Pressure-volume relationships in the interstitial spaces

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This paper will discuss the recent finding that the normal interstitial fluid pressure is negative rather than positive and will present a method for recording dynamic changes in interstitial fluid pressure. Especially important is the shape of the pressure-volume curve of the interstitial spaces. So long as the interstitial fluid pressure is negative, the interstitial fluid volume remains almost exactly constant; the amount of fluid in the interstitial spaces under these conditions is just that amount necessary to fill all the tissue voids. However, when the pressure rises into the positive pressure range, the stability of interstitial fluid volume regulation is lost, and the person very rapidly develops edema. Thus, interstitial fluid pressure is negative under normal conditions and is positive in edema.

Until the last few years it has been assumed that the interstitial spaces are similar to a multilocular elastic bag in which the pressure increases approximately linearly as fluid accumulates in the spaces. We shall see in the following discussion that this simple description of the interstitial spaces and their pressure-volume relationships is far from the truth. Indeed, now that we have reasonable estimations of normal interstitial fluid pressure, we find it to be less than atmospheric pressure, that is, a negative pressure instead of a positive pressure as has always been assumed.[1] Furthermore, the interrelationships between pressure and volume are very far from linear, and these nonlinearities play a major role in such factors as (a) regulation of interstitial fluid volume; (b) protection of the body against edema; and (c) even the mechanism by which the body tissues are held together.

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Measurement of interstitial fluid pressure

Until recent years, the method used almost universally to measure interstitial fluid pressure has been to insert a needle into the tissues and then to measure the pressure required to force fluid from the needle into the tissue.[2] In normal tissues, the force required to do this is approximately +1 to +3 mm. Hg, which is the value that has always been assumed to be the normal interstitial fluid pressure. However, the ridiculousness of this assumption is readily apparent when one realizes that the diameters of the smallest hypodermic needles are approximately 500 times as great as the width of the interstitial spaces into which the needle is supposedly protruding. Therefore, an understanding of interstitial fluid dynamics required the development of some method by which true interstitial fluid pressure could be estimated.

Several years ago we developed a method which we believe to estimate the true interstitial fluid pressure.[1] The theory of the method is to create a fluid space in the tissues that is large enough for a needle to be inserted into it without altering the normal pressure. To do this, a small perforated capsule, as shown in Fig. 1, is implanted in the tissues and left there until complete

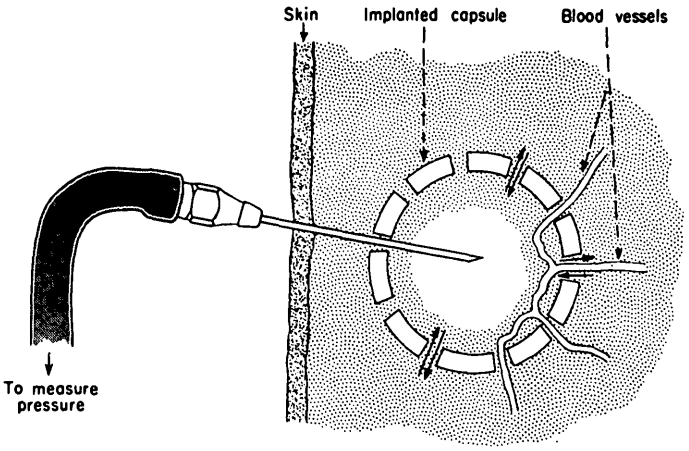

Fig. 1. Capsule method for recording interstitial fluid pressure. (From Guyton, Textbook of Medical Physiology, ed. 3, Philadelphia, W. B. Saunders Company, by permission of the publisher.) (In press.)

