EDEMA AND ITS TREATMENT *

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The attention of physiologists and clinical investigators has been focused with ever increasing intensity upon problems concerning the nature of edema and its causes, so that today we find innumerable pages given up to this subject in most current medical journals. This interest in the disturbances of water balance seems justified when we consider the fact that edema, either local or generalized, appears, for one reason or another, in a myriad of pathological conditions and frequently presents a challenge to our therapeutic ingenuity. Many of the fundamental processes involved in the maintenance of the normal fluid distribution in the body remain completely obscure; nevertheless, progress has been made in recent years which helps us to define our knowledge and to clarify some of the factors which play an active part in shifting biological equilibria in such a way that amounts of fluid greater than normal occupy the tissue spaces. I should like to discuss the rôle of the factors which are known to play a part in the production of edema, and also to point out that certain inconsistencies arise when they alone are applied to explain some changes in fluid equilibrium.

Edema fluid lies in the interstices between cells, and in most instances its accumulation is greatest in the loose subcutaneous areolar tissue of the body. There are consequently only two possible sources for this water, which contains various mineral and organic constituents. Either it must be liberated from the cells of the tissues themselves, or it must come from the blood-stream. While the cells of the body are freely diffusible for water and certain non-electrolytes under various conditions, depending chiefly upon the tonicity of their external environment, migration of fluid from the cells could not bring about significant edema. We know when edema develops that the weight and volume of the involved part increases and such changes cannot result solely from

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the transfer of water existing within cells to their adjacent spaces. Hence we are justified in stating that when edema develops for any reason whatsoever, the immediate source of this fluid must be the blood-plasma.

With this concept in mind, and the knowledge that the veins and arteries are impermeable, it follows that the capillary bed is the only portion of the vascular system which permits the interchange of fluids. Hence, any discussion of edema must take into detailed consideration the physical, chemical and physiological forces active within the capillary wall, at the capillary wall, and immediately outside of the capillary wall. This is true regardless of the remote etiological causes of fluid accumulation, even though they be as diverse in their nature as protein starvation and the sting of an insect. In other words, whether or not edema develops in a patient depends upon conditions in and around the capillaries and not upon the disease process.

Most edematous states are dependent upon two fundamental disturbances related to capillary physiology. Other disturbances also play a rôle, but chiefly quantitatively, and of these I shall have more to say later on. One of the two fundamental disturbances has to do with changes in the equilibrium which normally exists between the hydrostatic pressure within the capillaries and the osmotic pressure of the plasma proteins. The other has to do with changes in the permeability of the capillary walls for water and the solutes of the plasma including the proteins.

Before going on to discuss edema formation, let us review the mechanism by which fluid equilibrium is normally maintained across the capillary wall. In order to visualize the forces active in this process, we must first direct our attention to the blood-pressure or hydrostatic pressure present in different portions of the capillary loop. When the blood leaves the arterioles and enters the extensive capillary bed, there is naturally a sharp drop in the blood-pressure. We are chiefly indebted to Dr. Eugene Landis for having made direct measurements of the hydrostatic pressure in various portions of the capillary loop in man. Landis inserted cannulae into the arterial and venous ends of the capillaries at the base of the finger nail and found that the pressure at the arterial end is about 32 mm. of Hg. and at

the venous end it drops to about 12 mm. of Hg. Thus we find that even in the venous end of the capillaries there is a positive pressure tending to press fluid through the wall of the capillary into the tissue spaces. The following question immediately presents itself: How can fluid return to the blood-stream against this positive blood-pressure? This is accomplished by the osmotic pressure of the blood-plasma as Starling first suggested in 1896.

