ARTIFICIAL KIDNEY

Treatment of Acute and Chronic Uremia

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UNDOUBTEDLY the most important factors in the treatment of both acute and chronic uremia are the proper regulation of diet and maintenance of water and electrolyte balance. Too often the presence of anuria or oliguria encourages the administration of large quantities of fluids in vain attempts to initiate diuresis, resulting in an overload of salt and water and the appearance of symptoms erroneously attributed to uremia.[41]

Where dietary treatment, including rigid control of water and electrolytes, has been ineffective the use of one of the following methods should be considered: 1. artificial kidney, 2. peritoneal dialysis, 3. intestinal dialysis, 4. replacement transfusion. The first of these will be discussed herein.

Principles of the Artificial Kidney

Regardless of the type of artificial kidney used the patient's blood must be rendered incoagulable by the injection of heparin. The blood is then guided along a cellophane membrane on the other side of which is the rinsing fluid. By the process of dialysis a large part of the abnormally retained products of metabolism—urea, uric acid, creatinine, substances giving the xanthoprotein reaction such as phenols,[58] indoxyl, etc. pass from the blood through the cellophane membrane into the rinsing fluid. They become so diluted that return dialysis is negligible. In addition to this process an exchange takes place between the necessary electrolytes of the blood plasma water and those in the rinsing fluid. Hence, if the patient's blood electrolyte pattern is abnormal before treatment, it will tend to be corrected as it approaches the composition of the rinsing fluid inasmuch as the fluid contains normal concentrations of these ions.

Since water passes through the cellophane easily, careful attention must be given the osmotic pressure on the two sides of the membrane. On the inside the blood plasma protein tends to draw water from the rinsing fluid to the blood. This can be prevented by making the rinsing fluid isotonic with the addition of glucose. If so desired it can be made hypertonic and capable of withdrawing fluid from the patient,[56] a maneuver which may be particularly gratifying to patients with pulmonary edema.[16,20,26,39] Figure 1 shows Gamble's diagrams of blood plasma and rinsing fluid. In uremia, as may be seen, the urea accounts for a higher osmotic pressure than normal; however, this can be compensated for by adding glucose to the rinsing fluid. As shown in Figure 1, the total electrolyte content of uremic blood plasma is often lower than in

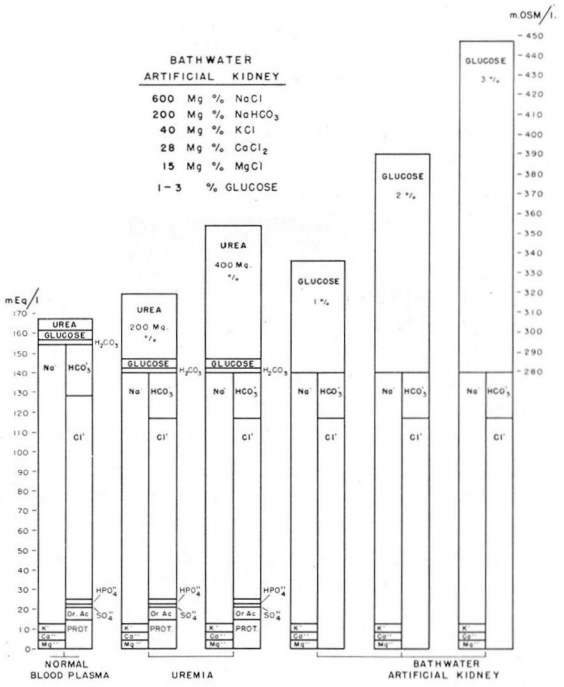

FIG. 1. Gamble diagrams of blood plasma and rinsing fluid. Urea accounts for a considerable rise in osmotic pressure which can be compensated with glucose.

(In this diagram values are expressed mEq/L blood plasma. What really counts however is the value mEq/L blood plasma water.)

normal conditions. A low chloride content cannot always be attributed to vomiting alone. It seems unwise to correct the electrolytes too much as nature may have reasons for lowering them.

Types of Artificial Kidneys

Since Abel, Rowntree and Turner designed the first kidney in 1913, the following types of artificial kidneys have been introduced:

1. Artificial Kidney Employing Dialysis (fig. 2).

The rotating type of artificial kidney which I described in Holland in 1943[21,29] and in Sweden[28] and France[30] in 1944 works purely by dialysis. A thin film of blood moves by gravity through a long cellophane tube wrapped spirally around a rotating drum which is partially immersed in rinsing fluid.