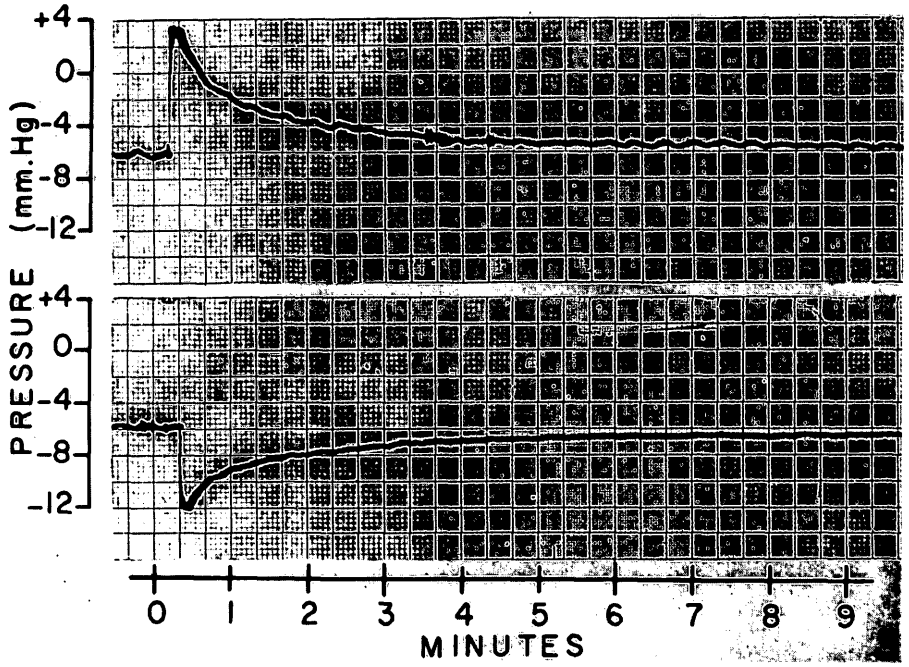

Fig. 2. Continuous records of interstitial fluid pressure, showing in the top panel a sudden rise in interstitial fluid pressure when 1 cu. mm. of fluid was injected into the capsule, followed by return of the pressure to the normal negative level. The lower panel shows the effect of removing 1 cu. mm. of fluid from the capsule, followed again by return of the pressure to the normal level. (From Guyton: Circulation Res. 12: 399, 1963, by permission of the American Heart Association, Inc.)

healing takes place in approximately four to five weeks. By this time, connective tissue has grown through the perforations and has lined the inside of the capsule. Furthermore, the remaining cavity in the capsule is filled with normal interstitial fluid. If a dye is injected into the cavity, one finds that this will diffuse into the surrounding tissue spaces, which indicates that the fluid in the cavity communicates freely with the fluid in the surrounding interstitial spaces.

To measure the pressure in the capsule cavity, a small hypodermic needle, usually No. 26 gauge, is inserted through the skin, through one of the perforations of the capsule, and into the central cavity. The pressure is then recorded, always referring the pressure to atmospheric pressure at the hydrostatic level of the capsule itself. Fig. 2 illustrates a typical record of the interstitial fluid pressure. In this instance the pressure measured -6 mm. Hg when the needle was inserted into the cavity. In the upper panel of the figure, 1 cu. mm. of fluid was injected into the cavity which elevated the intracapsular pressure to approximately +4 mm. Hg. Note, however, that within a few minutes the pressure had returned almost to the normal level.

In the lower panel of Fig. 2, 1 cu. mm. of fluid was removed from the cavity.The intracapsular pressure fell immediately to -12 mm. Hg. Again, however, the pressure re-equilibrated back to its normal level of -6 mm. Hg. This record illustrates that the negative interstitial fluid pressure recorded in the interstitial spaces by this method is actively re-established whenever some extraneous factor changes it from its normal value.

Another new method for measuring interstitial fluid pressure

The secret of measuring interstitial fluid pressure is to create a sufficient volume of fluid in an interstitial fluid space so that fluid communication can be established between the fluid in the space and the fluid in an inserted needle. Therefore, any procedure by which sufficient free fluid can be created within the body should provide an adequate means for measuring interstitial fluid pressure. Another new method besides the capsule method that we use to do this is to place a cup over the surface of the skin and then to draw the skin into the cup by a vacuum. Once in the cup, the skin is held there by a very strong adhesive material, and the vacuum is removed. Over a period of several hours free fluid accumulates in the tissue beneath the cupped skin, and within 48 to 96 hours the pressure measured in this free fluid comes to an equilibrium level. In preliminary studies the pressure measured by this means has varied between -3 and -9 mm. Hg, which is in the same range as the pressure measured by the capsule method.

