not reached normal. Known kidney disease, pyelonephritis, did not detract from the effect of operation. Results in our series of hypertensive patients with pyelonephritis, unilateral or bilateral, treated surgically have so far been the same as in those with so-called essential or malignant hypertension without pyelonephritis.

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EDEMA I

MECHANISMS OF EDEMA FORMATION

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Edema is an excessive accumulation of fluid in extracellular spaces. It may be manifest, i.e., felt and seen; occult, located in the viscera; or latent, only demonstrable by chemical means. It may be local, as in inflammation or urticaria, or general and part of a systemic disturbance, as in congestive cardiac failure or nephritis.

Edema fluid may accumulate to the point where it interferes mechanically with tissue function or nutrition, so that what is at first an annoying sign of disease may later cause disability and death. Modes of relief of edema have therefore interested clinicians since the beginning of historic time. Since successful treatment depends primarily on identification and correction of the faulty mechanism, it is based largely on an understanding of physiology.

The purpose of the reports of which this is one is to review (I) mechanisms of edema formation, (II) clinical manifestations and consequences of edema, and (III) means of treatment.

BODY FLUIDS

The water of a unicellular organism lies within the cell; that of a multicellular organism is partitioned into intracellular and extracellular compartments. During life the membranous cell wall which separates intracellular and extracellular fluids is extraordinarily selective, so that these two fluids, although in constant shift and osmotic equilibrium, are chemically very different. Intracellular water is rich in salts of potassium; extracellular fluid has little potassium and much sodium, approximately 6 Gm. sodium chloride and 2 Gm. sodium bicarbonate per liter. The death of cells, as from burns, destroys membrane selectivity, so that sodium enters into cells and potassium leaves them.

Some 75 per cent of the body weight is water, intracellular fluid accounting for about 50 per cent of body weight and extracellular fluid for only 25 per cent. The mass of the intracellular compartment is greater. Cytophysiologically, it may be thought the more important, since its content must be rigidly maintained for cells to survive. From the aspect of the body as a whole, intracellular fluid is no more important than extracellular fluid from which it must ultimately be derived. As concerns the genesis, manifestations, and treatment of edema, extracellular fluid is the more important.

EXTRACELLULAR FLUID

In animals that possess a circulatory system, some of the sodium-rich extracellular fluid circulates rapidly as plasma, whereas about three quarters of it moves slowly as interstitial fluid and lymph. The capillary membranes which subdivide extracellular fluid into interstitial fluid plus lymph and plasma are freely permeable to water and salt, so that these occur in the two fluids in almost equal concentration. They are much less permeable to protein. Thus the protein content of interstitial fluid is small in comparison with that of plasma. The remaining solids occur in almost equal composition and concentration. Actually, the protein content of interstitial fluid varies with the organ in which it rests: That of subcutaneous tissues contains about 0.1 per cent protein; that of the kidneys 3 per cent; and that of the liver—where the vascular capillary endothelium is discontinuous—about 7 per cent, equalling that of plasma.[1]

These chemical characteristics as well as the anatomic position of extracellular fluid indicate its function and its phylogenetic history. It is the fluid medium in which the cell lives. Its content of sodium and other salts represents quite faithfully the sea water of Cambrian Age,[2] when supposedly the development of multicellular organisms began.

Extracellular fluid is formed from plasma by filtration under pressure in the arterial end of capillaries. As the hydrostatic pressure falls towards the venous end of the capillary, the osmotic pressure of the protein held within the capillary draws the fluid back into the venous end of the capillary.[3] There is thus a constant movement of interstitial fluid out of and back into the plasma under the opposing influences of hydrostatic (arteriocapillary) and osmotic (protein) pressure. The protein of interstitial fluid and that fraction of filtered water not reabsorbed into capillaries are removed in the lymphatics. The energy for this movement comes partly from the pumping action of muscle movement and partly from pulsation of arteries and arterioles.

Edema may arise whenever a failure in the *movement* of interstitial fluid causes more to be filtered into the tissues than is removed by capil-

laries and lymphatics. Edema may result from (1) wide arteriolar dilatation, which increases the filtration pressure in the capillaries—as when histamine is injected intradermally. (2) It appears when hypoproteinemia reduces the osmotic pressure of plasma proteins to such a degree that capillary reabsorption of interstitial fluid is inadequate. (3) An increase in venous pressure which greatly increases hydrostatic pressure at the venous end of the capillaries may cause edema by preventing reabsorption. Finally (4) edema may result from obstruction of lymphatic channels, and since in this instance the fluid which accumulates is rich in protein, its osmotic pressure soon balances that of the capillaries and creates a vicious cycle of increasing edema, e.g., elephantiasis.

Of the causes of edema which interfere with fluid movement, only two, hypoproteinemia and venous congestion, commonly cause generalized fluid accumulation.

