REDUCTION OF OTHERWISE INTRACTABLE EDEMA BY DIALYSIS OR FILTRATION

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THIS article is concerned only with the removal of edema that either has been resistant to the usual forms of treatment, or is of such a nature that the latter are contraindicated for the patient. When salt-free diet, sodium-binding resins, digitalis, or mercury preparations fail, or cannot be used, artificial kidneys or other dialyzing methods may be useful; they have the additional advantage that during dehydration, retention products are also removed. (For details of technics see references 1 and 2.)

Dialysis With Hypertonic Solutions to Remove Edema

Most artificial kidneys use dialysis, which means purification through a semipermeable membrane, with the patient's blood on one side of a cellophane membrane and rinsing fluid on the other side.[1-4] In peritoneal lavage, dialysis occurs through the peritoneum and walls of the numerous capillaries in the subserosa. Electrolytes will equilibrate on both sides of the membrane; urea and other retention products are removed from the blood by the dialysis. Five to eight hours of treatment will suffice to reduce the patient's blood urea from very high levels to nearly normal values with efficient artificial kidneys.

In the artificial kidneys that use dialysis only, there is no difference in hydrostatic pressure between the patient's blood in the cellophane tubing and the rinsing fluid. Under these circumstances, while urea is moving across the cellophane from the blood to the rinsing fluid (fig. 1), water is being attracted to the uremic blood, as it will always pass from a place of lower concentration of solutes to one of higher concentration. The higher osmotic pressure on the side of the blood can be overcome by adding glucose to the rinsing fluid: an excess of glucose will reverse the process and water will be attracted from the blood into the rinsing fluid.

So far, we have discussed the cellophane as though it were a semipermeable membrane; however, it is impermeable only for larger molecules such as proteins. In fact, both urea and glucose move through the membrane quite rapidly. Figure 1, helpful as it is, does not give a true picture of the situation in the artificial kidney; but even when the membrane is not purely semipermeable,

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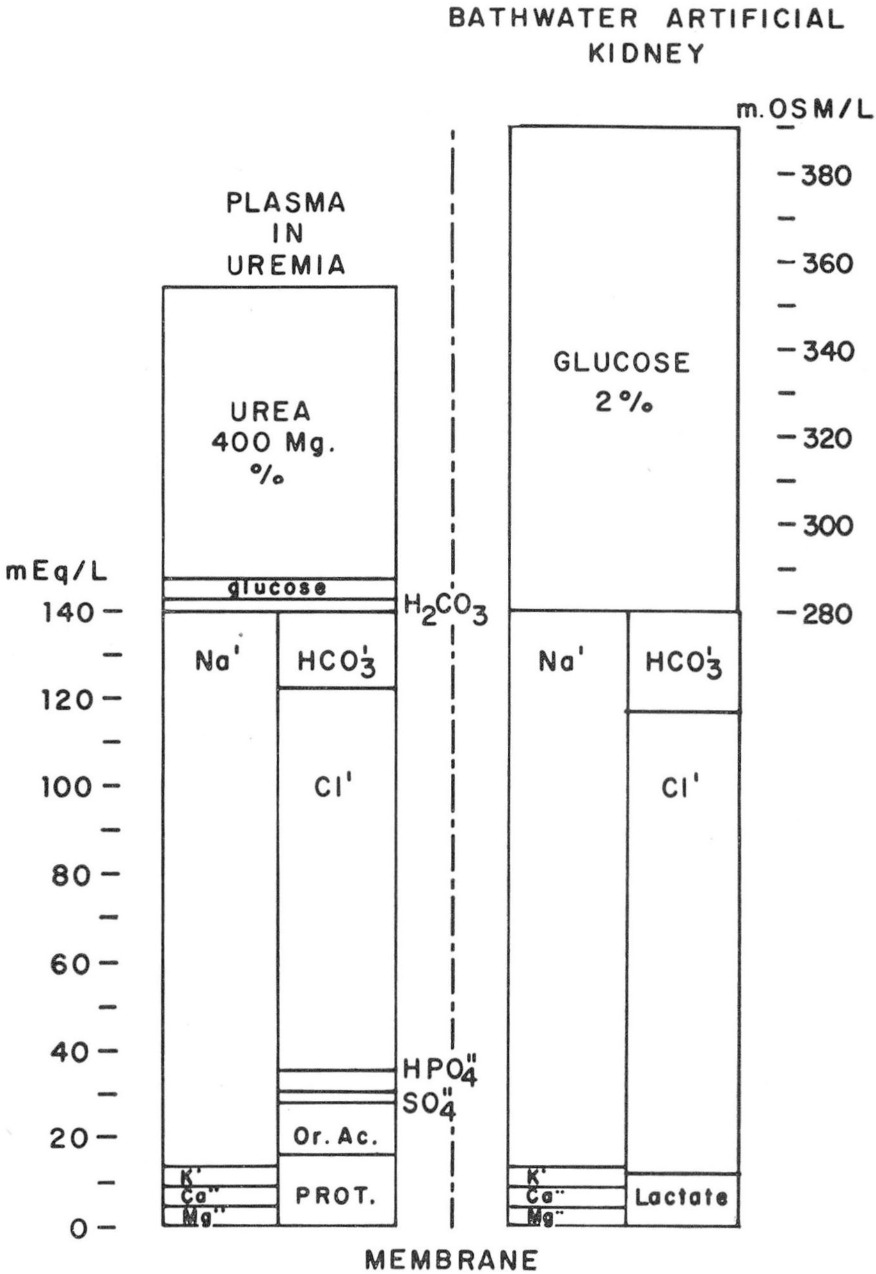

