Newer concepts of edema and ascites formation

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In recent years there have been several fundamental changes in the concepts of edema and ascites formation. The reason for this is that much more has been learned about the control of the interstitial fluid volume and the fluid volumes in the cavities of the body as well.

The most fundamental change in our thinking is that it is now believed that normal tissues contain almost no freely mobile fluid. Instead, the fluid in normal tissue spaces is bound in a gel form so that it cannot move easily through the tissues. Yet, when edema develops, much of the fluid then does become freely mobile; it is mainly this mobile fluid that constitutes the edema state. Let us explain this concept more fully and then return to a consideration of the development of edema and ascites.

Role of the Lymphatics in Maintaining the Non-edematous State. All physicians know that edema will occur when the lymphatics become blocked or otherwise nonfunctional. However, the reason for this development when the lymphatics become obstructed is not too widely understood. It is generally believed that when the interstitial fluid pressure rises to too high a positive level, the excess fluid simply overflows into the lymphatics; in this way edema is normally prevented. However, the lymphatics function not only as a system for simple overflow of fluid from the interstitial spaces, but they also act as small pumps, always pumping fluid out of the tissue spaces. Part of this pumping action results from motion of the tissues, such as the motion that occurs in the tissues of the leg when a person walks. Each time a lymphatic is compressed, fluid is displaced forward along the lymphatic, and it does not run backwards because of the lymphatic valves. In addition to this pumping action caused by tissue motion, experiments also show that both the lymphatic vessels and even the minute lymphatic capillaries undergo rhythmical contraction, this rhythmical contraction acting as a pump to propel the lymph along the lymphatic vessels. Therefore, even in the absence of tissue motion, it is now believed that the lymphatics provide a continual drainage system to pump away any excess mobile fluid that appears in the tissues.

Many experiments in the past 20 years have also shown that most of the soft tissues of the body have an interstitial fluid pressure that is less than atmospheric pressure. That is, the normal interstitial pressure is negative, not positive. This is believed to result from the fact that the lymphatics can actually create a slight degree of suction as they pump. In consequence, the pressure of the fluid in the interstitial spaces usually measures between −2 and −6 mmHg. Therefore, normal tissues contain almost no freely mobile fluid; instead there remains only the fluid in the tissue gel.

Role of the Tissue Gel. When normal tissues are removed from the body, compression of the tissues can often expel small to large amounts of a gel-like substance. This is known as the «ground substance» of the tissue spaces, or it is also commonly called the «tissue gel.» It is composed about 99 % of fluid and electrolytes and about 1 % of extremely large proteoglycan molecules (also called mucopolysaccharides). The proteoglycan molecules in turn are composed of small amounts of protein and very large amounts of hyaluronic acid. These molecules are very long, slender, coiled fibrils that intermesh with each other to form a physical structure that has a considerable amount of elastic resilience, similar to a wad of cotton. Therefore, it functions as a physical sponge; the elastic recoil of its structural fibrils causes fluid and electrolytes to be absorbed into the interstices between the fibrils. In addition, the proteoglycan molecules carry large numbers of negative electrical charges. These in turn attract large quantities of sodium and other positive ions into the gel mass; then, these ions create an osmotic force that pulls still additional quantities of fluid into the gel.

Therefore, because the tissue gel functions as a sponge, the suction created by lymphatic pumping can never eliminate all of the fluid from the tissue spaces. For this reason, even in normal tissues, between 15 and 20 per cent of the total tissue mass is usually represented by interstitial gel. It is in this gel that essentially all of the normal interstitial fluid resides. Also, since about four-fifths of the extracellular fluid is interstitial fluid, it is also in the interstitial gel that one finds most of the extracellular fluid of the body.

Yet, to repeat once again, there remains almost zero freely mobile fluid in the interstitium when the lymphatic system pumps normally and when all other conditions of the circulatory system are also normal.

What is the Functional Role of the Tissue Gel? One might wonder why we should have a tissue gel at all. The body would be much lighter if there were no tissue gel, and this would make it easier for a person to move. However, there are many very good reasons for having this gel. Let us mention some of these:

(1) The presence of gel in the tissues, rather than freely mobile fluid, prevents the fluid from flowing from the upper part of the body down into the legs when a person stands

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up. Otherwise, the fluid between the cells in the upper body would simply flow through the tissue spaces downward. Experiments have shown that fluid will flow as much as 250,000 times as rapidly when free fluid is in the tissues as when the fluid is only in the form of tissue gel.

