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The Energetics of Lymph Formation

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Summary

A very important unanswered problem is the source of the energy required for formation of lymph. The most widely held theory has been that fluid filters from the capillaries, flows through the tissues, and then enters the lymphatic as a result of a continuous positive pressure gradient from the blood capillary to the lymphatic capillary. However, this fails to account for the negative pressures that have been measured by implanted perforated capsules and by the wick technique, both of which suggest that the interstitial free fluid pressure is negative. Furthermore, because the fluid in the tissue gel is in equilibrium with the free fluid, it has a chemical potential equivalent to the negative pressure of the free fluid. At present, the only probable source of energy that could create the negative hydrostatic pressure in the free fluid and the equivalent negative chemical potential in the intragel fluid is a lymphatic suction pump. Unfortunately, the existence of this has not yet been proved, but mechanisms by which the terminal lymphatic system could act as a suction pump have been proposed.

Most physiologists agree on the general principles of lymph formation – that lymph originates mainly as an ultrafiltrate of plasma which is then modified and added to in its course through the tissues before entering the lymphatic system. On the other hand, there still remains an important problem that has not been solved. This is the energetics of lymph formation, a problem that we will discuss briefly in this paper.

The Interstitial Free Fluid Pressure. It is generally considered that the interstitium is composed of a biphasic fluid system (1). One of the phases consists of *tissue gel* while the other phase consists of *free, mobile fluid.* In normal tissue, almost all of the fluid is in the gel state and almost none in the free fluid state. However, a free fluid space can be created in the interstitium by implanting a perforated capsule. The capsule wall prevents the atmospheric pressure from being transmitted through the tissues to the cavity within the capsule and therefore prevents collapse of this cavity. When such a capsule is implanted in one of the soft tissues, the pressure measured in the free fluid inside the capsule is about –6 mmHg (2). And, because this fluid in the capsule flows freely into the interstitium and vice versa, the value of –6 mmHg is believed to be the approximate interstitial free fluid pressure in most soft tissues of the body.

Osmotic Pressure Difference Across the Tissue Gel-free Fluid Interface

The tissue gel contains about 0.5 to 1 per cent proteoglycans. These are strongly negatively charged and therefore create a Donnan equilibrium effect that in turn causes an osmotic pressure difference across the interface between the gel and the interstitial free fluid. This can be explained as follows: The negative charges of the proteoglycan molecules attract a large excess of positive ions, mainly sodium ions, into the gel matrix; the excess sodium ions then cause the osmotic pressure. However, the quantitative amount of this osmotic pressure difference at the interface is still in dispute. Several authors have estimated its value by measuring the colloid osmotic pressure of tissue gel against saline and then subtracting the estimated colloid osmotic pressure of interstitial fluid. In this way, the osmotic pressure difference at the gel interface with the free fluid has been estimated to be about 6 mmHg (reviewed by *Zweifach and Silberberg* [1]).

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However, this estimate itself is obviously based on a series of questionable assumptions. A second method that has been used to estimate this osmotic pressure difference has been to measure the imbibition pressure of tissue gel in its normal state and then again after the Donnan equilibrium effect has been nullified by exposing the gel to a concentrated salt solution. When this has been done, the change in imbibition pressure has been found to be about 2 mmHg (3, 4). Since theoretically, essentially all of the osmotic pressure difference is caused by the Donnan effect, these data indicate that the osmotic pressure difference across the tissue gel-free fluid interface is also about 2 mmHg. Because this method probably has far less potential for error than the other method, we suggest that, for the time being, the osmotic pressure of the gel be considered to be approximately 2 mmHg more than that of the interstitial free fluid.

Chemical Potential of the Interstitial Free Fluid and of the Intragel Fluid.

Since all the molecules and dissolved substances in the interstitial free fluid are freely mobile, if we express the chemical potential of this free fluid in terms of pressure, considering atmospheric pressure to be equal to zero, this chemical potential would have an equivalent value of –6 mmHg. Also, in the equilibrium state, by definition, the chemical potential of the intragel fluid is equal to the chemical potential of the free fluid, also equivalent to –6 mmHg. Thus, the chemical potentials of both the intragel fluid and the free fluid are the same. And, before fluid can be made to flow from either the free fluid compartment or the gel fluid compartment into the lymphatic capillary, the chemical potential of the fluid in the capillary must be more negative than the chemical potential in the interstitium.

What is the Energy Source for Formation of Lymph?

There are basically two different ideas concerning the energy source for lymph formation. The first of these, a concept that has been held for many years, is that the pressure in the capillaries causes transudation of fluid into the tissue spaces. This increases the interstitial fluid pressure which in turn drives the fluid toward and into the lymphatics even though the lymphatic capillary pressure is considered to be greater than atmospheric pressure. In other words, this theory proposes that there is a continuous positive pressure gradient from the blood capillaries to cause fluid movement all the way to the lymphatic capillaries and that all of the hydrostatic pressures in the interstitium are greater than atmospheric pressure because the lymphatic pressure itself is greater than atmospheric pressure (1).

A second theory proposes that, in addition to the driving force of the capillary pressure causing fluid filtration through the capillary membrane, a pump also exists at the terminal lymphatics to cause suction of interstitial fluid into the lymphatics (5, 6). This theory also proposes that under normal conditions the pump is powerful enough to create negative hydrostatic pressure in the interstitial free fluid and equivalent negative chemical potential in the intragel fluid.