Normal interstitial fluid pressure measurements. The normal interstitial fluid pressure has been measured several hundred times in the subcutaneous tissue spaces in almost all parts of the body, including the abdominal wall, the lower leg, the upper leg, the axillary space, the scrotom, and so forth.[1, 3] The pressure has also been measured in muscle and in the retroperitoneal space. In all of these, the pressure has measured in the negative range, averaging between -6 and -7 mm. Hg in the subcutaneous and retroperitoneal tissues, a millimeter or so less negative in the dependent areas of these tissues, and a millimeter or so more negative in the less dependent areas. The pressures measured in muscle have been about -4 mm. Hg. Attempts to measure pressure in such places as the lungs, the abdominal cavity, and so forth, have not yet been satisfactory because of the development of prolonged inflammation around the capsule, which gives nonrepeatable results.

Dynamic changes in interstitial fluid pressure under different physiologic conditions

Among the most compelling reasons for believing that the capsule method does indeed measure the true interstitial fluid pressure has been the demonstration that the pressure measured from the capsule changes in the appropriate direction when either capillary pressure or plasma colloid osmotic pressure is changed experimentally. We have demonstrated this in three separate ways as follows[1]:

Acute changes in interstitial fluid pressure when the venous pressure is elevated. The lower curve of Fig. 3 illustrates a continuous measurement of interstitial fluid pressure from a capsule implanted in the lower leg of a dog. On first measuring the interstitial fluid pressure it was –7 mm. Hg. Then, a blood pressure cuff placed around the thigh was inflated enough to elevate the venous pressure to 60 mm. Hg. Immediately, fluid began to transude out of the capillaries into the leg, and over a period of 13 hours the leg swelled to a diameter about twice the normal diameter, or a volume that was calculated to be about 4 times the normal volume. Note in Fig. 3 that the interstitial fluid pressure began to rise immediately after the venous pressure was elevated. This obviously was the effect to be expected, because such a high elevation of venous pressure would certainly cause rapid transudation of fluid into the interstitial spaces. After the pressure had risen into the positive range, continued transudation of fluid into the tissues did not cause very marked additional increase in pressure. The cause of this was the

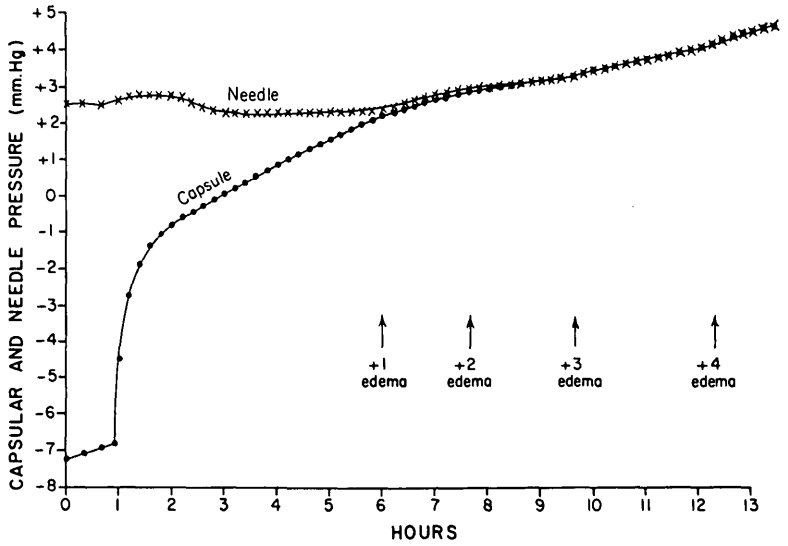

Fig. 3. Capsule (lower) and needle (upper) pressure measurements for 13 hours following sudden elevation of the venous pressure in a dog's leg to 60 mm. Hg; the capsule pressure measurements change as would be predicted theoretically, but the needle presssure measurements do not do so. (From Guyton: Circulation Res. 12: 399, 1963, by permission of the American Heart Association, Inc.)

tremendous nonlinearity of the pressure-volume curve of the interstitial spaces, as will be explained later in this paper.