Hypoproteinemia may result from severe protein deficiency. This may be dietary, as occurred in the prison camps of the Philippines, or alimentary, resulting from failure of intestinal function. Hypoproteinemia is a characteristic of chronic glomerulonephritis in the nephrotic stage and of nephrosis; to a lesser extent it is common in the eclamptogenic toxemias of pregnancy. In these diseases it is usually associated with severe albuminuria. If albuminuria is very profuse and the protein in the diet too rigidly restricted, part of a seemingly "nephrotic" hypoproteinemia may be nutritional and may be relieved by correcting the dietary deficiency. More commonly hypoproteinemia which accompanies renal disease cannot be relieved by adequate administration of protein in the diet or by transfusion. It is seemingly due to a change in the "set" of the control which regulates plasma protein content. Although evidence at hand suggests that hypoproteinemia in renal disease may be a homeostatic protective device, which acts to maintain urine formation by lowering the colloid osmotic pressure of the blood, the mechanism of this alteration is not clear.[4] Such hypoproteinemia varies with the course of the renal lesion and cannot be altered by changing the diet.

In congestive cardiac failure venous congestion is believed to participate in the edema. It is not the whole explanation, since in congestive cardiac failure the rise of venous pressure more often follows than precedes the onset of edema.[5] Also many patients with cardiac disease suffer from some degree of nutritional hypoproteinemia.

Thus, apart from hypoproteinemia, mechanical failure of interstitial fluid movement is only rarely and then terminally a cause of generalized edema. Rather the origin of edema in early congestive cardiac failure must be sought in the operation of controls of extracellular

fluid volume and content. The basic fact that determines shifts in body fluid is that changes in the osmotic concentration of ions in extracellular fluid may seriously interfere with cellular function by demanding a corresponding adjustment in the intracellular fluid.[6] Therefore attempts at changes in osmotic concentration of extracellular fluid are vigorously resisted by the controls, principally renal, which regulate the volume and content of extracellular fluid. In a tendency toward a change in electrolyte content of extracellular fluid, these controls act by altering the volume of this fluid to preserve its concentration. Thus, in sodium retention the body retains water and increases the extracellular fluid volume, even to the point of edema, to maintain its normal concentration. Such edema has no functional significance apart from the mechanical stresses it may impose, whereas were sodium retention not followed by edema, hypernatremia might result in death. To the extent that retention of water can balance retention of sodium and so preserve the electrolyte concentration of extracellular fluid, formation of edema is protective.

That the body responds more actively to changes in concentration than to changes in volume of extracellular fluid is easily shown. Ingestion of a fluid corresponding osmotically to interstitial fluid, such as 0.9 per cent sodium chloride, does not cause diuresis, for the fluid is retained. On the other hand, ingestion of water is countered promptly by diuresis, and excessive intake of salt is met at first by water retention. Conversely, salt deprivation results in water loss and shrinkage of interstitial fluid volume, and a water deficit is followed by salt loss and a corresponding diminution of interstitial fluid volume. In either of the latter instances the subcutaneous tissues lose their turgor, and the appearance is that of dryness and dehydration. Actually, what is lacking is not water, as the bastard word *dehydra*tion implies (L. *de* away Gr. *hydor* water), but rather extracellular fluid, which is a dilute alkaline brine. Such fluid loss is treated by administering physiologic saline and trusting to renal activity to excrete the excess chlorine and retain the needed sodium, or by giving a balanced mixture of sodium chloride and sodium lactate or bicarbonate.[7] Such a change is the exact opposite of edema in which salt in water, not water, is retained in excess.

SODIUM RETENTION

Thus the problem of generalized nonhypoproteinemic edema resolves itself into one of simultaneous retention of water and sodium ions. If water is retained, salt must be; if salt is, water must be In either case edema, at first latent and hypostatic and later manifest and generalized, develops. Of the two components of edema fluid, water is the more

readily disposable and less easily retained, since it has three pathways of excretion—respiratory, cutaneous, and renal. Salt, however, is largely excreted through the kidneys. A priori, sodium retention is of more significance than water retention in the genesis of edema.

Since sodium is not rapidly excreted, sodium retention and edema may result from an excessive and rapid intake of salt. When the intake of sodium is not excessive and the movements of interstitial fluid are normal, then sodium retention and edema can only result from failure of sodium excretion.

Such a failure of sodium excretion may be due either to functional or structural changes in the principal excretory apparatus, the kidney. Normally, plasma water contains about 580 mg. sodium chloride per 100 ml., and about 125 ml. of this fluid (720 mg. sodium chloride) is filtered per minute through the glomerular capillaries into the renal tubules. Thus about 1100 Gm. of salt a day is filtered off from the blood; of this only 5 or 10 Gm. appears in the urine. The 99 per cent difference between filtration and excretion of salt represents the activity of the renal tubules in reabsorbing salt from tubular fluid into the blood. Normally, an increased bodily need for salt is met by increasing — although to a very slight degree, for the control is already fixed near its maximum—salt reabsorption until all but the obligatory minimum (about 0.1 per cent) of salt remains. A hypothetical total tubular defect of reabsorption with loss of a kilogram of salt daily would require the excretion of about 80 liters of water, since the ceiling concentration of salt in the renal tubules is about 1.5 per cent.

