Scholander*'s (47) laboratories have demonstrated that pressures measured either from a perforated plastic capsule or a small cotton wick inserted into subcutaneous tissue are subatmospheric. Both methods of measuring tissue pressure are extremely sensitive to changes in tissue hydration; in fact, both pressures respond immediately to small changes in capillary filtration forces. These methods were criticized by *Stromberg and Wiederhielm* (54), especially the capsule method. These authors' basic criticism of the capsule method was that the membrane which forms around the capsule during the 4 to 5 weeks following implantation is impermeable to plasma proteins. Supposedly, an imbalance in protein between capsule and surrounding tissue fluids causes a negative pressure inside the capsule due to withdrawal of fluid out of the capsule into the tissue, although interstitial pressure is at or above atmospheric pressure.

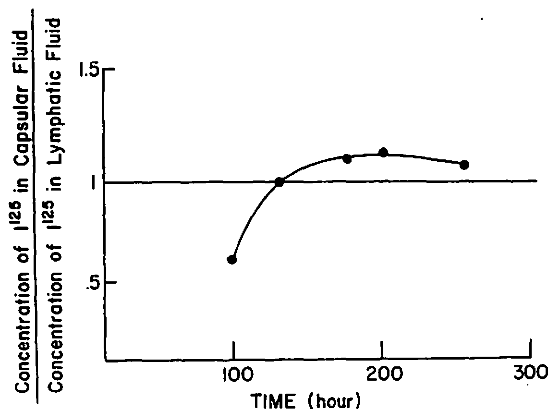

Fig. 2. A plot of the concentration ratio of I^{125} albumin in capsular and lymphatic fluid at different time intervals following intravenous injection of I^{125} labeled albumin. Note that after 100 hours the capsular I^{125} concentration is either equal to or greater than the lymphatic concentration.

Figure 2 gives results from several studies in this laboratory in which I^{125} labeled albumin was injected into the blood. Samples of lymph and capsular fluid (average capsular pressure measurement of -6.5 mm Hg) were analyzed for I^{125} concentration at different time intervals following the labeling procedure. After approximately 100 hours, the capsular and lymph I^{125} concentrations were very similar, if anything, the capsule

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fluid had slightly higher concentration of labeled protein than did lymph. Total protein concentration and A/G ratios of lymph and capsular fluid were not statistically different in these studies (Table 1) which demonstrates that globulins are also in equilibrium between capsule and lymphatic fluid (16).

Table 1. Protein analysis of blood, lymph and capsule fluid following infusion and venous occlusion*

	Control		After infusion		After venous occlusion	
	Total Protein (gm/100 ml)	A/G	Total Protein (gm/100 ml)	A/G	Total Protein (gm/100 ml)	A/G
Blood	6.50±0.95 (35)**	1.21± .80 (24)	3.04±0.69 (5)	1.42± .79 (10)	7.10±1.40 (9)	1.14± .99 (11)
Lymph	1.9 ±0.6 (54)	1.63±1.10 (38) N.S.	0.86±0.50 (8)	1.45± .65 (16) N.S.	1.50±0.55 (11)	1.99±1.50 (18) N.S.
Capsule	2.0±0.8 (30)	1.73±1.06 (20)	1.97±1.09 (9)	1.37± .51 (12)	2.85±0.55 (4)	1.35±1.40 (11)

* Values are mean ± S.D.
** ( ) number of observations

The fibrous tissue that grows around the implanted capsule was isolated by *Granger* et al. (18), and the filtration coefficient and protein reflection coefficients of this membrane were measured using the *Kedem-Katchalsky* approach (28). A simple "pore" computation from this data yielded an equivalent pore radius of 300 Å through the interstices of the tissue. In a steady state, no osmotic force will be exerted by plasma proteins across a capsular covering with pores of this size, and the measured capsular pressure will be in equilibrium with the surrounding tissue fluid pressure.

A complete review of the negative interstitial fluid pressure hypothesis was recently published (24), and we will not discuss this important tissue force in its entirety, except to point out that this force is responsive to small changes in interstitial fluid volume, increasing from negative to positive pressures with only a 20 to 40 per cent expansion of the interstitial fluid volume. Therefore, interstitial fluid pressure increases to oppose increases in capillary filtration forces before the tissue becomes grossly edematous. These changes in fluid pressure are not measured by the non-responsive needle method. However, once the interstitial fluid pressure has become positive and the tissue spaces have enlarged, capsular and needle pressure measurements become identical.