The dialyzing capacity of this kidney in terms of clearance, 100 to 200 cc. per minute as confirmed by others[39] has not been surpassed by any of the devices subsequently developed. While the original model was used by Mac Lean, de Leeuw, van Noorwijk, Palmer and Fishman, and details have been

altered by others (Bywaters and Joekes, Vanatta, Merrill, Kearns,* and Darmady), its main principle of a rotating drum has remained unchanged. This type of kidney has been used successfully on patients in Europe,[11,19,20-31,57,59] Canada,[14,34,46,47] and the United States.[16,37,39] The largest series, 120 cases, has been accumulated by Merrill, Smith, Walters, Callahan and Thorn in Boston. Recently they[39] published the results of 60 dialyses in 43 patients, and through their skillful handling of excellent equipment have confirmed the safety of the method and suggested entirely new possibilities for the use of the artificial kidney.

Vanatta, Muirhead and Grollman who used the artificial kidney in animal studies made an unfavorable preliminary report; however, after effecting some modifications they state: "It may be concluded that dialysis of the blood across a cellophane membrane removes adequately the waste products from the organism, and that death in uremia is a result of the accumulation of such waste products. The results also prove the efficacy of the artificial kidney in replacing known excretory functions."[55] The conclusions of Grollman, Muirhead and Vanatta[17] that bilateral nephrectomy in the dog results in hypertension is, however, not yet confirmed.[33] Reinecke reduced the size of the rotating kidney by winding the cellophane into a coil and subsequently employed it for potassium studies in the dog.[48]

2. Artificial Kidneys Employing Filtration

The purest example of a kidney that works by filtration only is that of Malinow and Korzon.[36] It might be called an artificial glomerulus. Malinow and Korzon discontinued their experiments when they realized the small amount of metabolites that could be removed by filtration as compared with the amount removed by dialysis. The human kidneys need a filtrate of 150 liters per 24 hours to produce 1.5 liters of urine per day. In constructing an artificial kidney that works with filtration, one might have to reinfuse 148.5 liters of fluid per day. The artificial kidneys of Alwall[2] and of Skeggs and Leonards,[50] though designed for dialysis, could be used for filtration if desired.

3. Artificial Kidney Employing Dialysis and Filtration (fig. 3)

With French ingenuity, Derot et al[15] dipped a rat's small intestine in a 10 per cent formol solution for fixation and sterilization. It was then rinsed and one end connected to the radial artery of a patient and the other to a vein. This dialyzing membrane was immersed in rinsing fluid. The older artificial kidneys used collodion tubes or peritoneum; the newer types utilize cellophane tubes or chambers through which blood is forced under pressure while negative pressure is applied through the rinsing fluid. The artificial kidneys designed by Abel, Haas, Necheles, Thalhimer, the dialyzer of Brinkman,[22,31] the kidneys of Alwall, Murray, Slotkin, Sterling, Darmady (laminated type), of Barnard, of Rosenak and MacNeill employ this principle. The most efficient is doubtless

**This type of kidney is manufactured by Allis-Chalmers Manufacturing Company, Milwaukee, Wisconsin.*

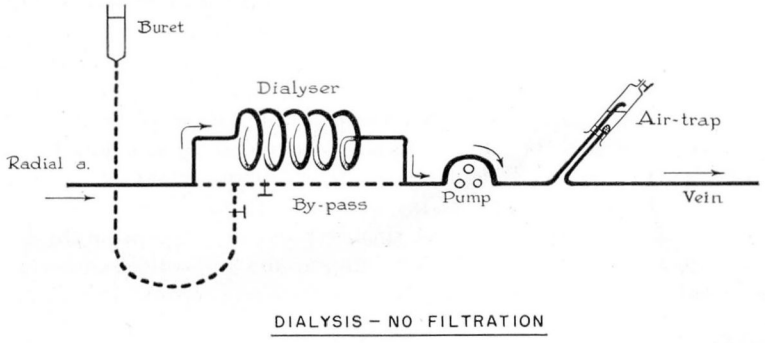

FIG. 2. Blood flows freely from the radial artery to the cellophane membrane where further movement is accomplished by rotation of the drum. The blood in the cellophane tubing is not under pressure. Either pump or the force of gravity returns the blood to the vein. There is practically no filtrating pressure.