Note also the upper curve in Fig. 3, which shows pressure measurements made by the subcutaneous needle insertion technique. During the first few hours after the venous pressure was elevated to 60 mm. Hg there was no significant change in pressure measurements made by this method even though it was very obvious to the eye that the leg was swelling rapidly. This experiment demonstrated the futility of attempting to measure normal interstitial fluid pressures by the needle technique. However, once enough free fluid was available in the tissues for free fluid flow into and out of the needle tip, the pressure measured by the needle method was equal to that measured by the capsule method. Thus, in frank edema the needle method can be a valid method for measuring interstitial fluid pressure, though it is not a valid method for measuring interstitial pressure under nonedematous conditions.

2. ***Changes in interstitial fluid pressure when the colloid osmotic pressure of the interstitial spaces is changed.*** The curve of Fig. 4 labeled *CAPSULE* illustrates another typical record of interstitial fluid pressure, in this instance measuring –4 mm. Hg at the outset. Then, three successive injections of 50 ml. each of 20 per cent large molecular weight dextran-Tyrode solution were given to the animal intravenously. Within a minute after each injection, the interstitial fluid pressure as measured by the capsule began to decrease, and within three to four minutes it had reached a new, much lower equilibrium level. Here again, this is precisely the effect that would be expected, because injection of such a concentrated dextran solution having a colloid osmotic pressure approximately four times that of normal plasma would be expected to draw large quantities of fluid out of the interstitial spaces into the circulation. And the decrease in fluid volume of the interstitial spaces would be expected to decrease the interstitial fluid pressure.

After the three injections of dextran, three subsequent injections, 150 ml. each, of normal saline were given intravenously. Following each of these, interstitial fluid

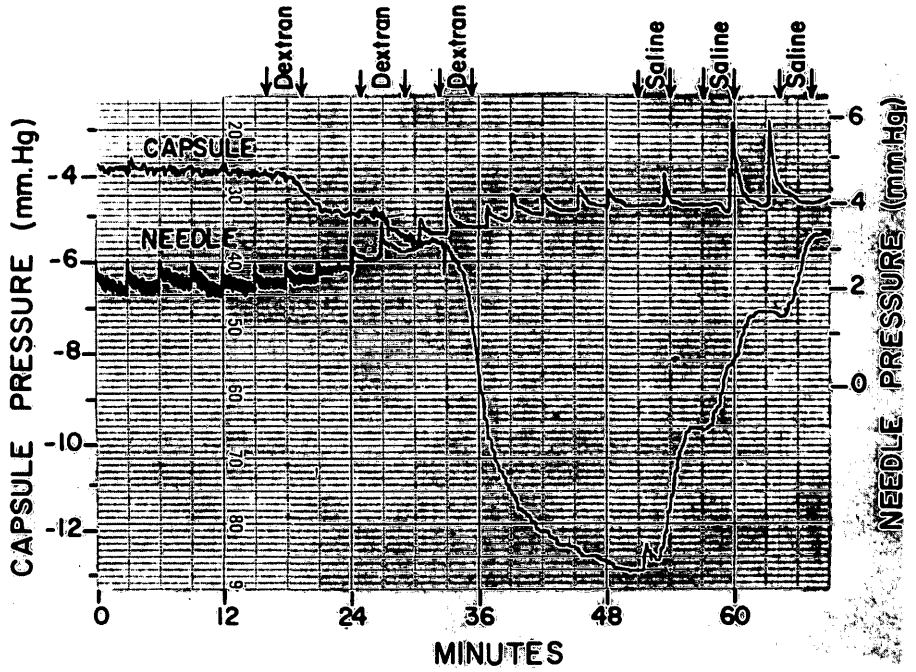

Fig. 4. Capsule and needle pressure measurements, showing first the effect of injecting 50 ml. doses of 20 per cent dextran solution and then 150 ml. doses of isotonic saline solution. The capsule measurements changed as would be predicted theoretically, while the needle measurements failed entirely to do so. (From Guyton: Circulation Res. 12: 399, 1963, by permission of the American Heart Association, Inc.)

pressure rose almost immediately. This, also, was the effect to be expected.