We have not presented here the arguments both for and against the validity of *Scholander*'s wick technique. However, a recent publication by *Prather* et al. (43) demonstrates that the wick and capsular pressures respond to increased filtration forces in the same fashion. The major differences between these measurements is that the wick pressure is less negative in the same tissue than is the capsular pressure.

Colloid Osmotic Pressure of the Plasma (π_p) and Tissue (π_T)

The colloid osmotic pressure of the plasma has been measured in several species and was in all instances found to be very closely related to the respective capillary pressures. This species effect implies that $P_c \cong \pi_c$ (30). This same relationship obviously does not hold true in different tissues of the same animal since the same colloid osmotic pressure

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is present within capillaries of different organs with different capillary pressure, e.g. lung, liver and intestine. The important force that describes the relationship between plasma colloid osmotic force and capillary pressure is $\Delta P_C - \sigma_C \Delta\pi_C$; hence P_T, π_T and σ_C must be included in any analysis of capillary filtration forces. The plasma colloid osmotic pressure varies from 20 to 30 mm Hg in most mammalian species; however, capillary pressures range from a low value of 7 mm Hg in the lung to an average pressure of perhaps 17 mm Hg in skeletal muscle.

Also, the experimental measurement of colloid osmotic pressure is not identical with the effective capillary colloid osmotic pressure since the membranes used for measuring the osmotic pressure do not have the same distribution of "pore" sizes found for capillaries. What actually must be measured in order to assess the effect of $\Delta\pi_C$ on fluid exchange in any particular capillary system is $\sigma_C \Delta\pi_C$, the effective colloid osmotic pressure of the particular exchange vessels under study. For a capillary exchange system that is impermeable to protein, $\sigma_C = 1$. If the protein is freely permeable across the capillary, then no osmotic pressure would be observed and $\sigma_C = 0$. In muscle, σ_C is close to one (39) but in gut, lung, and subcutaneous tissue, σ_C is less than unity (46, 53, 18). Therefore, the actual colloid osmotic pressure in a capillary exchange system for which $\sigma_C < 1$ does not equal the calculated *Van't Hoff* pressure or a value measured with a membrane more limiting to the passage of protein molecules than the capillary membrane.

Mayerson (48) demonstrated a "stretched pore effect" when venous pressures are elevated by plasma volume expansion. *Pietra and Fishman* (42) have demonstrated the same effect in dog lungs following elevations of pulmonary arterial pressure. Thus, there is also the possibility of a dynamic σ_C due to fluctuations in intracapillary pressure that alters the magnitude of σ_C in such a fashion that the effective colloid osmotic pressure across the capillary wall changes from moment to moment.

π_T is a parameter that is extremely variable from tissue to tissue, and an active controversy exists concerning the manner in which one can experimentally determine the exact magnitude of the force. *Drinker* (9) and *Yoffey and Courtice* (63) concluded from experimental measurements that lymphatic protein concentration represents a good cross sectional sample of tissue fluid. *Rusznyak* (46) and *Casley-Smith* (7) have presented data which implies that the protein concentration of lymphatic fluid is more concentrated than a calculated or measured tissue protein. Table 1 gives results from this laboratory by *Gibson* et al. (16). Total protein concentrations and A/G ratios were measured in the lymphatic fluids draining the paw region, and these values were compared with values obtained from fluids withdrawn from implanted capsules in the ankle region. The samples of capsular and lymphatic fluid in Table 1 are not statistically different for either total proteins or A/G ratios; therefore, lymph fluid which drains a specific region does seem to represent the average interstitial fluid since, at equilibrium, the capsular protein concentration must theoretically be equal to that of the tissues.

As volume ($J_{v,c}$) filters into the interstitial space, the net flux of protein out of the capillary into the space ($J_{p,c}$) can be altered in at least three different ways that can be described by the following *Kedem and Katchalsky* (28) equation:

$$J_{p,c} = \bar{C}_p \, J_{v,c}(1 - \sigma_c) + \omega \Delta\pi \quad \dots \quad (5)$$

in which $\bar{C}_p$ is the average protein concentration within the capillary and ω is the mobility of the protein across the capillary wall (ω = permeability coefficient/RT).

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Type I: If $\sigma_c = 0$ at some point in the capillary system, then an increase in filtration will cause an increase in the movement of protein into the tissue that is equal to $\bar{C}_p J_{v,c}$. This type of protein movement into the tissue will be observed if the venular end of a capillary filters a volume of protein rich filtrate that is much greater than the protein free volume that is filtered at the arterial end. A "stretched pore" effect would also lead to an increase in bulk movement of protein into the tissues (48). If protein leakage increases such that the ratio of the quantity of protein to the volume entering the tissues is exactly equal to the initial protein concentration of the tissues, then no change will be observed in tissue protein concentration. This type of protein exchange system is present under certain experimental conditions in sheep lung (53) and during fat absorption in the small intestine (63).