the Skeggs' and Leonards' model in which cellophane sheets are compressed between rubber plates; blood and rinsing fluid flow through grooves in the rubber on opposite sides of the cellophane. The dialyzing unit in the "serial counter-flow type of artificial kidney" described by Lowsley and Kirwin in the Urological Society, 1950, used plastic instead of rubber, but is essentially similar to Skeggs' and Leonards' first model (Science 1948).[50] These authors[51] have in the meantime developed a newer, better artificial kidney wherein the blood is retained between sheets of cellophane without coming in contact with the rubber or plastic walls. The kidney designed by Bodo van Garrelts in Stockholm deserves mention as it is little known although its principle is excellent; a large sized cellophane tube is wound together with a long strip of wire mesh into a stationary coil.

I have so far treated a dozen patients with a new type of stationary artificial kidney (fig. 4) designed in collaboration with de Groot, in which cellophane tubing is compressed between specially grooved plastic plates. Our purpose was to compare the clinical results of the stationary and the rotating artificial kidneys.

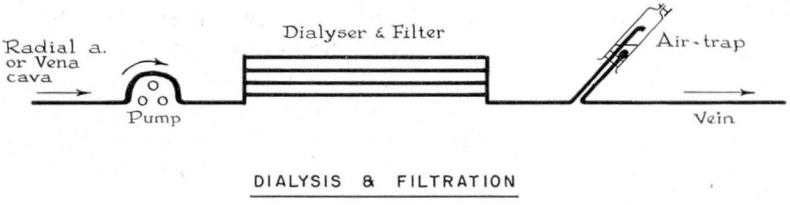

FIG. 3. Blood is forced into the apparatus either by arterial blood pressure or by a pump or both. The blood in the apparatus is under pressure varying from 260 to 20 mm. Hg. In addition, suction may be applied to the rinsing fluid which increases the filtration pressure.

It seems of little importance to me which type of artificial kidney is used although some investigators tend to discredit models other than their own.

Use of the artificial kidneys listed in Section 3 (Artificial Kidney Employing Dialysis and Filtration) necessitates consideration of the water and electrolytes lost by filtration. While apparently simple, these electrolyte and fluid problems may account for clinical disaster. Leonards,[33] for example, suspected that the dehydration and demineralization due to filtration may have accounted for the death of some of the dogs used in his earlier experiments. He now gives a slow infusion of sterile rinsing fluid to compensate for this loss—in his hands a safe procedure. Alwall compensates the colloid osmotic pressure of the blood with filtration. Some authors, however, ignore this problem.

4. Artificial Kidney Employing Exchange Resins

Although promising, this type of kidney is still in its formative stages. The artificial kidney designed by Muirhead and Reid[40] consists of a resin base composed of nine parts cation exchange resin and one part of anion exchange resin. Retention products are absorbed by these substances.

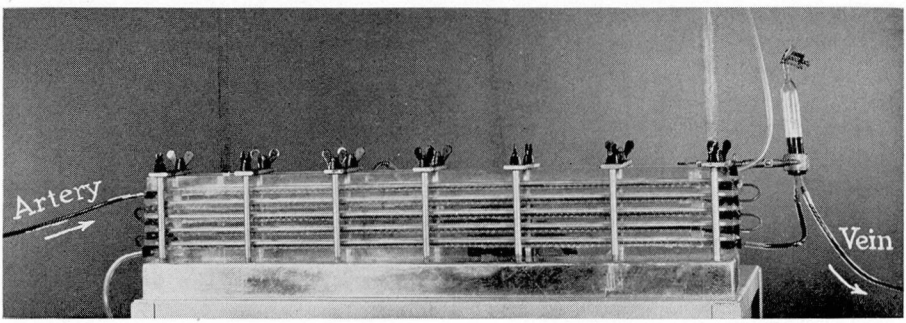

FIG. 4. One dialyzing unit of a stationary type of artificial kidney. Cellophane tubing is compressed between grooved plastic plates. The blood circulates through the cellophane tubing by artificial pressure. No pump is required. The rinsing fluid flows in counter flow either by gravity or propelled by a pump.

Clinical Experience with the Artificial Kidney

Acute Uremia

At present no statistics indicate that the life of a patient may be saved by the action of the artificial kidney (Snapper[52]) because of the comparatively few and heterogenous types so far treated. Muirhead[41] has sought to compare the results observed in 2 patients having mercury poisoning. However, any comparison is debatable. The anuria is usually relieved after 10 days, occasionally after 4 or after 16 days, but sometimes never.