To quell still further the idea that the needle insertion method can measure normal interstitial fluid pressure, we need only to observe the record labeled *NEEDLE* in Fig. 4 which shows successive needle pressure measurements. Note that the needle pressure rose at times when it should have been falling, and at other times it fell when theory predicted that it should have been rising. Thus, again, one sees the futility of using the needle method for measuring normal interstitial fluid pressure.

3. ***Interstitial fluid pressure measurements following intravenous infusion of Tyrode solution.*** In more than 10 experiments we made dogs edematous by infusing Tyrode solution in quantities as great as one-half to three-fourths the weight of the dog within one hour's time. Invariably, the interstitial fluid pressure, as measured by the capsule method, rose from its normal negative value of approximately –7 mm. Hg up to and into the positive pressure range.

We also created local edema many times by local injection of fluids. In all of these experiments, the pressure measured by the capsule rose into the positive range, as would be predicted from theoretical considerations.

Other reasons for believing that there is normally a negative interstitial fluid pressure

Many observations made in the past, both clinically and experimentally, are consonant with the concept of a negative interstitial fluid pressure. Some of these are the following:

1. Pressures measured in the different cavities of the body have all been negative, such as in the intrapleural space,[4] in the

pericardial space,* and in the joint cavities.[5] The pressure in the abdominal space has not yet been measured, but, since open communications occur frequently between the abdominal space and the intrapleural space, it is reasonable to believe that the pressure in the abdominal space must also be negative, for otherwise fluid would flow continually from the abdominal space into the negative pressure area of the intrapleural space.

2. A blister that does not become infected always becomes reabsorbed. One can almost see the negative pressure in a resorbing blister, because the skin is pulled down against the base of the blister in a wrinkled fashion for which a negative pressure is required.

3. Skin is held in the concavities of the body even though the tension of the skin is attempting to pull it away from these concavities. Thus, in the axillary space, the natural tendency is for the skin to pull away. Yet it is held there by some force. When one injects fluid into the axillary space, he finds that almost no pressure is required at the tip of the needle to inject the fluid,[1] illustrating that there are not adequate fibers to hold the skin in this concavity. On the other hand, a negative interstitial fluid pressure could easily explain this effect. Likewise, when a skin graft is placed on the body surface, fluid beneath the graft is absorbed, and the skin is actually sucked downward against the bed onto which it has been placed.

4. Granulation tissue does not continue to weep as would be expected if the fluid pressure between the cells were positive. A negative interstitial fluid pressure could account for this failure of fluid to leak from this tissue.

5. We shall see later in the paper the failure of edema to develop following severe loss of plasma protein or when the venous pressure is elevated; a moderate amount can also be explained on the basis of a normal negative interstitial fluid pressure. But we need more discussion before attempting to explain this concept.

*E. H. Wood: Personal communication.

Mechanism of the normal negative interstitial fluid pressure

Thus far, we have discussed simply the evidence for the existence of negative pressures in the normal interstitial spaces; we have said nothing about the mechanism by which this negative pressure develops. Indeed, all features of the mechanism have not yet been elucidated, but the general concept is the following:

Recent measurements of capillary pressure by means of the isogravimetric method[6] have indicated that the normal capillary pressure of the body ranges between 12 and 22 mm. Hg with an average of about 17 mm. Hg. On the other hand, the normal plasma colloid osmotic pressure is about 28 mm. Hg. Thus, there is 11 mm. Hg more colloid osmotic pressure than capillary pressure, which means that one would expect an absorptive force at the capillary membrane averaging about 11 mm. Hg. This, however, is partially compensated for by the fact that protein in the interstitial fluid causes about 4 mm. Hg colloid osmotic pressure outside the capillary membrane that tends to move fluid out of the capillaries. This makes a net imbalance at the capillary membrane of 7 mm. Hg attempting to absorb fluid from the interstitial spaces, which obviously could create the negative pressure. Thus, it is our supposition that the negative interstitial fluid pressure is created simply by the osmotic forces that occur at the capillary membranes.