Fig. 1. Diagram of the composition of blood plasma of a patient with uremia, left, and of the rinsing fluid of an artificial kidney or peritoneal lavage, right. It will be noted that the Na is low, as it is in most patients with uremia. Urea moves to the right, and glucose to the left, and the osmotic difference causes a fluid shift from left to right.

it is still possible to effect a movement of water from the blood plasma to the rinsing fluid by adding glucose to the latter. This principle was demonstrated by Van den Bossche and one of us[5] in 1946, by means of the small dialyzing apparatus in which the volume of blood plasma that circulated along a cellophane membrane could be accurately measured. The rinsing fluid also circulated continuously and any desired small difference in hydrostatic pressure between the blood plasma and the rinsing fluid could be accurately set and maintained. When identical solutions were run on both sides of the membrane in this apparatus, no changes in volume occurred. However, when blood plasma was used in one compartment and glucose was added (4 per cent) to the usual composition of the rinsing fluid, a continuous fall in the plasma volume took place (fig. 2). The experiments established that it is possible to remove water from the blood plasma by adding extra glucose to the rinsing fluid of a dialyzing system even when the membrane used is permeable for glucose.

Rotating Type of Artificial Kidney Using Hypertonic Rinsing Fluid. The rotating type of artificial kidney depends on dialysis only for the exchange of electrolytes and the removal of retention products. There is no hydrostatic pressure difference on the two sides of the cellophane. It has often been reported[1,2,6,7] that pulmonary edema was reduced by treatment with the artificial kidney, especially when extra glucose was added to the rinsing fluid. Lewis and collaborators[8] described a loss of weight of 4 Kg. in 6 hours. To remove such large quantities of fluid, up to 5 per cent glucose in the rinsing fluid was necessary. As a consequence, the glucose concentration of the blood coming out of the artificial kidney is greatly increased; the patient's blood sugar may increase to more than 700 mg. per cent. Merrill and associates[6] gained the impression that high concentrations of glucose caused vomiting and drowsiness in the patient. This concurs with our experience. We now combat the high blood sugar levels with insulin intravenously, 10 to 20 U. every half hour; the blood sugars should be determined.

The rotating type of artificial kidney may conveniently be used to remove up to two liters of edema fluid per dialysis by adding 2 or 3 per cent glucose to the rinsing fluid. The following case history offers an example.