Type II: If σ_c is close to unity then the filtered fluid will be low in protein since $J_{p,c} \doteq \omega\Delta\pi$, and tissue protein concentration will decrease to some value which is equal to:

$$C_{p,T} = \frac{\int_o^t (J_{p,c} - J_{p,L})\,dt + Q_{T,O}}{\int_o^t (J_{v,c} - J_{v,L})\,dt + V_{T,O}} \quad \ldots\ldots \quad (6)$$

Assuming uniform mixing: $Q_{T,O}$ = initial amount of protein in the tissue; and $J_{p,L} = J_{v,L} \cdot C_{p,T}$. Equation 6 predicts that, if the second term in Equation 5 (diffusional term) is small to the volume flow, then the protein concentration of the tissue will decrease in the limiting case to:

$$C_p = \frac{\int_o^t (\omega\Delta\pi)\,dt}{\int_o^t (dV_T/dt)dt} \quad \ldots\ldots \quad (7)$$

This type of capillary filtration system has been described in skeletal muscle (39), subcutaneous (56), intestinal (29) and lung tissue (12).

Type III: If $\sigma = 1$ then no protein leaves the microcirculation even with increased infiltration. The first term in Equation 5 is zero and the last term in also zero. This type is best represented by brain capillaries.

In most tissues, increased filtration causes a fall in tissue proteins due to wash-out of protein (Equation 6), low bulk movement of protein, and a simple dilution of existing tissue proteins. The fall in average tissue protein increases the osmotic head across the capillary, $\sigma_c (\pi_c - \pi_T)$ and acts to retard further fluid filtration. Table 1 shows the effect of increasing filtration forces across the capillary in subcutaneous tissue by saline infusions and venous occlusion. In the infusion studies, the tissue proteins are decreased (Type II), and with venous occlusion a Type I and II tissue protein is formed.

π_T as discussed above is assumed to be uniform throughout the tissues; however, the arterial end of the capillary would have a lower tissue protein relative to the venular end. This imbalance in tissue protein concentration must also be considered when assessing the actual osmotic force across the capillary (30).

Volume Flow Into the Lymphatic ($J_{v,L}$)

Pressure Head Between Initial Lymphatic and Tissue (ΔP_L)

McMasters measured positive needle tissue pressures (tissue resistance) which were slightly greater than intralymphatic pressures indicating that a driving force for lymphatic

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filling was present in normal tissues (36). Since we now believe that interstitial fluid pressure is subatmospheric and that many measured intralymphatic pressures are positive, then we must explain the major objection to the negative interstitial fluid pressure concept: How can fluid move from a negative to a positive pressure region? The intralymphatic pressure must fall below the negative tissue pressure in order for lymphatic filling to take place. The necessary decrease in intralymphatic pressure could be provided by at least three different processes:
(1) *An active lymphatic pump:* The pump would provide the necessary driving force to propel fluid away from the tissues. Relaxation of a lymph vessel after an active contraction would provide the necessary suction force, and many examples of lymphatic pumps have been demonstrated in a variety of tissues (25, 34, 37). Figure 1 is a diagrammatic representation of an initial lymphatic. The endothelial cell junctions, inlet valves, are thought to be opened during the filling phase. When the initial lymphatic contracts, overlapping endothelial processes act as valves and prevent reflux of lymphatic contents into the tissues. If the initial lymphatic does not contract, then the concept of opening of the overlapping endothelial processes during the filling phase is not necessary and the initial lymphatic will fully communicate with the tissues at all times.

An active contraction at any point in the lymphatic system can easily overcome the difficulty of filling the initial lymphatic with fluid from a subatmospheric region. In fact, a recent article by *Browse* (2) describes a negative pressure in the thoracic duct which averages -1.6 mm Hg in the conscious dog, indicating that either active thoracic lymphatic contractions and/or respiratory movements are necessary to propel lymph into the venous system.