However, there remains an important problem in this explanation: how can the protein content of the interstitial spaces be maintained at a low enough level to create only 4 mm. Hg tissue colloid osmotic pressure? We have the following experimental clue that might answer this question: When an animal is first anesthetized and is completely still, the interstitial fluid pressure measures about –7 mm. Hg, but, as the animal remains immobilized over a period

of several hours, the interstitial fluid pressure rises progressively toward the 0 pressure level. Then, if the animal is awakened or is subjected to movement in any other way, the interstitial pressure becomes more negative again. This observation demonstrates that movement is essential to the development of the negative interstitial fluid pressure. Therefore, we presume that movement causes a pumping action in the tissues and that the pumping causes intermittent positivity in the different tissue spaces to force fluid into the lymphatics; because of the valves in the lymphatics, the fluid then will not flow back into the interstitial spaces when the intermittent positivity is gone. Thus, the average interstitial fluid pressure can remain very negative, and yet intermittent positivity can cause the flow of lymph and the continual removal of protein from the interstitial spaces, thereby maintaining the very low tissue colloid osmotic pressure that is necessary for operation of the capillary osmotic mechanism described above for maintaining a negative interstitial fluid pressure.

Pressure-volume curve of the interstitial spaces

Perhaps even more important than the observation that the normal interstitial pressure is negative is the actual shape of the pressure-volume curve of the interstitial spaces. We have estimated this curve in four separate ways.[3] To do this, the interstitial pressure has been measured continually while we have progressively increased the interstitial fluid volume by (a) infusing fluid into the whole animal; (b) elevating the venous pressure so that fluid would transude into the tissues; (c) injecting various amounts of concentrated dextran solution to alter the colloid osmotic pressure and thereby to decrease the interstitial volume; and (d) perfusing the vascular system of an isolated leg with fluid so that the interstitial fluid volume could be changed. The results from this last method for measuring the interstitial fluid pressure-volume curve are summarized as follows:

Fig. 5 illustrates the average pressure-volume curve measured in four isolated hind-leg preparations of the dog. The legs were removed very rapidly and placed on a scale so that the changes in interstitial fluid volume could be recorded as weight changes. The vascular system of the leg was perfused, first, with concentrated dextran-Tyrode solution to decrease interstitial fluid volume and then with Tyrode solution to increase interstitial fluid volume. Interstitial fluid pressure was measured continuously from a capsule that had been previously implanted in the lower leg.

At the beginning of the experiments, the interstitial fluid pressure averaged –7 mm. Hg in the four isolated legs. Following perfusion of 10 per cent dextran-Tyrode solution through the vascular system for 20 minutes, the pressure fell to an average of –27 mm. Hg, and the average weight of the legs had decreased 3 per cent. These results illustrate that removal of only a very small amount of fluid from the normal interstitial spaces changes the interstitial fluid pressure markedly.

Following perfusion with dextran-Tyrode solution, Tyrode solution without dextran was perfused. Fluid began to transude into the tissue spaces, and the weight of the leg began to increase. Toward the end of the experiment, the veins from the leg were partially occluded to elevate the venous pressure to approximately +30 mm. Hg, which caused still more rapid transudation of fluid into the tissues. During this progressive accumulation of fluid in the leg, the interstitial fluid pressure was continually measured. The average results from the four experiments are shown in the pressure-volume curve of Fig. 5.