Let us now consider the source and magnitude of this plasma osmotic pressure. The normal capillary wall acts as a semi-permeable membrane permitting free diffusion of water, salts, and most organic solutes, but not permitting the diffusion of the large protein molecules of the plasma. The non-electrolytes such as glucose and urea are consequently present in the same concentration on both sides of the membrane. The sodium and the chloride ions, which are quantitatively the most important electrolytes, are also distributed on both sides of the capillary wall in nearly equal concentrations and in accordance with a membrane equilibrium known as the Donnan equilibrium, which we need not consider here. Hence the osmotic pressure of the salts and non-electrolytes within the capillary is equalized by the same forces acting outside the capillary. By exclusion, the only substances which are present in the capillaries in relatively high concentration as compared with the interstitial fluid are the serum proteins. These ionized serum proteins can and do exert an appreciable osmotic pressure. This can be easily demonstrated by the following experiment. If blood serum is placed in a collodion sac containing a manometer and the sac is immersed in a beaker of normal salt solution, the pH of which is adjusted to about 7.4, the fluid enters the sac and rises in the manometer. After a few hours, equilibrium is reached and the height of the fluid column in the manometer naturally represents the osmotic pressure of the proteins of the serum. This simple method, or a modification of it, is frequently used for the clinical determination of the osmotic pressure of the proteins in a sample of blood serum. The normal osmotic pressure of serum thus measured and translated in terms of a column of mercury lies between 20 and 25 mm. This is the pressure exerted by human serum normally containing between 6.5 and 7.5 per cent of protein.

Before returning to the discussion of the significance of the serum of plasma proteins in the regulation of fluid exchange across the capillary wall, I should like to say a few words about their physicochemical properties, as these are of importance in understanding the cause of certain types of edema. As you know, the plasma proteins are made up of albumin, globulin and fibrinogen fractions. The last need not be discussed as it is present in such small amounts, that, for our purpose, it is of no importance. Normally, human serum contains about 4.4 per cent of albumin and 2.6 per cent of globulin according to Peters' analyses. The globulin molecule is approximately twice as large as the albumin molecule and consequently 1.0 gram of globulin will exert an osmotic pressure just half as great as 1.0 gram of albumin dissolved in the same amount of fluid. Thus the major part of the osmotic pressure of normal serum can be attributed to the albumin fraction. From this brief discussion it becomes apparent that we need to know the relative amounts of albumin and globulin in the serum as well as the total protein content, when we wish to consider the osmotic pressure of the serum proteins.

Let us now see how the osmotic pressure of the serum proteins accomplishes the return of fluid from the interstitial spaces to the vascular bed. The hydrostatic pressure at the arterial end of the capillary loop is about 32 mm. and this gradually falls so that the pressure at the venous end is about 12 mm. As has already been indicated, this tends to push water out of the capillary. We have seen that the serum proteins normally exert an osmotic pressure of about 23 mm. That means that they tend to draw fluid into the blood-stream with this force. The result is apparent. Capillary pressure is greater than osmotic pressure at the arterial end of the loop and fluid is squeezed into the intercellular spaces; osmotic pressure is greater than capillary pressure at the venous end of the loop and fluid is drawn back into the circulation. In this manner the normal fluid content of the tissue spaces is maintained. On the basis of this discussion we may conclude that edema may develop for one of the following reasons: First, if the concentration of the serum proteins is reduced so that the osmotic pressure is lower than the hydrostatic pressure in the venous end of the capillary; second, if

the pressure in this part of the capillary is increased so that it exceeds the osmotic pressure of the serum proteins. The edema fluid resulting from one of these disturbances should contain very little protein, as the capillary wall has not changed its structural characteristics.

The second type of fundamental change in the physiological behavior of the capillaries which may result in the development of edema is dependent upon the histological structure of these vessels. When the capillaries are dilated as the result of pharmacological stimulation, inflammation, or for any other reason, the pores between the cells of the vessel wall are opened, permitting the transfer of the serum to the intercellular spaces. In edema resulting from this disturbance we naturally expect to find the interstitial fluid relatively rich in serum proteins. It should be pointed out that in reality such edema fluid never contains as much protein as does the blood-serum. This may be explained by the fact that when serum is transferred to the outside of the capillary, this tends to counterbalance the effective osmotic pressure of the proteins within the capillary, thus inhibiting the return of water and salts normally forced out through the arterial end of the loop.