(2) *A tissue pump:* Any motion of the tissue will propel lymph in the following fashion. The lymphatic is compressed by surrounding tissue, and fluid is propelled through the upstream valves. When the compression is released, the anchoring filaments tend to pull the lymphatic open, and fluid will move from the interstitium into the lymphatic through the inlet valves. The lymphatic cannot normally refill until sufficient fluid is in the surrounding tissue. One can easily see how the removal of lymphatic fluid determines not only tissue protein but also alters the hydrostatic balance across the capillary. First, the evacuated space will provide a force to remove fluid from the gel surrounding the lymphatic and the free fluid channels. Secondly, fluid will be removed from the immediate vicinity of the capillary, and fluid will actually be filtered from the capillary due to the gradient into the gel and free fluid spaces. This pressure allows the lymphatic to empty and fill in a smooth fashion when the tissues are in their normal dehydrated state. The "tissue lymphatic pump" has been described in detail by *Allen* (1), *Leak and Burke* (31) and *Casley-Smith* (6).

(3) *Arterial Pulsations: Parsons and McMasters* (40) demonstrated that arterial pulsations are necessary for lymph flow in the ear of an anesthetized rabbit. The force generated by arterial pulsations would be similar to the tissue movement described in the previous paragraph.

The lymphatic fluid in any single tissue will be moved by a combination of the above three factors, and the contribution of each "lymphatic pump" may be quite different from tissue to tissue.

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Osmotic Pressure Head Across the Initial Lymphatic Wall $[\sigma_L(\pi_T - \pi_L)]$

π_L is equal to the tissue osmotic pressure during the filling phase since the endothelial junction (inlet valves) are open, i.e. $\sigma_L = 0$. When the initial lymphatic is collapsed by tissue movement and the inlet valves close, the outlet valves in the upper portion of the lymphatic open and fluid is propelled in that direction. It is conceivable that some fluid could be filtered backward across the lymphatic wall or through the inlet valves during the contraction cycle, but, if the inlet valve junctions are tight, then the volume flow will be quite small. Unless the resistance of fluid movement across the lymphatic wall is less than outlet lymphatic valve resistance (assuming equal pressure gradients), then only a small volume flow in the backward direction could occur across the lymphatic during the propulsion stage. If the resistance to flow out of the intercellular gaps is less than the outlet valve resistance, then it is difficult to see how the endothelial cells could act as efficient valves during the contraction phase.

Ruznyak et al. (46) and *Casley-Smith* (7) have recently proposed a model that attempts to explain how the concentrations of lymphatic fluid and tissue fluid could be quite different from each other due to the possible concentrating effect discussed in the previous paragraph. Figure 3A is a schematic drawing of a terminal lymphatic that will be used here to develop a simple model of lymphatic and tissue protein concentrations. Assume that the terminal lymphatic fills with volume V_{IN}. During the propulsion cycle, a volume is lost back into the tissue which equals V_{LEAK}. The amount of volume removed by the lymphatic is V_{OUT}. The relationships between the volumes, quantity of protein (Q_i), and concentration (C_i) in this model are:

$$V_{OUT} = V_{IN} - V_{LEAK}$$

$$Q_{OUT} = Q_{IN} \text{ (no protein in leak)}$$

or

$$V_{OUT}\, C_{OUT} = C_{IN}\, V_{IN}$$

$$V_{OUT}\, C_{OUT} = C_{IN}\, (V_{OUT} + V_{LEAK})$$

$$C_{OUT} = C_{IN}\, \frac{V_{OUT} + V_{LEAK})}{V_{OUT}}$$

or

$$\frac{C_{OUT}}{C_{IN}} = 1 + \frac{V_{LEAK}}{V_{OUT}} \qquad \ldots\ldots (8)$$

Figure 3B is a plot of C_{OUT}/C_{IN} as a function of V_{LEAK}. As the leak increases, the ability of the lymphatic to concentrate apparently increases. Note that for a 20 per cent leak, the lymphatic fluid is concentrated 25 per cent above the concentration of the fluid which entered the lymphatic. The first impression is that the lymphatics could easily leak a small percentage of the initial volume and result in a substantial concentrating mechanism. However, the evacuated space must fill with the leaked fluid plus fluid from the surrounding tissue. When this factor is considered, this simple model predicts a very important result: Suppose that the volume moved away from the tissue is replaced by some tissue fluid with a protein concentration C_{TISS}. Then, regardless of the leakage volume the concentration of the lymphatic can only be concentrated to a value equal to C_{TISS}.