I do not and never did claim that I ever saved a patient with the artificial kidney although many of my patients have now recovered from severe uremia. In judging the possibilities of the artificial kidney we have learned more from

unfavorable cases with protracted courses. For instance, Joekes treated a patient twice with an artificial kidney but discontinued treatment when a diagnosis of renal cortical necrosis became evident after 20 days of anuria. Death did not occur until 8 days later. Alwall, when writing "On the Artificial Kidney, V", had a patient in fair condition who had glomerulonephritis and complete anuria for 30 days. One of my patients, aged 37, died from pneumonia 74 days after the onset of almost complete renal cortical necrosis. She had been given the Borst forced high caloric diet, had been treated twice with the artificial kidney and twice with peritoneal dialysis. With further experience in this field we may prolong life indefinitely. It is obvious that death from acute uremia should be extremely rare. There is no reason to be content with a mortality rate of 15 per cent, claimed by Muirhead,[40] for so-called conservative treatment.

The first dramatic improvement in a patient's clinical condition, followed by complete recovery, was seen in Holland in 1945. A woman of 67 had a cholecystitis with hepatorenal syndrome and anuria of 7 to 10 days' duration. The blood urea was 400 mg. and potassium 55 mg. per hundred ml. She was almost comatose, snored constantly, but answered (usually incorrectly) when shouted at. After treatment with the artificial kidney the blood urea was reduced to 120 mg. and the serum potassium to 19 mg. Although she had not produced any urine, the following day she was completely clear of mind and made reasonable plans for the future. While it is not possible to say whether the clinical improvement was due to the removal of retention products or to the correction of water and electrolyte balance, it was probably due partly to both. The patient recovered completely.

As examples of the treatment of acute uremia with the artificial kidney, histories of 2 cases with mercury poisoning are presented. Other cases which have been treated with equal success include patients with acute glomerulonephritis, lower nephronnephrosis due to sulfonamides and unknown agents.

Case Reports

Case 1. A 26-year-old man swallowed 10 Gm. of bichloride of mercury. Two days later BAL was available and was given in large amounts. The blood urea rapidly rose not withstanding a forced high caloric, low protein diet. The patient was completely anuric and had a temperature of 38 C. Penicillin was prescribed. On the eighth day after taking the bichloride of mercury, the blood urea was 337 mg. per hundred ml. Serum chloride was 525 mg. per hundred ml. (calculated as NaCl) and potassium was 20. On this day we saw the patient and decided that delay might be more dangerous than dialysis. In 6 hours 40 liters of blood flowed through the cellophane tubing; 83 Gm. of urea was removed. Blood urea fell to 154 mg. per hundred ml. After dialysis his general condition was good and no undesirable reactions occurred. His blood urea rose again; however, from the twelfth day his kidney function improved and by the twenty-first day after taking the bichloride of mercury the blood urea was normal.

Case 2. The history of a second patient with mercury poisoning is shown in Figure 5.

Chronic Uremia

The majority of the 24 patients treated by Alwall had chronic nephritis,

polycystic kidney or chronic pyelonephritis.[3] Many of those patients have been benefited by the dialysis. The Boston group of investigators consider the artificial kidney a valuable adjunct in the treatment of severe chronic uremia.[39] In our own experience dialysis has been extremely helpful in chronic uremia. The clinical condition of the patient may be improved so that he is able to take a high caloric diet. It is admitted that the psychosomatic factor plays an important role, but the patient may be in urea balance for many months after the dialysis.