Case 1. A 31 year old woman accidentally drank carbon tetrachloride after sensitizing herself to it by the use of excessive doses of alcohol. She became anuric and vomited persistently. On the 11th day after the onset of anuria, she was icteric, irrational, and extremely difficult to manage. The abdomen was distended; blood pressure was 160/80 mm. Hg, and the urine volume had slowly progressed from 2 to 180 ml./24 hours. There were extensive subcutaneous ecchymoses. On the 12th day she was treated with the rotating type of artificial kidney, 2 per cent glucose being added to the rinsing fluid. Blood urea was reduced from 270 to 150 and creatinine from 26 to 16 mg./100 ml.; serum sodium was purposely maintained at the low level of 126 mEq./L., and CO_2 combining power increased from 13.5 to 16 mEq./L. as a result of the 5-hour dialysis. The patient lost 6 pounds (2.7 Kg.) in weight. Her clinical condition the day after treatment was greatly improved. Diuresis started a few days later and recovery was uneventful.

While in this case the primary indication for treatment with the artificial kidney was the necessity to remove retention products, the additional removal of 6 pounds of edema fluid was certainly most helpful.

Peritoneal Lavage Using Hypertonic Rinsing Fluid. It is possible to remove edema fluid with peritoneal lavage using the same principle of adding glucose to the dialyzing fluid. In the laboratory, using the intermittent peritoneal lavage as described by Grollman, Turner, and McLean,[9] it is possible to maintain a nephrectomized dog in a controlled state of hydration by varying the amount of glucose that is added to the usual electrolyte composition of the rinsing fluid. Thus, if glucose is added (2 to 5 per cent) to the rinsing fluid, it is almost certain that two hours later a larger volume of fluid may be removed from the peritoneal cavity than that which was instilled. Peritoneal lavage is effective, though not as practical in patients as in dogs. The patient's discomfort often required use of a continuous rather than an intermittent method.[1,2,10]

Case 2. A 16 year old boy was admitted to Cleveland Clinic in the terminal stage of a subacute glomerulonephritis with uremia and nephrotic syndrome. Many methods, including the administration of cortisone, had been unsuccessfully used to reduce the edema that had become so severe that respiration was difficult.

To remove ascites a plastic cannula was introduced into the abdomen and 1100 and 850 ml. of fluid, respectively, were drained on consecutive days. An x-ray of the chest showed pulmonary edema and marked cardiac enlargement. Respiration became exceedingly difficult, and as a tube was already in the abdomen, it was decided to treat the patient with peritoneal lavage. The composition of the rinsing fluid in mEq./L. was as follows: sodium 124; potassium 1.3; calcium 4.5; magnesium 2.7; chloride 104; HCO_3 20; HPO_4 1.8; and lactate 6.7. In the beginning of the treatment, 5 per cent glucose was added to the rinsing fluid—later 7.5 per cent. This greater amount caused pain and the 5 or 6 per cent glucose was again used. Total measured in- and outflow over the two-day period was 20 liters. However, large unmeasured amounts leaked out and were lost into the bed. The patient's weight decreased from 164 to 149 pounds. About 64 Gm. of urea was removed. The urea concentration of the abdominal fluid, which is a rough measure of the blood urea, decreased from 360 to 260 mg. per cent. The following day the pain in the abdomen gradually subsided, and the patient was in much better clinical condition than before, although there was still much edema in the lower extremities. He ate well and even asked for more food. His weight continued to fall the following days, but the urine output decreased. On the fourth day after peritoneal lavage, his condition began to deteriorate rapidly and he died on the fifth day.

The postmortem examination revealed that the patient had uremic pericarditis, hydrothorax, pulmonary edema, and early bronchopneumonia. Fifteen hundred ml. of fluid was found in the peritoneal cavity, but there was no peritonitis. The underlying disease was subacute glomerulonephritis.

It may be remarked that while in this case the edema was the primary indication for treatment with peritoneal lavage, uremia was also relieved to some extent.