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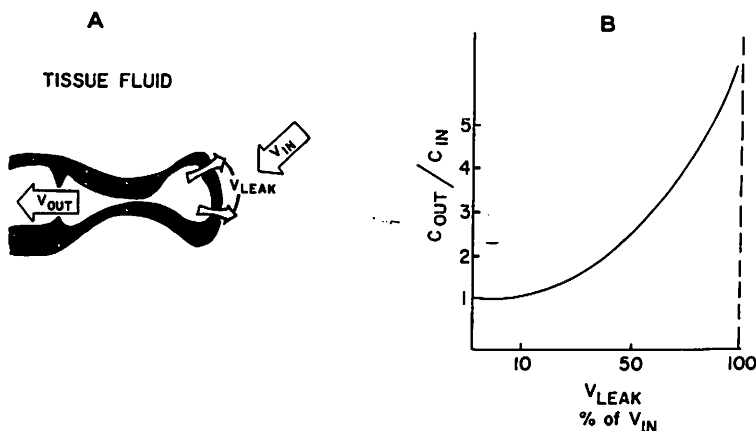

Fig. 3. A is a schematic representation of the emptying phase of the initial lymphatic which had been previously filled with V_{IN}. Following the contraction, a volume leaks back into the tissues through the inlet valves, V_{LEAK}. The volume removed by the lymphatic would be V_{OUT}.
B represents a plot of C_{OUT}/C_{IN} versus per cent of V_{IN} that leaks back into the tissues, V_{LEAK}. At leaks of 10 and 20 per cent, the concentration in the lymphatic is increased only 10 and 25 per cent, respectively. This change is really a fortuitous one as discussed in the text since the removed volume must be replaced by some tissue volume $V_{TISS} = V_{OUT}$.

The volume of the leak that enters the tissue immediately surrounding the initial lymphatic will finally be mixed with a volume that is equal to V_{OUT} and contains C_{TISS} for its protein concentration. The protein concentration in the immediate vicinity of the initial lymphatic equals

$$\frac{V_{OUT} \cdot C_{TISS}}{V_{OUT} + V_{LEAK}}$$

Substituting this into Equation 8 yields:

$$C_L = \frac{(V_{OUT} + V_{LEAK})}{V_{OUT}} \quad \frac{(V_{OUT}\, C_{TISS})}{V_{IN}}$$

Now $V_{OUT} + V_{LEAK} = V_{IN}$ and therefore

$$C_L = C_{TISS} \qquad \text{.... (9)}$$

Therefore, the concentration in the lymphatic represents the average protein concentration in the tissue that is responsible for movement into and out of the capillary. The concentration of protein in the immediate vicinity of the lymphatic would be less than the lymphatic or the tissue protein concentration active at the capillary wall. Some concentrating ability might be produced in a more central lymphatic, especially if capillaries there were in a close approximation to the lymphatic such that the fluid which enters the surrounding tissue is removed by these capillaries.

The above analysis does not consider the diffusion of protein from the surrounding tissue into the volume ejected by the initial lymphatic. The final concentration of protein in the lymphatic is a very complex function of diffusion distances to lymphatics as well as lymphatic leakage. It is our opinion that the lymphatic does not concentrate

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to any great extent and a more extensive model is now in progress concerning the regulation of this important problem.

Filtration Coefficient of the Initial Lymphatics ($Kf_{,L}$)

The filtration coefficient of the terminal lymphatics is high during the filling cycle and low during the propulsion cycle. Excessive intralymphatic pressures and various drugs cause the endothelial cells to disrupt and results in increases of $Kf_{,L}$ (5). After injury to the overlapping endothelial processes at the initial lymphatics, then the lymphatic cannot be as efficient in removing tissue fluid as one which contains a closed ended system. Compression of a lymphatic would cause fluid to be propelled backwards into the tissue as well as downstream.

Change in Interstitial Fluid Volume [$\int (dV_T/dt)dt$]

The concepts of "lymphatic overwhelming" and "lymphatic safety factor" have been developed by *Ruznyak* (46) and *Guyton* (23), respectively, to describe the lymphatics' contribution to the overall regulation of interstitial fluid volume. The change in tissue volume is the time integrated difference between the net capillary volume filtration minus the lymph flow. Lymph flow has been shown to increase from 3 to 15 fold following increases in venous pressure or decreases in plasma colloids in many different tissues (9, 16, 29, 59). Once $J_{v,c}$ becomes greater than $J_{v,L'}$, fluid begins to accumulate in the tissue. A safety factor for lymph flow can be computed for any tissue, in terms of the pressure drop across the capillary wall by first measuring normal total lymph flow and the filtration coefficient of the capillary bed. Assuming $J_{v,c} = J_{v,L'}$ and $\frac{dV_t}{dt} = 0$, then the pressure drop associated with the formation of lymph (P_{DROP}) is related to $Kf_{,c}$ and $J_{v,L'}$ by the following relationship:

$$P_{DROP} = \frac{J_{v,L'}}{Kf_{,c}} \quad \ldots. \quad (10)$$

If for example, the normal P_{DROP} were 1 mm Hg and lymph flow increased 20 fold before increases in filtration forces produced edema, then the calculated lymph flow safety factor would be 20 mm Hg. The lymph flow safety factor calculates to be 7 mm Hg for subcutaneous tissue (17) and 2 to 3 mm Hg for dog lung tissue. Other tissues could have higher or lower lymph flow safety factors depending on the normal pressure drop across the capillary and maximum lymph flow for that tissue. A second mechanism by which the lymphatics can effect tissue fluid volume is seen with chronic elevations of venous pressures. The long-term lymph flow safety factor is a result of growth of new lymphatics and increases in the diameters of existing lymphatic vessels. An example of this long-term regulation occurs with chronically elevated left atrial pressure in dogs. An acute elevation of left atrial pressure causes an immediate increase of pulmonary lymph flow of 2 to 3 fold; however, after 40 days of increased left atrial pressures, lymph flow has increased 10 to 30 times (57). The long-term lymph flow effect provides the pulmonary capillary exchange system with an additional safety factor such that great excesses of fluid leave the pulmonary tissue by way of the lymphatics rather than elevating tissue pressure and forcing intra-alveolar edema.

The equation used here for tissue volume indicates that any capillary filtration above normal would be immediately carried away by the lymphatics until the attainment of maximum lymph flow. For our simple approach, this is sufficient; however, if the

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lymphatic pump is stimulated by increases in lymphatic transmural pressure and/or tissue volume, for which there is good evidence, then some expansion of interstitial volume would be necessary in order to increase lymph flow from an organ.

Relationship between Interstitial Fluid Volume (V_T) and Interstitial Fluid Pressure (P_T) in Subcutaneous Tissue

Figure 4 is an approximate plot of extracellular fluid volume versus interstitial fluid pressure for man from the work of *Guyton* et al. (21); note that the curve has two different slopes: (1) The compliance of the curve ($\Delta V_T/\Delta P_T$) in the negative pressure range is 5 ml/mm Hg-kg, and increases to 144 ml/min Hg-kg after the tissue pressure has increased to values above zero mm Hg. Thus, tissue fluid pressure changes very markedly for only small changes in interstitial volume in the negative pressure range; however, once the fluid pressure becomes greater than zero, the tissue pressure increases only very slowly with very large increases in tissue volume. Any model that fails to incorporate this non-linear change in tissue compliance cannot describe the tissue force changes that occur during the formation of edema.

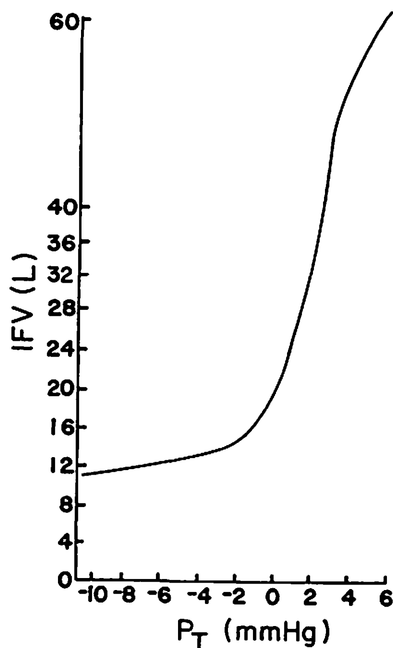

Fig. 4. Interstitial fluid volume versus interstitial fluid pressure (21).

Effect of Tissue Pressure (P_T) on Lymph Flow ($J_{v,L'}$)

Figure 5 is a curve showing the changes in lymph flow and tissue fluid pressure following rapid intravenous saline infusions from the work of *Gibson* et al. (16) studying lymph flow in the dog leg. Lymph flow increases very rapidly as tissue pressure begins to increase toward atmospheric pressure. When interstitial fluid pressure rises to between +1 to +2 mm Hg, the lymph flow attains a maximum flow rate which is about 20 times normal in this experimental series. Further increases in tissue pressure to 8 mm Hg did not increase lymph flow above that value which was obtained at +1 to +2 mm Hg.