The question that we now need to address is which of these two theories is more likely to be correct. The first of the theories (that there is a continuous positive pressure gradient) demands that the chemical potential of both the intragel fluid and the interstitial free fluid be greater than that in the lymphatics. That is, it demands that the chemical potential of both these fluids have a pressure equivalent greater than atmospheric pressure – a positive pressure – because the pressure in the lymphatics themselves, in this theory, is considered to be positive. However, we have already seen that the pressure equivalent of the chemical potential in the fluid in the interstitium, as measured by the capsule technique, averages approximately –6 mmHg which does not support this positive pressure gradient theory. Also, in the recent review by *Zweifach and Silberberg* (1) in which the positive pressure gradient theory for lymph formation was considered to be the correct one, the following values were given for tissue and lymphatic pressures: an osmotic pressure difference between the gel and the free fluid of 6 mmHg, an intragel fluid pressure equal to 0 mmHg, and a pressure in the lymphatic capillary of approxi-

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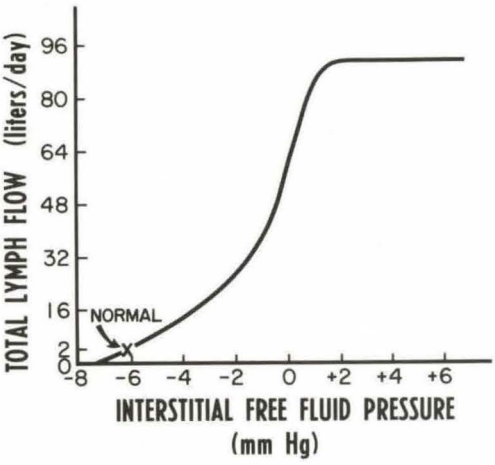

Fig. 1 Relationship between interstitial free fluid pressure, as measured by the implanted capsule technique, and total lymph flow, as extraplated to the entire body of the human being from data obtained in our laboratory by *Gibson* in the dog (12).

mately 0 mmHg. If one considers this carefully, he will see that these values would be impossible without a lymphatic pumping mechanism, because the chemical potential in the gel, in terms of pressure, would be 0 minus 6 or –6 mmHg. And this is 6 mmHg less than the 0 mmHg in the lymphatic capillary. Therefore, fluid would flow from the lymphatic capillary into the tissue gel rather than forward into the lymphatics.

Thus, the problem with the continuous positive pressure gradient theory for fluid flow toward the lymphatic capillaries is that the quantitative values simply do not add up.

Evidence in Favor of a Lymphatic Pump that Can Cause Negative Interstitial Fluid Pressure. The evidence that the second theory for lymph formation (that there is a sucking lymphatic pump) is correct is mainly: 1) both capsule (2) and wick pressure measurements (7) suggest that the interstitial free fluid pressure is quite negative, 2) the tissue gel has a chemical potential equivalent to the negative pressure in the interstitial free fluid, and 3) at least one pair of investigatos, *Nicoll and Hogan*, using the micropipette method for measuring pressure, finds pulsatile negative pressure

pressures both in terminal lymphatics and in the interstitial fluid surrounding the terminal lymphatics (8).

A number of old observations also suggest that the lymphatics can suck fluid from the interstitium. First, *McMaster* showed that when a very small needle is inserted into loose subcutaneous tissue, fluid is intermittently sucked from the needle once every few minutes into the tissue, but fluid never flows outward from normal interstitium (though fluid will flow outward from edematous tissue) (9). Second, both *Allen* (10) and *Blocker* (11) demonstrated that the central ends of transected intermediate-sized lymphatics will suck enough to create negative pressures of several millimeters of mercury.

Finally, let us consider some of the quantitative requirements of a lymphatic suction system that would be needed to create the negative pressures found in the interstitium. Fig. 1 illustrates the relationship between interstitial free fluid pressure (as measured by the capsule technique) and lymph flow in the entire human body as extrapolated from studies in dogs (12). Note that when the interstitial free fluid pressure is –6 mmHg, the total lymph flow is only 2 liters per day. This translates to approximately 50 nl lymph/gram of tissue/minute. This is such an infinitesimal amount of lymph flow that even the slightest rate of lymphatic pumping could produce this much flow. The intermittent suction that was observed by *McMasters* from a needle inserted into subcutaneous tissue, occurring only once every few minutes (9), would be more than adequate to provide this much lymph flow. Therefore, from a quantitative point of view, it is quite conceivable for the lymphatic system to suck these few nanoliters of lymph from the tissues per minute, even though the suction is intermittent.

But, how do the lymphatics provide this negative suction? This was discussed extensively in a recent review by *Casley-Smith* (6). First, it is well known that the collecting lymphatics are well endowed with valves. In addition, the junctions between the endothelial cells of the lymphatic capillaries probably also function

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as valves because in many places one endothelial cell loosely overlaps the next cell in such a way that fluid can move easily through the cell junctions into the lymphatic, but the overlapping endothelial cells close the junctions when fluid attempts to move back out of the lymphatic capillaries. Because of this extensive valve system, any movement that occurs in the tissues whatsoever would tend to propel fluid in only one direction, centrally along the lymphatics.

Aside from the possibility of a physical lymphatic pump, *Casley-Smith* has also suggested that an intermittent osmotic effect might also occur to cause movement of fluid through the pores of the lymphatic capillary (6). Though the mechanism that he has porposed is complex and not everyone agrees that it is thermodynamically feasible, nevertheless, it is a possibility that must be considered in our quest to learn how the lymphatics cause suction of fluid from the interstitium.

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