EDEMA, ITS CAUSES AND TREATMENT

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In this article on the mechanism and management of some of the more common sources of edema, I shall begin by stating that edema manifests itself by swelling of the body tissues which is due principally to expansion of the extra-cellular tissue spaces.

In the formation of edema, one must first consider the normal physiological mechanisms of fluid exchange, one or more of which are deranged. The local factors in the formation of edema include:
(1) Blood flow; (2) Hydrostatic fluid pressure, within the capillaries; (3) Colloid Osmotic pressure of the tissues; (4) Capillary permeability; (5) Fluid and Electrolyte exchange between plasma and extracellular spaces; (6) Tissue pressure; (7) Colloid Osmotic pressure of blood; (8) Return of fluid from the tissues by way of the lymphatic system.

The (1) hydrostatic capillary pressure which is **higher** at the arterial end, (2) the degree of capillary permeability, and (3) the colloid osmotic pressure within the extra-cellular fluid spaces are the three factors which favor the flow of fluid across the capillary membrane into the extra-cellular tissue spaces.

Factors known to oppose transudation are (1) the colloid osmotic pressure of the blood chiefly due to plasma albumin, (2) the healthy capillary barrier and (3) the actual tissue pressure. Normally there is a reabsorption of fluid from the extra-cellular space into the capillary due to the lower capillary hydrostatic pressure at the venous end of the capillary, and also the relative increase in the colloid osmotic pressure.

Because there is a free interchange of electrolytes across the capillary membrane, one finds nearly identical composition of electrolytes in plasma and in the extra-cellular tissue spaces. The main electrolyte involved is sodium and when you find a retention of this element in the plasma you also find a retention of water and when the quantity is sufficient to expand the extra-cellular tissue spaces, edema results.

The maintenance of normal body fluids and electrolytes is mainly due to the kidneys. By varying the rate of renal tubule reabsorption of water to electrolyte, a normal stable control is kept on the sodium and water excretion. But even the normal kidney will retain sodium and water for deposition in the tissues as edema under certain conditions—such a state is seen in excessive salt intake. In a desperate attempt to maintain a normal equilibrium, the adrenal steroids decrease the excretion by the tubules of sodium and water and likewise lower the content of sodium in sweat. In response to the increased crystalloid osmotic pressure of the plasma, the osmo-receptors in the

carotid vessels stimulate the production of the anti-diuretic hormone in the posterior pituitary gland, which in turn forces the tubules to retain water. It has also been postulated without complete evidence that there are also volume receptors for the control of body water and electrolytes.

Now, having described the subject and briefly mentioned the local factors in edema, I will proceed to some of the mechanisms involved in edema formation and the varying alterations in some clinical syndromes, for an understanding of these mechanisms is necessary before rational treatment may be proposed.

Generally, when excessive fluid is retained in the body, it transudes in a local or general area where derangement of physiological function is greatest, for example: (1) **Venous obstruction** due to thrombo-phlebitis or mitral stenosis and left ventricular failure with increased pulmonary capillary pressure where you have the single factor of increased hydrostatic pressure locally predisposing to the transudation of fluid locally into the extremities or the lungs. (2) **Reduced tissue pressure** accounts for the swelling of feet and ankles of patients who have been confined to bed for a long time and who probably have had a weight loss. (3) **Capillary dilation** presumably due to liberation of histamine (or H-like substances) accounts for the picture of angio-neurotic edema. (4) **Increased hydrostatic pressure is seen** in prolonged motionless standing and sitting, with tight garters and clothing, all these promote edema formation. (5) **Reduction in plasma colloid osmotic pressure** with resulting edema is seen in various nutritional deficiency states. (6) **Obstruction to lymphatic system** results in browny edema and may be due in part to local retention of colloids in the extra-cellular tissue space with increased colloidal osmotic pressure.

For the purposes of classification these were placed in the simple group—the second group are the more complex and comprise: (1) edema of renal impairment, (2) liver disease and (3) heart failure.

Under renal impairment there are three subgroups, the first of which is acute glomerulo-nephritis. The mechanism here is a decreased filtration by the glomeruli and the normal absorption of sodium by the tubules. This leads to sodium and water retention which in turn gives rise to edema. The second sub-group comprises true nephrosis and the nephrotic stage of chronic glomerulonephritis. The fundamental pathophysiology here is the loss of colloid osmotic pressure secondarily to marked lowering of the plasma protein especially albumin. Here there is a normal sodium intake but loss of sodium to the extra-cellular tissue spaces. The last subgroup is chronic nephritis with insufficiency (i.e. loss of glomerular and tubular function) and increased excretion of basic ions. Edema is absent here unless complicated by secondary hypertension or decreased plasma proteins.

Next in line of the three complex groups is hepatic disease—the commonest single entity being cirrhosis.

An increase in portal pressure occurs as a result of destruction of liver cells and subsequent widespread scarring. Low resistive pressure within the abdomen combined with the increased pressure leads to ascites formation. An inadequate protein synthesis by the liver accentuates the formation of ascites by a reduction in plasma proteins and thus colloid osmotic pressure.