Case 3. A woman of 35 years of age cleaned a rug with carbon tetrachloride on a warm day, and then drank a few glasses of beer. On the 13th day after inhaling the carbon tetrachloride fumes she was sent to the Cleveland Clinic. On arrival she was extremely

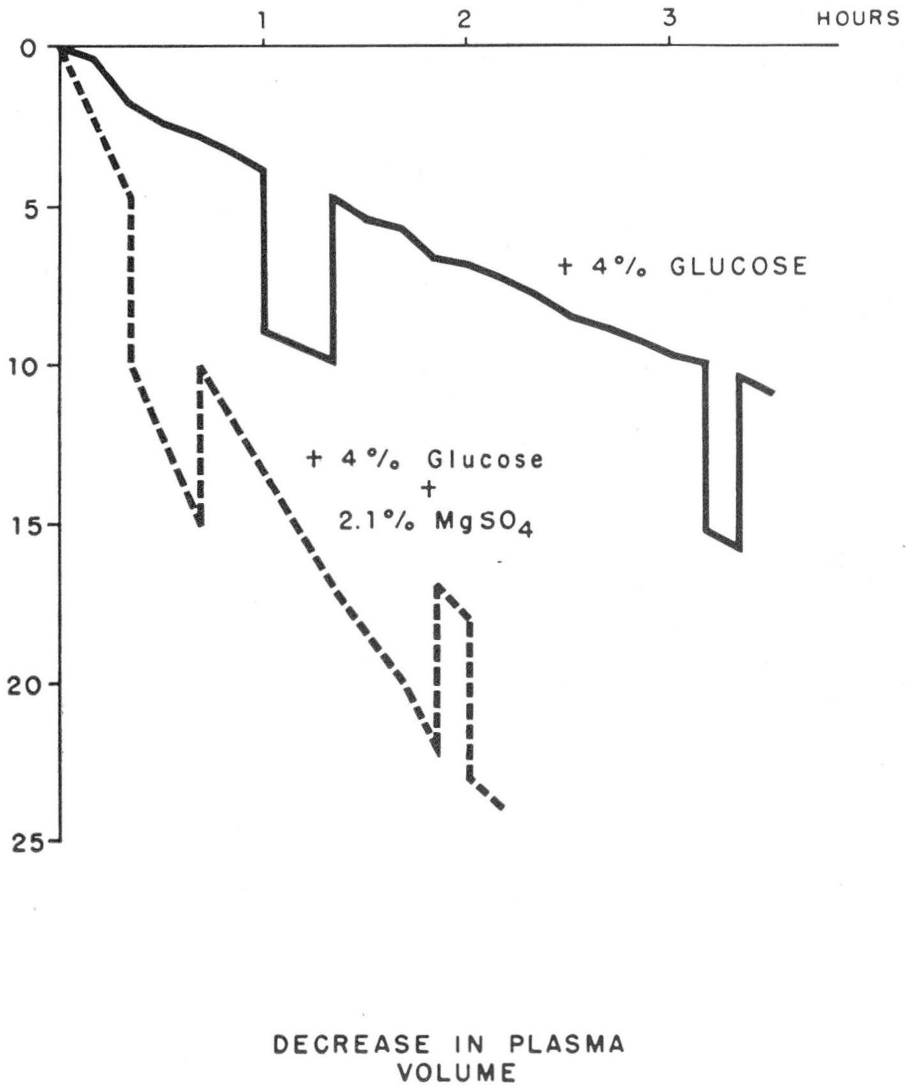

Fig. 2. One of the graphs published in reference 5. The volume changes in ml. are indicated of 200 ml. of blood plasma circulating along a cellophane membrane (254 sq. cm.) while "rinsing fluid" circulated on the outside of the membrane and the colloid osmotic pressure of the blood plasma was, in this particular experiment, compensated for with a hydrostatic pressure difference. Under these conditions the volume of the blood plasma remained constant during circulation. However, when 4% glucose or 4% glucose plus 2.1% $MgSO_4$ was added to the rinsing fluid, a decrease of the plasma volume took place. The sudden decreases and increases in volume indicate checks on the accuracy of the apparatus when 5 ml. of plasma was withdrawn or added.

cyanotic, severely dyspneic and had rales in both lungs. There was edema and the abdomen was distended. Urine output had been negligible. The blood pressure was 130/70 mm. Hg, but sometimes it dropped to under 100. Peritoneal lavage was begun immediately while the patient was in an oxygen tent. The electrolyte composition of the rinsing fluid was the same as that used in the patient mentioned previously (case 2). Glucose was used in the concentration of 5.1 per cent. The inflow of the peritoneal fluid was 8.1 L.; the outflow was 11.95. There was 3850 ml. of fluid removed during approximately 10 hours of peritoneal lavage. Serum sodium increased from 111 to 123 mEq./L.; potassium decreased from 6.8 to 6.3. The blood pressure the next morning was 150/80 mm. Hg. It seemed that the immediate danger caused by pulmonary edema was subsiding. Treatment in the oxygen tent and with antibiotics was continued. Fluid intake was restricted. Urine output gradually increased and she made a complete recovery.