(2) The gel entraps bacteria and impedes the movement of these from one tissue area to another.

(3) The tissue gel holds the cells apart. This allows molecules of nutrients and electrolytes to diffuse from the capillaries to the outlying cells. Without the tissue gel to hold the cells apart, all nutrients would have to pass through those cells near the capillaries before reaching the outlying cells, and in most instances this would not be possible.

(4) The tissue gel provides a large reservoir of extracellular fluid that can be called upon in times of need to replenish the circulating blood with needed fluid and electrolytes.

Role of the Lymphatics to Remove Protein from the Interstitial Spaces. Thus far we have spoken mainly about the role of the lymphatics to remove fluid from the tissue spaces. However, equally as important is the role of the lymphatics to remove protein. The reason for this is that plasma proteins leak continually through capillary pores into the interstitium. This decreases the colloid osmotic pressure of the plasma while at the same time increasing the colloid osmotic pressure in the interstitium. Furthermore, there is no known means by which the proteins, once they enter the interstitium, can return to the circulation except by way of the lymph. Therefore, in the absence of lymph flow, the protein concentration in the interstitial fluid gradually increases until it becomes almost equal to that of the plasma. Once this occurs, there is then approximately as much colloid osmotic pressure pulling fluid into the tissues from the capillaries as pulling fluid back into the circulation from the tissues. Therefore, the *net* colloid osmotic force at the capillary membrane can no longer oppose the capillary hydrostatic pressure that always attempts to force fluid outward through the capillary pores into the interstitium. Thus, it is absolutely essential for the proteins that leak into the interstitium to be returned continually to the circulation.

Nearly half of all the plasma proteins in the circulating blood leak into the interstitium each day. Without lymphatic drainage, essentially all effectiveness of the colloid osmotic pressure mechanism to hold fluid in the circulation would be lost within 24 to 72 hours. And, without this function, edema (as well as ascites, swollen joints, and so forth) would become so severe that death would ensue within a few days after total lymphatic blockage.

The «Dry» State of Normal Tissues. What we have described in the above paragraphs is basically a state of «dryness» in normal tissues. This does not mean that there is no fluid present. However, the tissues are «dry» of significant amounts of freely mobile fluid. The tissue fluid is normally present either in the cells themselves or in the interstitial gel, and if any of the fluid from either of these two sources becomes freely mobile, it is almost immediately pumped away from the tissues by the lymphatics.

The «Wet» State of the Tissues in Edema. Typical edema is normally characterized by a «wet» state. This means simply that the tissues now have large amounts of freely mobile fluid. One can actually displace the fluid in the tissues by compressing an edematous area with a finger, which causes the phenomenon known as «pitting.» After the pit is created, fluid will flow back into the pitted area of the tissue in a few seconds, illustrating that fluid can now be translocated freely from one part of the tissue to another. Also, the edema is frequently «dependent.» For instance the lowermost breast of a grossly edematous woman lying on one side will likely be much more swollen than the uppermost breast. Then, when she rolls to the opposite side, it is not long before the fluid literally flows through the tissue spaces from one breast to the other so that the opposite breast now becomes the one that is swollen.

Therefore, the «wet» state that occurs in edema means simply that the tissues are «wet» with excess quantities of *mobile* fluid.

Abnormalities That Can Cause Wetness of the Tissues, That Is, That Can Cause Edema. Almost all clinicians are highly knowledgeable of the different clinical conditions that can cause edema. However, let us list briefly the frequent causes of edema and perhaps clarify some of the issues:

(1) *Lymphatic blockage.* We have already discussed the development of edema in lymphatic blockage. This results partly because of failure of the lymphatics to carry fluid away from the tissues. However, even more important is failure to carry protein away from the tissues, which causes the colloid osmotic pressure of the interstitium to become equal to or almost equal to the colloid osmotic pressure of the plasma; therefore, there is no longer any net colloid osmotic force to oppose filtration of fluid out of the capillaries into the tissues.