Salt reabsorption is partly controlled by the secretion of the adrenal cortex; deficiency of its salt-retaining elements, as in Addison's disease, results in sodium loss and shrinkage of extracellular fluid. In this situation the control is lost while the mechanism remains intact. When the kidney is structurally diseased, the situation is reversed. If the damage is chiefly glomerular, and the tubules are well preserved, filtration rate is reduced, say to 50 ml. carrying 290 mg. of salt a minute; the tubule cells, seemingly unaware that half the salt which should have been filtered is being retained in the body, take back a normal absolute amount of salt from the small volume of tubular fluid presented to them. Salt retention results. Such deficient filtration with active reabsorption seems to account for much of the edema of acute glomerulonephritis and of eclampsia and pre-eclampsia. More commonly both tubule and glomerulus are diseased, and the presence or absence of edema will then be determined by the preponderance of lesions, the dietary stresses, and levels of plasma protein. Seriously damaged tubule cells are incapable of reabsorbing salt or of responding normally to bodily demands; through injured

glomeruli at least some filtration of salt and water continues. The result may be salt loss, shrinkage of extracellular fluid, and ultimately hyponatremia and dehydration with consequent disturbances of renal and cellular function. Thus, uncontrolled renal disease may result in salt loss with shrinkage of extracellular fluid or salt retention with edema. Because the renal control is defective, the margin between these extremes, which in health is wide, may in disease be very narrow.

However, the commonest cause of clinical edema is not renal disease, with salt retention or with hypoproteinemia or with both, but congestive heart failure. The mechanism of edema in congestive heart failure is not clear. It was once supposed, largely from the analogy between congestive failure in man and heart failure in the isolated heart-lung preparation, that edema results from a combination of increased venous pressure, which would tend to decrease reabsorption of interstitial fluid, and an anoxic increase in capillary permeability, which would increase its formation. Cardiac edema would thus be due to deficient *movement* of extracellular fluid. Actually, congestive failure may be well advanced before either venous pressure rises significantly or arterial oxygen content is notably reduced.[5] However, in many patients with heart failure there is a great reduction of renal blood flow, which disappears as heart failure is relieved.[8] This decrease of renal blood flow is vasoconstrictive and is associated with a decrease in glomerular filtration rate. Therefore it is suggested that the edema of congestive heart failure, as does that of acute glomerulonephritis, arises in renal failure of salt excretion due to functional rather than to structural change.

From the aspect of treatment, which will be discussed later in detail, the fact that edema fluid, however formed, must contain sodium has the corollary that sodium deprivation must prevent its formation and cause its reabsorption.

SUMMARY

Edema is an excessive accumulation of interstitial fluid. Its cause lies either in failure of the normal mechanisms of movement of this fluid (mechanical, vascular, lymphatic, and hypoproteinemic edema) or in the operation of controls which protect the body from changes in concentration of electrolytes, principally sodium, in interstitial fluid by permitting changes in volume. The specific stimulus which commonly provokes fluid controls to permit edema formation is sodium retention. Sodium retention is therefore often the key to the origin of generalized edema. Since the principal site of sodium excretion is the kidney, sodium retention is therefore associated with functional or structural disturbances of renal function. In either case, restriction of dietary sodium below the minimal level of sodium excretion must ultimately result in loss of water and salt and therefore in correction of edema.

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CARCINOMA COMPLICATING ULCERATIVE COLITIS

Report of Two Cases

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Because the complication seemed to be uncommon, we have reviewed our experience with carcinoma complicating ulcerative colitis. Between 1934 and 1943 one of us saw 2 cases of carcinoma in 336 cases of ulcerative colitis. This was an incidence of 0.59 per cent. During the same period 1608 cases of carcinoma of the colon were seen at the Cleveland Clinic.

Because both patients herein reported were under 30 years of age, our attention was directed to this age group. One per cent (17 cases) of all cases of carcinoma of the colon and 38 per cent (128 cases) of all cases of ulcerative colitis occurred in persons under 30. In this same age group the incidence of carcinoma of the colon with chronic ulcerative colitis (1.5 per cent) was slightly higher than the incidence without ulcerative colitis (1 per cent).

Ewing[1] considered it significant that carcinoma rarely occurred in ulcerative colitis. Matzner and Schaefer[2] reported 1 case of carcinoma complicating ulcerative colitis. The patient was a 29 year old man. Yeomans[3] reported 7 cases of malignant neoplasm developing in rectal adenoma, 1 of which occurred with ulcerative colitis. This patient was a 33 year old woman. Hurst[4] stated that an adenomatous polyp might become malignant and that carcinoma might complicate ulcerative colitis, but that most malignant adenomas were not secondary to or associated with colitis. Swinton and Warren[5] stated that they had not observed progression of polypoid changes in ulcerative colitis to malignant disease. On the other hand, Ganshorn[6] demonstrated a greater frequency of carcinoma in the presence of adenomatous hyperplasia of the