It is our impression that the removal of 3850 ml. of fluid by peritoneal lavage marked the turning point in recovery from the pulmonary edema and extreme dyspnea, and made the patient's condition amenable to further treatment.

Ultrafiltration With Artificial Kidney to Remove Edema

We speak of filtration instead of dialysis when a pressure difference exists on the two sides of a membrane and fluid moves from one side to the other. It will be recalled that in the glomerulus, ultrafiltration takes place; this process is imitated in some kinds of artificial kidneys. Malinow and Korson[11] constructed an artificial kidney that worked with filtration *only*. It would be quite useful in the removal of edema; however, it is of little use in the treatment of uremia since the filtering process is so much slower than is dialysis in the removing of retention products.

Many types of artificial kidneys have some pressure difference across the cellophane membrane. Their effectiveness in terms of volume of ultrafiltrate removed depends upon the filtering area and upon the pressure difference. Not all types will stand the rather large pressure difference required to make them effective. Alwall (Sweden) brings about ultrafiltration by producing suction on the rinsing fluid side of the membrane.[12] He accomplishes this by lowering the outflow tube for the rinsing fluid to the next lower floor of the hospital, thus creating a siphon.

In the artificial kidney described by Skeggs, Leonards, and Heisler[3] it is possible to apply negative pressure from a water aspirator to the outflow tank of the rinsing fluid while partially clamping the inflow. It also would be possible to constrict the outflow line returning blood from the artificial kidney to the patient, and pump the blood in at a higher pressure, although this is less efficient. The cellophane membranes are, of course, supported by fine ridges; otherwise the space that contains the blood would expand. By this means it is possible to remove 1000 to 1200 ml. of ultrafiltrate from the blood per hour while the blood is being dialyzed at the same time. One has to be extremely careful not to dehydrate the patient too rapidly. In the laboratory, normal dogs could be killed by removing about 800 ml. of ultrafiltrate from the blood stream. Dogs rendered edematous by decreasing their plasma proteins would stand removal of a larger volume;[13] they died, however, after removal of 2000 ml. of ultrafiltrate even when approximately 5000 ml. of edema fluid was present.

In treating patients with this equipment the hematocrit should be determined repeatedly to avoid too rapid dehydration and too great a reduction of circulating blood volume. Guided by the hematocrit and the blood pressure, we found it useful to replace some of the reduced blood volume with dextran. Thus far, four patients with edema have been treated with the help of ultrafiltration.

Case 4. A 45 year old woman had been under treatment since 1918 for recurrent congestive heart failure on the basis of rheumatic heart disease. She was readmitted to the Cleveland Clinic on October 18, 1952, with severe cardiac decompensation, and was treated with digitalis, salt restriction, and mercury preparations. After some initial improvement, however, her weight steadily increased from 122 to 134 pounds, and the blood urea rose to 120 mg./100 ml. She was very short of breath and developed massive edema of the legs which were tense and painful. All attempts to reduce the edema failed. On November 26, 1952, before treatment with ultrafiltration, the pulse was weak, the blood pressure could not be obtained (later it was 100/80 mm. Hg) and she was severely cyanotic. There were rales over the chest and very extensive edema over the lower part of the body. The liver was large; ascites was present.

In five hours of combined ultrafiltration and dialysis, 4 liters of ultrafiltrate was removed. The blood pressure continued to be low, 82/48 at the end of treatment. The patient was tired but otherwise all right. She sat in a chair immediately after treatment. During the ultrafiltration, after the initial hematocrit reading of 41 had increased to 46 per cent in one hour, an infusion of dextran was given. The rate of ultrafiltration was decreased and the hematocrit was maintained at 46 for the remaining period of the treatment. The patient's weight decreased from 134 to 128 pounds. Urine output, which had been 350 ml. the day before, was 500 ml. on the day of dialysis and ultrafiltration. On subsequent days it was only 50, 37, 50, 125, and 130 ml., respectively. Her weight stayed down for several days and she felt better. The edema in the legs was decreased and she had no pain. Urine output slowly increased to 900 ml., but her general condition regressed to that before treatment with the artificial kidney. The dialysis reduced the blood urea from 120 to 42 mg. per 100 ml.