It is further theorized that the pressure of the ascitic fluid on the renal and abdominal veins enhances sodium retention by the kidneys and enhances increased hydrostatic pressure in the legs. Increased protein of the ascitic fluid, once formed, may be a factor in inhibiting return of fluid to the capillaries.

Congestive heart failure, the most common cause of edema, is the third consideration and the factors involved are even more complex and subject to argument.

Acute injury to the left ventricle as when myocardial infarction occurs may result in decreased output of the left ventricle, the right ventricle still maintains its normal output to the lungs and thus the pulmonary circuit pressure may rise rapidly with acute pulmonary edema often resulting due to increased hydrostatic pressure in the lungs although the circulating volume of blood is normal. There is never a sudden rise in the systemic venous pressure after acute injury to the right ventricle due to the distensible and large reservoir behind the failing ventricle.

Probably the general concensus of opinion is that chronic congestive failure is accompanied by decreased cardiac output so that in cases of moderate to massive edema, there is a reduction in cardiac output except in thyrotoxicosis, beriberi and anemia which are special cases. Reduced cardiac output goes hand in hand with a reduced renal blood flow to as little as one-third to one-fifth of the normal volume and the glomerular filtration rate is one-half to one-third of normal. Glomerular filtration of sodium falls, tubular reabsorption remains normal resulting in increased amounts of sodium being held in the body and retention of water is secondary. So it becomes apparent that an adequate cardiac output becomes the first step in the genesis of congestive failure. Edema initially will occur in the lungs where the pulmonary venous pressure is increased and in the legs where the hydrostatic pressure is greatest. The increased venous pressure favors capillary anoxia, increased capillary permeability and transudation. Secondary contributing factors may be (1) the adrenal steroids, due to the fact that in congestive heart failure "sweat" sodium is lower than normal and (2) interference with disposal of pituitary antidiuretic hormone, which is due to swelling of the liver.

Before proceeding to management it is important to emphasize that as soon as the basic mechanisms in fluid exchange are altered, an increased or normal sodium and water intake favors water retention and tissue edema unless disposed of by the kidney.

In angio-neurotic edema treatment is directed at the underlying state which is usually allergic. Antihistaminics and local applications of ice packs bring about some amelioration.

Lowering the salt intake ameliorates postural edema in those susceptible to it. Avoiding constricting garments, exercise, and elevation of the extremities while at rest are also helpful.

In acute thrombo-phlebitis it is necessary to prevent the spread of the obstructive phenomenon with anticoagulants; elevating the extremities decreases venous pressure. Support in the chronic stage with elastic stockings is indicated. Surgical treatment is probably required for varicose veins producing local edema. Salt restriction and judicious use of mercurials may be helpful.

Lymphatic obstruction with edema presents a great problem in management. Iocal support, diet and diuretics are of little avail.

Edema secondary to recurrent chronic infection may be decreased by clearing up the infection.

In cardiac edema recent notable advances in management have been made. Four basic factors are involved:

1. Rest.
2. Modification of diet and fluid control.
3. Use of diuretics.
4. Digitalization.

Rest should be continued until compensation is complete, thus decreasing demands on a heart which already has an inadequate output. The recumbent position in a bed or chair with the head up prevents the mobilization of fluid from the legs and abdomen to the lungs and improves orthopnoea. Venous thrombosis due to stasis is a danger in the aged. Sedatives and simple hypnotics used judiciously help promote rest and relaxation. In arteriosclerotic patients, Cheyne-stokes respirations may result from the injection of narcotics.

Dietary regimé of the patient should include reduction of the sodium to at least 800 mg./day and 150 mg./day in marked edema. Compensation cannot be restored on the normal diet of four to ten gm. of NaCl but once compensation is restored on the low sodium diet, as much as 1 gm. may be given daily. Once sodium is drastically reduced fluid restriction becomes unnecessary and a free fluid intake up to 2000 to 2500 cc. should be encouraged daily in order to maintain a satisfactory urinary output. Diets at first should be liquid or semi-solid to avoid expending energy in the effort of chewing—a good one is the famous Karrell diet and with improvement a shift is made to a solid low sodium diet. A useful supplement to the low sodium diet is the cation exchange resins. They are synthetic polymers, exchange amonium for cations within the gut and bind sodium, calcium, and magnesium, whence they are excreted in the faeces. Most resins are saturated with potassium in order to prevent hypokalemia. They are of some benefit to patients who

are unable to adhere to a strict low sodium diet. Administration is orally and the dosage is 15 gm. t.i.d. in fruit or other juices accompanied with meals. Each gm. of resin will absorb up to 23 mg. of sodium depending on the level of sodium ingested. If used with mercurial diuretics there is probably a tendency to potentiation of diuretics. Supplementary calcium is necessary. G.I.T. disturbance is usually manifested as constipation. The drug is contraindicated in patients with renal insufficiency, for acidosis is easily induced in this group due to the inability of the kidneys to maintain an acid-base equilibrium.