It was mentioned before that processes other than the two which we have described in some detail may play a rôle in the development of edema. Among these are lymphatic flow and the pressure exerted on the outside of the capillaries, as a result of tissue tension. On the bases of the recent studies of Drinker and of Weech, it seems likely that the lymph flow is of greater importance in maintaining fluid equilibrium than we had formerly believed. It is, however, impossible to state at the present time what quantitative significance the lymphatics may have in the removal of fluid from the tissue spaces under normal conditions, and when edema develops from other than mechanical reasons. It is well established that lymph flow in the extremities practically ceases in dogs with the animal at rest and becomes marked only with physical activity. There is real hope that the quantitative studies in progress in various laboratories at the present time may extend our knowledge of this subject.

The influence of tissue elasticity or tension in regulating fluid equilibrium in the body is even more obscure than is the

rôle of the lymphatics. Schade has for some years stressed the fact that the tension of tissues on the outside of the capillaries tends to counteract the hydrostatic pressure which forces fluid out of these vessels. As evidence in favor of this idea numerous investigators have pointed to edema which may first appear about the eyes where the tissue tension is admittedly low. This, however, is at best an unconvincing argument as it is not based upon quantitative measurements. Recent attempts to show differences in tissue resistence to the inflow of fluid under a constant pressure in normal and edematous individuals have yielded entirely negative results. Unfortunately, more accurate investigation of this subject must be carried on before we can properly evaluate the significance of tissue elasticity.

In view of the fact that edema fluid is derived from blood, the discussion of this subject necessitates a consideration of the various substances which contribute to the electrolyte pattern of the plasma. As we know, the plasma consists essentially of a solution of sodium chloride. The other electrolytes such as calcium, potassium, phosphate and sulphate are present in small but definitely fixed amounts and bicarbonate is combined with the excess of sodium not needed for union with other anions. Life is incompatible with any great change in this electrolyte pattern. This is particularly true of the cations. Chloride and bicarbonate ions may change their relationships within fairly wide limits without deleterious effects upon the organism. However, a small increase in the amount of potassium or a comparatively small decrease in the concentration of calcium or sodium in the blood plasma leads to disastrous disturbances. By some mechanism which is still wholly obscure, the body, through selective action by the kidney, protects its electrolyte structure. Thus, regardless of the quantities of calcium, potassium or sodium salts which may be ingested, the kidney selectively removes just the proper quantities of these cations so that the normal relationships are maintained in the blood and tissue fluids. This is not only true of the normal individual but is likewise true of any patient with edema, because, as has already been pointed out, edema fluid is essentially a blood filtrate.

It naturally follows from this discussion that in the production of edema, sodium chloride must be retained, as this constitutes the "backbone" of blood-plasma and interstitial fluid. Water alone can not be retained without salt. The increase in edema following the administration of salt is common to the experience of all clinicians, but was first commented upon by Widal thirty years ago. Widal ascribed this effect of salt to specific retention of the chloride ion, but this idea was disproved by Magnus-Levy and by Leon Blum who showed that the chlorides of potassium, calcium and ammonium do not cause edema and frequently induce a diuresis. We now know that the retention of sodium chloride and water is not dependent upon disease of the kidneys. This is shown by the fact that normal individuals who have been deprived of salt for some time, retain sodium chloride and water for a time to build up depleted stores of plasma and interstitial fluid. The development of edema appears to result from the same processes, but to an exaggerated extent, because of the existing disturbances in capillary physiology.

Having devoted much of my time to some of the physiological aspects of fluid equilibrium, I should now like to discuss their applications to clinical medicine. It has already been pointed out that most edema results from one of two fundamental disorders of capillary physiology. First, a disturbance in the balance between hydrostatic and osmotic pressures as suggested by Starling in 1896, and second, to changes in capillary permeability.