The increase in lymph flow as the interstitial fluid pressure changes from negative to positive values can be caused by a combination of several processes: (1) increase in (P_T - P_L) across the lymphatic; (2) increase in amplitude and rate of lymphatic pump activity which is stimulated by an increase in transmural-lymphatic pressure (34), (3) tissue conductance increases quite markedly as the tissue becomes more edematous. This simple model incorporates only a simple $Kf_{,L}$ for lymphatic filling. In reality, the $Kf_{,L}$ is at least a function of tissue conductance ($Kf_{,T}$) from capillary wall to lymphatic as well as lymphatic wall conduction, $Kf_{,LW}$. Since the two conductances

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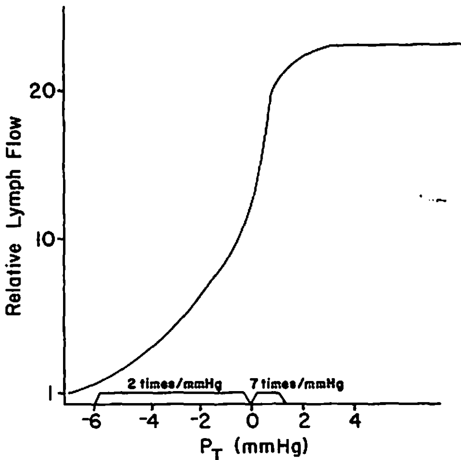

Fig. 5. The relationship between tissue hydrostatic pressure (P_T) and lymph flow when tissue edema was produced by intravascular infusion of Ringer's. Note the rapid increase in lymph flow especially in the tissue pressure range of 0 to 1 mm Hg and the lymph flow plateau at tissue pressures greater than +1 mm Hg.

are in series, they add as follows:

$$Kf_{,L} = \frac{Kf_{,T}\ Kf_{,LW}\ *}{Kf_{,T} + Kf_{,LW}} \qquad (11)$$

If $Kf_{,T} < Kf_{,LW}$ then the tissue fluid conductance limits lymphatic filling. When $Kf_{,T} > Kf_{,LW}$ then the reverse is true. As interstitial fluid pressure changes from -7 to 0, the tissue conductance changes very slowly such that the pressure immediately outside the capillary minus the intralymphatic pressure is increasing and provides the larger force for moving fluid into the lymphatic. At tissue pressures between 0 and +1, the lymph flow shows the greatest increase per mm Hg (see Figure 5). This is the same tissue pressure at which tissue conductance and tissue volume change very markedly (22). In a recent communication *Intaglietta* (26) stated that one would need large distances from capillary to lymphatic before the tissue conductance term would be more limiting than the capillary $Kf_{,c}$. Therefore, it is doubtful that the increase in tissue conductance observed during the formation of tissue edema causes the increase in lymphatic filling. The most probable mechanism for the increased lymph flow in the pressure range of 0-1 mm Hg is the increased tissue volume which either pushes the lymphatics open to a greater diameter or, by changing tissue pressure, stimulates an active lymphatic pump.

The plateau of lymph flow as tissue pressure becomes positive can be caused by either one or a combination of the following three mechanisms: (1) When tissue pressure increases into the positive range, the increase in filling pressure also is attempting to collapse the larger lymphatics. The anchoring filaments, as postulated by *Starling* (50, 51) and demonstrated by *Leake and Burke* (32), *Casley-Smith* (6) and *Casley-Smith and Florey* (4) normally oppose this tendency to collapse. If any point in the lymphatic system is not anchored, then the elevated tissue pressure will exert exactly the same pressure on the outside of the lymphatic wall as it contributes to the lymphatic filling pressure and results in a zero change in filling pressure at positive tissue pressures. (2) The maximum lymphatic pump activity and/or maximum lymphatic capacity is reached at a tissue pressure which is between 0 to +2 mm Hg in normal subcutaneous tissue. The lymphatic vessel constricts maximally following each filling, and the lymphatic system will not be able to increase the frequency of contractions above this pressure range. (3) *Collin* has demonstrated that the lymphatic endothelial cells pull apart during edema causing incompetence of the inflow valves (8).

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*The Kf's should be in terms of cm of path length and cm^2 of surface area in order for this equation to be valid.

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The first effect is identical to the "water fall" effect discussed by *Permutt and Riley* (41) for pulmonary alveolar vessels exposed to different alveolar pressures and is also similar to the mechanism proposed by *Rodbard* (45) for control of local blood flow. We feel that this is the most likely mechanism to explain the plateau of lymph flow; however, a "maximum lymphatic activity" effect would produce the same end result.