The compliance of a tissue space is defined as the rate of change of volume divided by the rate of change of pressure. One sees from Fig. 5 that the compliance of the interstitial spaces was very slight as long as the pressure remained in the negative pressure range. However, just as

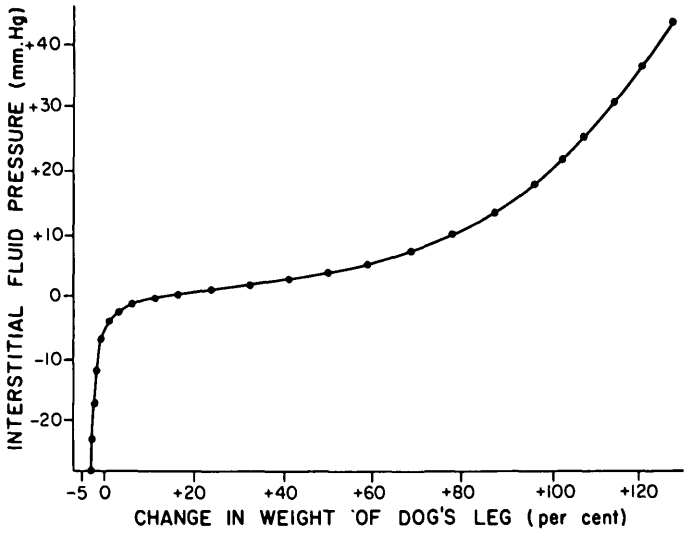

Fig. 5. The average pressure-volume curve measured in four isolated dog legs. Note almost zero compliance of the interstitial spaces in the normal negative interstitial pressure range but tremendous compliance of the spaces once the interstitial pressure rose into the positive pressure range (that is, above atmospheric pressure).

soon as the interstitial pressure rose above atmospheric pressure (that is above 0 mm. Hg), the compliance of the tissue spaces suddenly became tremendous, so that only a fraction of a millimeter rise in pressure now was associated with tremendous increase in fluid volume. Then, when the volume of the tissue spaces had increased so much that the skin was obviously beginning to be stretched, the interstitial fluid pressure began to rise once again, and the compliance began to fall once more.

With a little thought, one can understand that the pressure-volume curve of Fig. 5 is almost precisely the same as that which one would obtain from an elastic bag. When the bag is completely empty and suction is applied to the bag, the compliance will be essentially zero because more and more suction does not cause the bag to become more empty. On the other hand, when the bag begins to fill, almost no pressure is required at first to cause rapid filling. But when the walls begin to stretch, the pressure once again begins to rise.

One can also observe the basic principles underlying the pressure-volume curve of Fig. 5 by looking at the back of one's outstretched hand and rolling the skin from side to side. The skin obviously is not held in place by fibers, and there is no obvious fluid space present. Thus, the bag is sucked "dry." However, in an edematous person, all the concavities of the back of the hand disappear, and an observer can actually feel free fluid. In early edema the skin is not stretched, but in late edema the skin does become stretched.

Significance of the pressure-volume curve

When the pressure-volume curve in Fig. 5 is first observed, its significance is not particularly impressive but upon thinking about it for a while one will begin to understand many features of bodily function that perhaps have not been clear in the past. Some of these are the following:

Negative pressure as the factor that holds tissues together. It can be readily understood that a negative pressure in the tissues could hold the tissues together. Anyone who has dissected the body knows that many tissue planes exist—such as where tendons pass through fasciae, where muscles slide within muscle sheaths, and so forth—where there are no fibrous attach-

ments between the successive layers of the planes; yet these tissues are held together by the negative interstitial pressure. It is very likely, indeed, that almost all tissues are held together by this means, because in the condition of edema essentially all tissues are spread far apart from each other.

Explanation of the "margin of safety" before edema develops. Clinicians have known for a century that the plasma proteins can decrease to less than one half normal without causing edema and that the central venous pressure can rise in some conditions to as much as 10 mm. Hg without causing generalized edema. This "margin of safety" can be explained at least partially by the presence of negative pressure in the interstitial fluid spaces, because the capillary pressure must rise high enough to overcome the negative interstitial fluid pressure before the spaces will swell to cause edema. Indeed, in actual experimental studies we have measured interstitial pressures in different types of edema in more than 100 instances. In all of these, the pressure was positive, ranging usually between +1 and +5 mm. Hg, which is on the flat, extended portion of the pressure-volume curve illustrated in Fig. 5.