In this case there was a definite but temporary improvement of the clinical condition of the patient, lasting about three or four days immediately after treatment with ultrafiltration and dialysis. However, postdialytic oliguria counteracted the improving effect of treatment.

Case 5. A 45 year old man who had been a professional boxer in his younger years began to show the signs of chronic nephritis, hypertension, uremia, and anemia four months prior to admission to the Cleveland Clinic, February 24, 1953. He then had congestive heart disease, gallop rhythm, edema, and continuous vomiting. He could retain nothing fed by mouth, and he was maintained with invert sugar (Travert*) 20 per cent for 10 to 14 days. He developed a cerebral accident causing partial paralysis of the legs and retention of urine. His condition progressively deteriorated. On March 20, 1953, he was treated with the rotating type of artificial kidney. After treatment he was able to eat and did not vomit. The mobility of his legs gradually improved. He had

* *We are indebted to Dr. Robert P. Herwick, Baxter Laboratories, Inc., Morton Grove, Ill., for providing the 20 per cent Travert.*

a noticeable postdialytic oliguria and, as his fluid intake was not sufficiently restricted after treatment, he became more markedly edematous. Therapy with sodium lactate as described by Neubauer[14] was attempted; edema increased and the blood urea went up to the level where it had been before treatment with the artificial kidney; he developed pulmonary edema, pericarditis and Cheyne-Stokes respiration.

On April 2, 1953, he was treated with the stationary type of artificial kidney (dialysis and filtration) with the dual purpose of removing retention products and edema; 8100 ml. of ultrafiltrate was removed in 8½ hours. Hematocrit reading increased from 21 to 26 per cent and was maintained at 24 with the help of 100 cc. dextran intravenously. There were no undesirable reactions but a rise in temperature of 1 degree F. The night after treatment he was somewhat more confused mentally than he had been before treatment. There was great improvement of the respiratory rate, but, because of his mental confusion, it was decided not to give him a second ultrafiltration as had been originally planned. There was a slight reduction in the urine production the days after dialysis and ultrafiltration but certainly not a very evident postdialytic oliguria. His fluid intake was now restricted and edema did not increase. His blood urea went up again in the course of a week; however, he was not as uncomfortable as he had been prior to treatment. In regard to blood chemistry during treatment with the artificial kidney, the blood urea was reduced from 345 to 225 mg./100 ml., and the creatinine from 20.5 to 14.7 mg./100 ml.