One of the most distressing problems with which the physician is confronted is that of the "water-logged" nephritic patient whose edema is frequently massive and of long duration. Until 1917, very little progress had been made in our understanding of this disorder. As a matter of fact confusion reigned supreme, theories of "colloidal swelling", based upon incorrect observations and inaccurate analogies, having for years occupied the mind of clinicians and physiologists. In that year (1917), Albert Epstein first pointed out that this edema might result from a disturbance between the balance of capillary and osmotic pressures, because these patients, since the days of Richard Bright, have been known to have a marked decrease in the protein content of their blood serum—usually less than 4 per cent. Following Epstein's suggestion Govaerts made an intensive study of

the osmotic pressure of sera from patients suffering from nephrotic edema. He showed that the osmotic pressures were definitely below the normal of 20 to 25 mm. of Hg. Furthermore, he found that the osmotic pressure was lower than that found when normal serum was diluted to the same protein concentration as that of the edematous patient. The explanation for this unusually low osmotic pressure was found in the observation that the blood of these patients had been depleted of albumin, whereas the globulin content was normal or even increased in amount. This explanation offered by Govaerts is entirely in harmony with the fact previously mentioned that albumin exerts a greater osmotic pressure than does globulin. Govaerts' findings have been confirmed by numerous investigators and it is now certain that the edema of nephrotic patients primarily results from depletion of the serum proteins, particularly albumin. Whether the decrease in serum proteins is due to the excretion of large amounts of albumin or in part to a disturbance in the genesis of serum albumin has not yet been established. Just as edema develops when the albumin of blood serum is depleted, so edema disappears as the serum proteins approach their normal concentrations.

Another clinical situation in which depletion of the serum proteins is of primary importance in bringing about a disturbance in the hydrostatic and osmotic pressure equilibrium with consequent fluid accumulation, is nutritional edema. This condition first became widely recognized during the World War when under-nourishment became prevalent in Germany. Since that time it has become apparent that the edema of beriberi and of the severe wasting diseases, such as tuberculosis and carcinoma, may find its origin in protein starvation. Peters has suggested that depletion of serum proteins by prolonged under-nutrition may be a factor in the production of edema in patients with chronically decompensated cardiac disease, as he has shown that the serum protein of such patients is frequently decreased in amount. These clinical impressions all receive laboratory confirmation from the numerous experiments in which edema is produced by protracted protein starvation. In these experiments as well as in patients, edema usually appears when the proteins of the serum fall below 5 per cent and particularly if

the albumin fraction is reduced to less than 2.5 per cent. The importance of the decrease in serum proteins, *i. e.* in the osmotic pressure of the blood has been repeatedly demonstrated in the laboratory by plasmapheresis experiments. In this work animals are bled daily, the red blood cells are washed and returned to the animal without the plasma proteins. The serum protein concentration falls and the albumin fraction is decreased more rapidly than is the globulin fraction. Edema then develops exactly as in nephrotic nephritis or in malnutrition. In these animals whose kidneys are normal, sodium chloride restriction decreases the edema and the addition of salt to the diet increases it. Thus we see that it is possible to reproduce in the laboratory the characteristic edema which results in certain diseases from protein loss with a consequent decrease in osmotic pressure of the blood plasma.

The second important capillary disturbance responsible for the development of edema was said to result from increases in the permeability of these vessels, due to opening of the pores. I have indicated that the edema fluid resulting from this change should be relatively rich in proteins and I wish to mention briefly some clinical states where this disorder leads to edema. The simplest example is that of the histamine wheal. This drug being a great capillary dilator allows fluid rich in protein to be forced through the pores by the hydrostatic or blood pressure in the capillary loop. Angioneurotic edema and urticarial wheals have exactly the same origin. Govaerts has shown that the edema fluid resulting from chemical irritation of the skin contains almost as much protein as does blood serum. The edema fluid which accumulates in patients with acute glomerulonephritis is rich in proteins as compared with the edema fluid of nephrotic patients. Furthermore, edema develops in acute nephritis with very little decrease in the serum proteins. For these reasons, and because capillary damage is found histologically in this disease, it is now generally believed that the edema results from increased permeability of the vessels. It is no longer thought that it is primarily dependent upon a decrease in the osmotic pressure of the blood serum as is the case in nephrotic edema.