(2) *Edema caused by elevated capillary pressure.* Two of the most common causes of elevated capillary pressure are congestive heart failure and kidney failure. In heart failure, the venous pressure rises very high and causes marked back pressure in the capillaries, thus increasing the capillary pressure to very high levels. In renal failure, excessive quantities of fluid accumulate in the body, causing the blood volume to increase, and either all or some of the pressures in the circulation increase. The rise in venous pressure elevates the capillary pressure, and the rise in arterial pressure also increases the capillary pressure. Experiments have demonstrated that the normal capillary pressure in the systemic circulation is probably about 17 mmHg. This can usually rise to as high as 25 to 30 mmHg before significant amounts of edema will occur. The reason why the capillary pressure must rise this high is because the lymphatic vessels pump more and more actively as greater quantities of fluid filter into the interstitium, and this keeps the interstitium still in a dry or almost dry state even when the capillary pressure has risen to almost two times the normal level.

(3) *Edema caused by decreased plasma colloid osmotic pressure.* Another cause of edema is greatly decreased plasma protein. This occurs frequently in liver disease that prevents the formation of plasma proteins by the liver, and also in kidney disease that allows protein wasting in the urine. The plasma protein concentration usually must fall below 2.5 to 3 g/dl before edema appears. The same factors that prevent edema with high capillary pressure also operate in conditions of low plasma protein to prevent edema devolepment. That is, lymph flow increases as much as 20-fold, and this in turn decreases the interstitial fluid colloid osmotic pressure from normal values of 6 to 12 mmHg to as low as 1 mmHg. And another factor that undoubtedly helps in preventing or correcting edema, especially in long-term conditions, is growth of new lymphatics into edematous tissue areas to carry away the excess fluid and proteins.

(4) *Edema caused by increased permeability of the capillaries.* Many different conditions can increase greatly the permeability of the capillaries. This especially occurs in anaphylaxis, also in response to some drugs, or also in some hyperthermic states. The increased permeability can then cause several separate functional changes that in turn lead to extreme edema. Among these are: (a) decrease in plasma protein concentration because of loss of proteins into the tissues, (b) increase in tissue proteins, thus increasing the tissue colloid osmotic pressure and thereby pulling excessive amounts of fluids into the tissue spaces, (c) decreased capability of that protein which is still present in the plasma to cause colloid osmotic pressure because it is essential for the protein molecules not to go through the pores if they are to create an osmotic force; and (d) occasionally coagulation of plasma proteins in the interstitium because of leakage of fibrinogen into the tissue spaces.

The «Safety Factor Against Edema.» In several of the above paragraphs we noted that either the tissue capillary pressure must rise very high or the plasma colloid osmotic pressure must fall very low before edema will occur. In general, the tissue capillary pressure must rise to almost double normal before edema will occur, or the plasma colloid osmotic pressure must fall below one-half normal. Therefore, it is said that there is a large *safety factor against edema.* From what we have already said, it is clear that one of the most important factors in creating this safety factor is the capability of the lymphatic system to remove excess fluid and proteins from the tissue spaces.

Ascites, Hydrothorac, Swollen Joints, and Pulmonary Edema. Almost exactly the same principles that we have discussed for the development of edema in the peripheral tissues apply also to the development of ascites, hydrothorax, swollen joints, and pulmonary edema. That is, blockage of the lymphatics, excess capillary pressure, decreased plasma colloid osmotic pressure, or increased permeability of the capillaries can all cause these special edematous conditions. It is noteworthy that the fluid pressure in both the pleural space and the joint cavities normally averages between −5 and −10 mmHg. And it is the lymphatics that cause these negative pressures, thus playing the same role in maintaining a degree of suction in the pleural cavity and in the joints as in the other tissues. It is likely that the same principles apply also to the fluid in the abdominal cavity, though appropriate research studies on this are yet to be made.

In the case of the lungs, there is usually an even greater safety factor against edema than in the rest of the body. The reason for this is that the pulmonary capillary pressure is only about one-half as great as the capillary pressure in the systemic circulation. An important advantage of having this very high safety factor against edema in the lungs is that conditions that cause generalized fluid retention, such as kidney disease or decreased plasma colloid osmotic pressure, will usually cause peripheral edema and ascites long before pulmonary edema will occur. This delayed onset of pulmonary edema can be very valuable, for otherwise the person would drown in his own edema fluid.

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