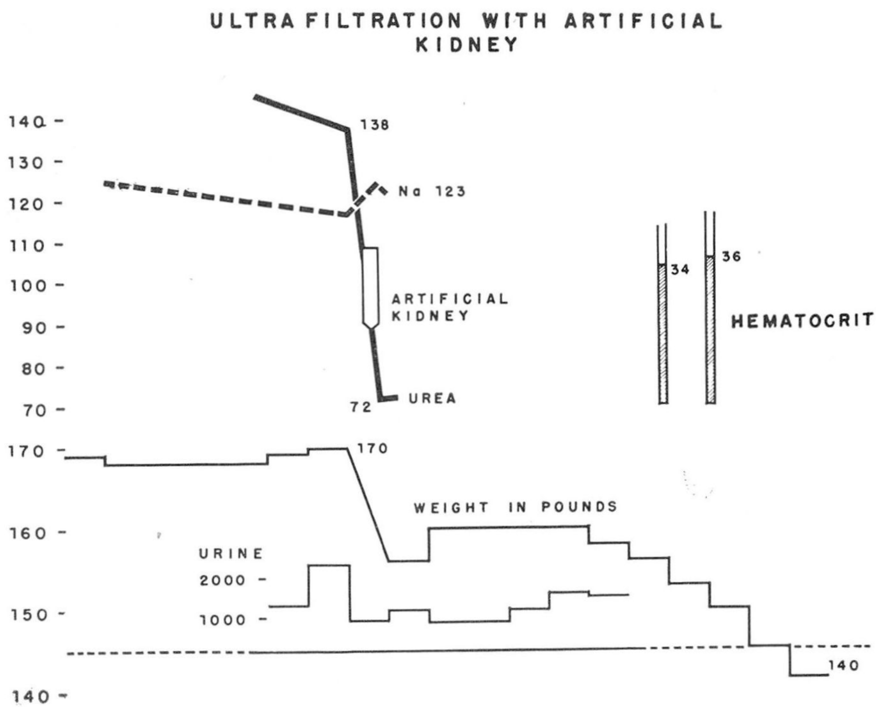

Fig. 3. (Case 6) 47 year old man with polycystic kidneys and intractable edema was given one treatment with the dialyzing-filtering type of artificial kidney. Fall in weight during treatment is indicated; it marked the beginning of a fortunate but unexplained progressive elimination of the edema. Urea is indicated in mg. per hundred ml. Na is indicated in mEq. per liter.

In retrospect, it may be concluded that the treatment with the rotating type of artificial kidney caused the disappearance of the vomiting, which had been the most important clinical symptom before treatment. The stationary artificial kidney was mainly used to relieve the edema that had caused serious respiratory embarrassment. This was accomplished and the edema did not recur during the further downhill course of the disease.

Case 6. A 47 year old man was known to have polycystic kidneys for at least 10 years. He had been maintained on a high-caloric, low-protein diet for a year and a half. He entered the Cleveland Clinic, September 25, 1952, with extensive edema, mostly in the lower part of the body. With digitalis, bed rest, low-sodium diet, and Mercuhydrin, his weight was reduced from 172 to 168 pounds. After that, it was impossible to reduce it further. Blood urea varied from 186 to 222 mg. per 100 ml. There was ascites with drum-like tension of the abdomen. He was treated with the stationary artificial kidney with simultaneous ultrafiltration and dialysis for 7 hours (fig. 3). The usual composition of the rinsing fluid was used with 135 mEq. of sodium per liter. During the day he was treated, he lost 13½ pounds in weight. The amount of ultrafiltrate removed could be measured during the second half of the procedure and amounted to almost 1200 ml. per hour.

Toward the end of the treatment, the patient enjoyed eating a ham sandwich allowed for the occasion. During four days following treatment with the artificial kidney, there was some increase in weight, but later there was a steady decrease. He left the hospital much improved without edema, and able to take a 1000 to 2000 calorie diet, and with a blood urea content of 90 mg. per 100 ml. A dermatitis developed which caused his death six weeks later.

In this case, it seems as though some vicious circle was broken; we have no explanation as to why there was a sudden increased ratio of urine volume to fluid intake. The edema did not recur.

Case 7. A 48 year old man came to the hospital on August 27, 1953, with the diagnosis of chronic glomerulonephritis with nephrotic syndrome. He was uremic and edematous; he vomited and had felt miserable for several weeks. A high-caloric, 20-gram protein diet was first prescribed. But, on account of anorexia and vomiting we did not succeed in feeding him more than 500 or 1000 calories per day. A course of watermelon was tried; there was increase in diuresis but no decrease in weight. It was thought that his clinical condition might be improved greatly if the edema was reduced. Attempts to remove edema began with paracentesis. Two and one half liters of fluid was removed and the patient's weight was reduced from 190 to 182 pounds. Next, treatment with the filtering type of artificial kidney was given (fig. 4). Eight hundred to 1000 ml. of ultrafiltrate per hour was removed during five hours of filtration and dialysis; body weight was further reduced from 182 to 169 pounds. To avoid postdialytic oliguria, urea was added to the rinsing fluid in a concentration of 120 mg./100 ml.[15] The patient's serum electrolytes were practically unchanged by the procedure.