Congestive heart failure is, of course, frequently characterized by the accumulation of large amounts of fluid in the

tissue spaces. The factor of protein starvation which probably plays a minor part has already been discussed. There are two other forces which are probably of greater significance. One of these is dependent upon increase in capillary permeability and the other upon an upset in the hydrostatic-osmotic pressure equilibrium. Landis has shown that anoxemia leads to capillary dilatation with consequent opening of the pores. Since inadequate oxygenation is present in congestive failure, we may expect that plasma including its proteins may tend to be squeezed out of the capillaries. Another typical feature of congestive heart failure is an increase in venous pressure. This is probably reflected back to the venous loops of the capillary so that the pressure within these vessels is raised from the normal of 12 mm. of Hg. to a level which tends to counterbalance the osmotic inflow of water into the capillaries. Under these conditions edema would be expected to develop.

From the foregoing physiological and clinical discussion I may have conveyed the impression that the mechanisms involved in the development of edema are all clearly understood and that they are amazingly simple in their nature. I should now like to correct that impression. It is perfectly true that the two processes which I have dwelt upon are of tremendous importance and that their application has clarified many of our problems. Nevertheless, there are still many questions concerning edema for which our explanations are quite inadequate. For example, I have stated repeatedly that if the osmotic pressure of the serum is lowered, the return of fluid to the venous limb of the capillary is inhibited and fluid pushed out of the arterial limb stays in the tissue spaces. If we apply the same reasoning to the capillaries of the kidneys, we should have less resorption of fluid from the glomeruli and consequently an augmented urine output. This is obviously entirely contrary to the situation which exists when edema develops. Of course we can circumvent our difficulties with numerous assumptions, but until proved correct, assumptions they must remain.

Now for another difficulty: I have said that as the concentration of serum protein falls, edema tends to develop; and that as serum protein increases, edema disappears. This is true, and, furthermore, it is the rule. There are, however, exceptions. We have all seen patients with serum proteins

reduced to 3 per cent who, contrary to expectation, have undergone a spontaneous diuresis without any increase in protein concentration. Finally it is well recognized that certain inorganic salts, notably calcium chloride and ammonium chloride, may bring about a diuresis without obviously altering the physiological disturbances in the capillaries. The locus and means of action of these salts is still a mystery. I have not mentioned these disquieting facts to destroy the edifice of experimental evidence which has been built up, but to show that we still have much to learn and more to explain in relation to fluid equilibria in the body.

Finally, I should like to say a few words about the treatment of edema due to the loss of protein from the serum. By far the most important measures are dietary. In view of the nature of the disturbance present the liberal administration of protein is indicated. The diet should contain approximately 100 grams a day. We have as yet no information as to whether any type of protein will particularly enhance the synthesis of serum albumin, but we are certain that beef protein is not injurious and that most patients find it more palatable in large amounts than other meats. I have already indicated that sodium chloride is an important constituent of edema fluid. Consequently, if salt restriction is rigidly enforced, edema will not increase rapidly. Unfortunately, it is impossible to prepare a balanced salt-free diet, but with care the ingestion of salt can be kept below 2.0 grams a day. I might add that food should be selected on the basis of their sodium content rather than on the content of chloride. Fluids are arbitrarily limited to amounts of 1,000 c.c. to 1,200 c.c. a day.

Of all the diuretics at our disposal, salyrgan is perhaps the most efficient and least objectionable to the patient when administered intravenously. Its use is absolutely contraindicated in the presence of inflammatory renal disease and when renal function, as measured by the usual tests, is seriously impaired. In the presence of severe albuminuria it should only be used as a last resort. This drug is most useful in the treatment of edema due to congestive heart failure and in nutritional edema. Diuretics of the purin group are less efficient than salyrgan and also increase renal irritation when inflammatory disease is present. Ammonium

chloride and calcium chloride in large doses occasionally cause nausea and frequently fail in their purpose. There are other therapeutic agents which may be employed, but the results are so inconstant that they need not be considered here. I should, however, like to mention the fact that Dr. Richards and Dr. Barach of our clinic have shown in recent years that oxygen therapy will bring about a diuresis in many patients suffering from chronic congestive heart failure when digitalis, diuretics and other measures have failed.

In conclusion, may I say that I have tried to outline some of the things we know about edema, a few of the things we do for it and some of the things we don't know about it.