Total Safety Factor Against Edema

We have discussed how an increase in lymph flow provides a safety factor against the formation of tissue edema, a value equal to about 7 mm Hg in subcutaneous tissue. The tissue colloidal osmotic pressure in this same study decreases from 4 to 1 mm Hg because of lymphatic transport of protein back to the circulation and produces a "protein washout" safety factor of 3 mm Hg. Also, tissue pressure must increase from the normally negative value of about -6 mm Hg to above 0 before the compliance of the tissue changes markedly (21); once it becomes positive, large amounts of fluid enter the tissue with almost no buildup of back pressure. Thus, gross edema develops only after the tissue pressure becomes positive. Therefore, normally negative tissue pressure provides an additional 6 mm Hg to the tissue safety factor. The sum of these tissue forces – lymph flow, interstitial fluid pressure, and protein washout – is 17 mm Hg for subcutaneous tissue. The importance of the "edema safety factors" is readily apparent in subcutaneous tissue since capillary filtration forces usually must increase by 17 mm Hg before gross tissue edema will occur.

Intestinal Capillary "Secretion" Safety Factor

Normally, the intestinal lymphatics and capillaries remove the fluid volume which is associated with active transport of solutes from the intestinal lumen to the interstitial spaces. When capillary pressures are altered such that net capillary filtration occurs into the interstitium, then the lymphatics must remove not only the actively transported volume but also the excess capillary filtrate. If the intestinal tissue pressure increases to pressures greater than 4 cm H_2O (62), then the mucosal filtration properties are altered and fluid actually moves into the intestinal lumen, even in the face of an intact sodium pumping mechanism. Although the exact "secretion" safety factors have not been measured in the intestine, it is clear that the same factors, i.e., tissue pressure changes, lymph flow increases, and tissue protein washout, are forces that must be altered before the tissue pressure will increase to values greater than 4 cm H_2O (10, 11). Intestinal lymph flow can increase at least 10 fold (29), tissue protein concentration decreases by at least 50 per cent, and tissue pressure must change by at least 3 mm Hg and perhaps much more. If the normal pressure drop across the intestinal capillary is 1 mm Hg, then the lymphatic contribution to the "secretion" safety factor would be 10 mm Hg. The decrease in tissue proteins from a normal of 10 mm Hg to 4 mm Hg (29) yields a 6 mm Hg "protein washout" safety factor. The increase in tissue pressure accounts for at least 3 mm Hg. The total safety factor for intestinal tissue that must be overwhelmed before secretion into the intestinal lumen is observed, therefore, calculates to be at least 20 mm Hg. Also, the calculated intestinal capillary filtration coefficient decreases with increasing capillary pressure due to closing off of previously opened capillary beds, and this acts as an additional safety factor since the capillary filters less volume for a given pressure head (27).

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Pulmonary Edema Safety Factor

Erdmann et al. have recently measured the capillary "pressure drop" in normal sheep lungs (12) and also measured changes in lymph flow and tissue protein concentration following elevations of left atrial pressures. The normal P_{DROP} was 3 to 4 mm Hg and lymph flow increased from an average of 4.5 to 14.5 ml/hr which yields a lymph flow safety factor of 9-12 mm Hg. Tissue colloidal osmotic pressure decreased by approximately 3 mm Hg. The total safety factor, therefore, calculates to be 12-15 mm Hg. Since the lung did not become edematous at the left atrial pressures used, the lymph flow theoretically could have increased further to 6 fold, and the edema safety factor would then calculate to be 21-27 mm Hg. If the pulmonary tissue pressure were subatmospheric, then an edema safety factor could easily be 30 mm Hg for that tissue. Actual measured values in dog's lungs have averaged about 18 mm Hg (19, 15).

The lung, subcutaneous tissue, and intestinal tissue all appear to have very similar "tissue safety factors" even with different lymph flows, changes in tissue proteins, and perhaps different normal tissue pressures. One might suggest that in highly permeable capillary systems, the major mechanism by which the tissue forces change to oppose the development of edema are by increasing lymph flow, whereas in tight capillary membrane systems, tissue pressure increases play the more dominant roles.

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FORTHCOMING CONVENTIONS

9th International Congress of Angiology,
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Information: Prof. *F. Pratesi,* Via della Robbia 5, I-50132 Florence

5th International Congress of Cytology,
May 29 to June 2, 1974, Bal Harbor, Miami, USA.
Information: Prof. *A. Meisels,* Univ. Laval, 1050 Chemin Ste-Foy, Quebeck 6, Canada.

2nd International Congress of Immunology,
July 21 to 26, 1974, Brighton, U.K.
Information: Dr. *G.L. Asherson,* Clinical Research Centre, Watford Rd., Harrow, Middlesex, HAI 3UJ, U.K.

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September 1974, Jerusalem, Israel.
Information: Dr. *M. Schlesinger,* Experimental Med. and Cancer Res., Hadassah Medical School, P.O.B. 1172, Jerusalem, Israel.

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