The following days, there was a marked change in the patient's general well-being. His appetite increased and he took with pleasure 1500 and, later, over 2000 calories per day. Diuresis was a little more than before the watermelon period. There was no postfiltration oliguria, perhaps thanks to the addition of urea to the rinsing fluid as indicated above. His weight remained stable for five days and then increased on the sixth. The following day, the first of two courses with ACTH was started. After the second, diuresis occurred. Unfortunately, it did not last long. However, after his return home he lost considerable edema; he followed a 2000-calorie, 40-gram protein diet. He was able

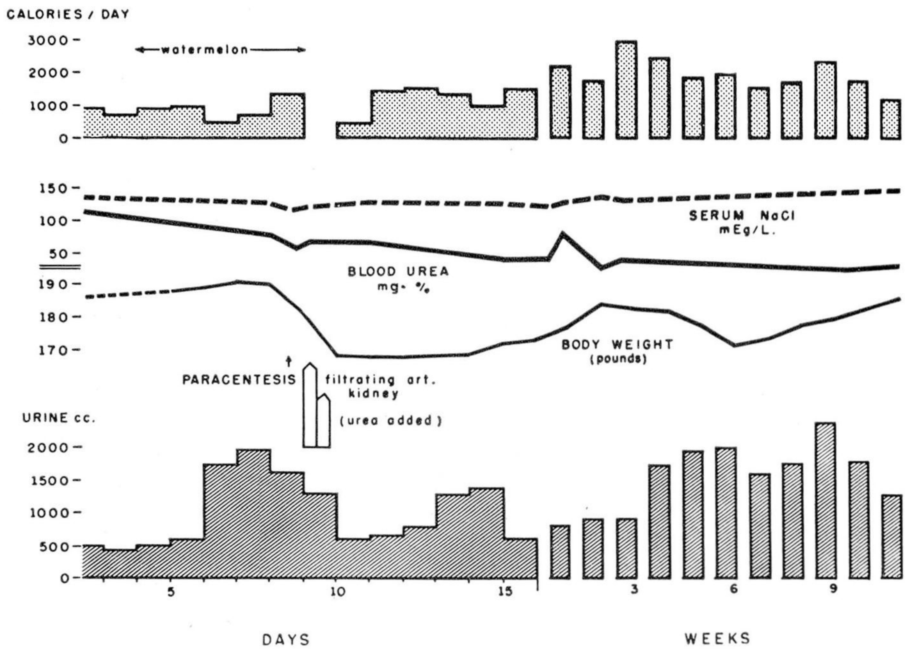

Fig. 4. (Case 7) 48 year old man with chronic glomerulonephritis and nephrotic syndrome; greatly incapacitated by edema. The caloric intake as indicated before treatment is too optimistic as vomitus was not taken into account. Note the increased diuresis during the watermelon diet, without concomitant fall in weight. After one treatment with dialysis and filtration his clinical condition improved markedly. Note that his blood urea did not fall during dialysis and filtration because of the addition of urea to the rinsing fluid. There was no postfiltration oliguria.

to do some of his work until almost two months later when the edema began to recur. He is now under treatment for this recurrence.

In this case, the improvement in the patient's well-being, which was perhaps partly due to the removal of some retention products but mostly due to the removal of the edema, made his condition amenable to further treatment. Despite recurrence of the edema two months later, his general condition was very much better than it was prior to treatment with filtration and dialysis.

SUMMARY

Edema, otherwise intractable, may be treated by:

1. A dialyzing type of artificial kidney with glucose (2 to 5 per cent) added to the usual composition of the rinsing fluid. Losses of weight of 4 to 5 Kg. have been reported in the literature and an example is given in which a loss in weight of 2.7 Kg. was effected in one treatment.

2. Peritoneal lavage with glucose (2 to 10 per cent) added to the usual composition of the rinsing fluid. An example is given in which 4 L. was removed in 10 hours.

3. A filtering (and dialyzing) type of artificial kidney that will remove 1000 ml. of ultrafiltrate per hour. This is the most rapid method of dehydration. Hematocrit determinations are necessary to avoid undue hemoconcentration, reduction of circulating blood volume, and shock. Four patients were treated; all were benefited temporarily. In one patient, there followed spontaneous elimination of the remaining edema, and in another, continued improvement. Addition of urea to the rinsing fluid in one case may have helped to avoid postdialytic oliguria. Fluid restriction the first few days after the treatment is recommended.

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