Two other factors also contribute to the "margin of safety" before development of edema. First, as the interstitial fluid pressure rises to approach zero pressure, lymphatic flow increases by as much as 10 to 15 fold.[7] This rapid flow of tissue fluid into the lymphatics washes most of the tissue protein out of the interstitial spaces, decreasing the tissue colloid osmotic pressure almost to zero[8] and thereby allowing more effective osmotic absorption of fluid into the capillaries. Second, as the lymphatic flow increases, the outward flow of fluid from the capillaries creates a pressure drop across the capillary membrane. This brings into being a further safety factor to help prevent a rise in interstitial fluid pressure into the positive pressure range.

To recapitulate, so long as the interstitial fluid pressure is negative, edema will not occur. However, just as soon as the circulation becomes abnormal so that the interstitial pressure rises into the positive range, the tissue spaces suddenly begin to fill and will continue to fill as long as the pressure remains in this positive range or until the skin becomes stretched. As an example, this effect occurs dramatically when a person with a failing heart becomes "decompensated." The cause of this is that the capillary pressure finally exceeds the critical level beyond which edema fluid begins to collect unabatedly. This accumulation of edema will continue until the death of the patient unless therapy is instituted to reduce the capillary pressure below atmospheric pressure level.

Regulation of interstitial fluid volume. Now that we know the pressure-volume curve of the interstitial spaces, we can also formulate a reasonable mechanism for the regulation of interstitial fluid volume as follows:

The normal interstitial fluid pressure is approximately –7 mm. Hg, which is on the steep, noncompliant portion of the pressure-volume curve. Furthermore, if we consider all the three factors listed above which prevent development of edema, (a) the negative interstitial fluid pressure, (b) the washout of proteins from the interstitial spaces, and (c) the pressure drop across the capillary membrane that occurs when lymph flow becomes rapid, we can calculate that the capillary pressure probably has to rise from its normal value of 17 mm. Hg up to above 35 mm. Hg before edema will develop.

Even under moderately abnormal conditions of the circulation, the capillary pressure only rarely rises to this level of 35 mm. Hg. Therefore, the interstitial fluid spaces will remain "dry" so long as the capillary pressure remains below 35 mm. Hg. This allows a tremendously wide range of circulatory function in which the volume of fluid in the interstitial spaces remains very constant because of the extremely steep slope of the pressure-volume curve in the negative interstitial pressure range.

However, even in this negative pressure range there still are tremendous numbers of minute spaces among the fibers of the tissue spaces and between the folds of the cell membranes from which it is impossible to remove fluid. It is this fluid that makes up the normal interstitial fluid volume.

Another way of explaining the regulation of the interstitial fluid volume is to consider the pressure-volume curve of Fig. 5 as a "buffer curve." So long as the interstitial fluid pressure remains in the negative range, the interstitial fluid volume is "buffered" to a stable value. However, just as soon as the pressure rises into the positive range, very minute changes in pressure thereafter will cause tremendous changes in interstitial fluid volume. This creates an unstable state of interstitial fluid volume regulation. That is, the regulatory system has gone beyond its normal regulatory limits, and the pathologic state of edema has developed.

The interstitial spaces as a pressure release system for the circulation. Finally, we must note that the interstitial spaces serve an important function in the prevention of excessive engorgement of the circulatory system. For instance, if one infuses 10 L. of balanced electrolyte solution into the veins of a 20 kilogram dog over a period of one hour, this still will not engorge the circulation. The first liter will distribute itself approximately evenly between the blood and the interstitial fluid, but by this time the interstitial fluid pressure will have risen into the positive range in which the tissue spaces become extremely compliant. Therefore, any further infusion of fluid simply causes very rapid transudation of the fluid into the tissue "bag." In this way, the interstitial spaces act as a volume relief system to keep the circulatory system from becoming overly filled.

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