Diuretics are the third consideration and promote excretion of fluid and electrolytes by the kidney giving rise to a decrease in blood volume, venous pressure and tissue edema. Xanthines presumably act through an increased renal flow, the duration of effect is short and action weak. Aminophylline in 0.5 gm. doses by rectal suppository may help. I. V. administration may be serious and even produce fatal collapse reactions. Mercurials, notably mercurhydrin (I.M.) and thiomerin (S.C.) and Neo-hydrin (oral) act upon the tubules and prevent reabsorption of sodium. These are not given I. V. due to occasional servere toxic reactions. The initial dose is 0.5 cc. every other day with increments in dosage gradually to 2 cc. but never more than this in a single dose. A loss of two to four lbs./day is satisfactory, it is best to avoid too rapid a weight loss. The urine should be watched for signs of irritation, i.e., albumin or R.B.C. Acid-forming salts augment diuretic effect. Too profuse a diuresis results in sudden loss of sodium, potassium, calcium, etc. This is suspected if the patient suddenly develops the following symptoms: weakness, drowsiness, lack of appetite, thirst, and muscular cramps. When salt restriction is extreme, a low salt syndrome develops in which the serum Na^+ and Cl^- fall rapidly with concomitant rise in NPN followed by rapid deterioration of the patient's condition. Three to five per cent solution of NaCl must be used as replacement therapy. Hypo-chloremic alkalosis is the other complication where the sodium concentration may be normal but the choride concentration falls from 100 mEq/l to 85 mEq/l and CO_2 combining power goes up. Treat by correcting with 4 to 6 gm. NH_4Cl/day.

Recently an orally administered diuretic came on the market which previously was known as 6063 to chemists or ACETAZALEAMIDE (Dionox-Lederie). It is a specific carbonic anhydrase inhibitor and results in renal loss of K, Na, Ca, and Water. It can be used alone or with the mercurials and has no untoward toxic effect other than a sense of numbness and pins and needles in the face and extremities and moderate to extreme drowsiness when the dose is more than 1 gm. It has its best diuretic effect in the presence of anasarca and renal decomposition.

Digitalis, the most effective single agent, increases the cardiac output while restoring the mechanical efficiency of the heart. With improve-

ment in systemic as well as renal flow, diuresis will follow its injection as a therapeutic response. In cases of unsaturation of the blood with oxygen, 100% oxygen inhalation may be helpful to improve the oxygen supply to myocardium.

Emergency measures are necessary in acute pulmonary edema. Subcutaneous morphine and atropine along with the slow administration (I. V.) of 250 mg. aminophylline usually aborts the attack. Cuffs on the limbs also induce stasis and delays the venous return to the lungs. Venisection and removal of 500 to 700 cc. of blood will tend to decrease venous congestion. Oxygen combats anoxia and relieves dyspnoea. Rapid digitalization is indicated.

In early cirrhosis measures should be directed toward treating the underlying disease with a diet low in fat and high in protein with lipotropic substances and vitamins.

In late stages with ascites this is

Abdominal distentions and respiratory difficulty are indications for paracenthesis but otherwise it is preferably avoided because of its high content of protein and the rapid depletion of body protein stores. The ascites tends to recur rapidly in the presence of increased hydrostatic and low tissue pressure thus further reducing plasma proteins and colloid osmotic pressure. On the other hand it is argued that relief of abdominal pressure may decrease the pressure on the renal veins and vena cava which increases salt and water excretion and decreases hydrostatic pressure in the legs. A tight abdominal binder should follow.

In acute nephritis, the edema is due to sodium and water retention. At the inception of the disease the administration of antibiotics and chemotherapy may shorten the disease by reducing the antigen present. The use of ACTH and cortisone is still experimental. Squire found that it reduced albuminuria without decreasing glomerular filtration of sub-

A high protein diet is then used ranging from 100 to 120 gm. per day unless associated with renal insufficiency and azotemia in which case a low protein diet of 10 gm. per day is used.

Restriction of sodium to 150 to 200 mg. is worthy of a trial since fluid excretion is difficult.

Exchange resins are liable to produce electrolyte imbalances.

Measures aimed at directly inincreasing the colloid osmotic pressure of the plasma seem to meet with varying success. Whole blood, plasma and sodium-free human serum given I. V. may be beneficial.

Squire obtained transient diuresis with I. V. salt-free dextrose infusions in six of eight patients, and in the other two patients with repeated infusions, diuresis lasted two or three weeks respectively, both patients being cleared of edema. This is merely an indication that this procedure may be worthy of further trial.

In uncomplicated cases of nephrosis the prognosis is better than is generally thought and the achievement of positive nitrogen balance by high protein feedings is recommenned by Orgaine.

ACTH produces diuresis in the majority of uncomplicated cases supposedly by a renal tubular action and probably is the most recent substance in the therapy of this condition.

Nitrogen mustard has also been used in the production of diuresis in a few patients. In children with true nephrosis recovery is the rule.

References:

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