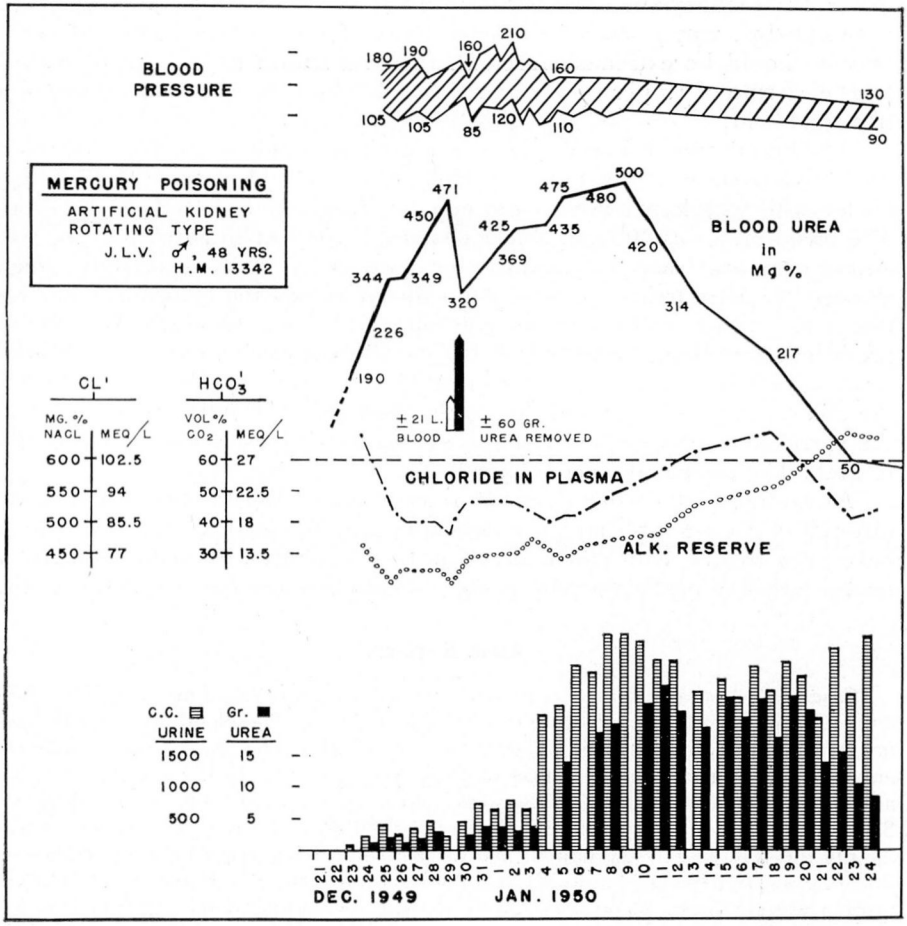

FIG. 5. Graph of a patient with mercury poisoning treated with the artificial kidney, rotating type. Rapid rise in blood urea was due to toxic protein destruction. The forced high caloric diet met with considerable interference due to mercurial colitis accompanied by meteorism and ascites. When the blood urea had risen to 471 mg. per hundred ml. the patient's condition appeared ominous. After dialysis the blood urea rose again to an even higher level, but 14 days after onset of anuria diuresis increased and the patient did not appear unusually ill. He was discharged on the thirty-fourth day with normal blood urea.

Case 3. A college teacher of 27 years (fig. 6) was reported to have had chronic nephritis with albuminuria for 10 years; edema and hypertension for at least 2 years. In addition, there was a history of renal calculi and a deformed left pelvis. He came to the Research Division of the Cleveland Clinic on July 10, 1950, in the last stage of the disease, with rapidly declining urinary output. He was restless and cyanotic, had definite pulmonary edema, a gallop rhythm and pleuritis. His blood pressure was 180/120. To save time a venesection was done. The next morning he was treated with 2 units of our new stationary type of artificial kidney. However, before the beginning of treatment he had a severe convulsion. Three subsequent convulsions occurred during treatment and the patient was comatose during the procedure. One hundred and eighteen grams of urea was removed. The patient's blood urea was reduced from 420 to 147 mg. per hundred ml. Alkali reserve was improved from 14 to 32 volume per cent. Plasma chloride and sodium were purposely reduced. Twenty-four hours later he was greatly improved. His edema had practically disappeared; no gallop rhythm could be heard. His blood pressure was 150/110. However, he now presented symptoms of pulmonary disease. The fine rales of pulmonary edema had disappeared but he showed signs of bronchopneumonia with pleural and pleuropericardial frictions. As his blood urea rose again he was given a second treatment with the artificial kidney on July 15. The same cannulas in the vein and artery were used. The patient was given 250 mg. of sodium amytal and slept during treatment. Not the slightest undesirable reaction was noticed. One hundred and four grams of urea was removed. The blood urea fell from 294 to 84 mg. per hundred ml. The serum potassium was lowered from 7.4 to 4.5 mEq/L. Physical improvement was evident during the next 2 days. The lungs cleared completely; he was clear of mind and resumed his interest in life. The patient's appetite was good and he took his high caloric diet in addition to a normal breakfast; he was ambulatory although still shaky on his feet. His diuresis, however, did not improve. We hoped to treat him with dialysis through an isolated intestinal loop to give him at least a chance to survive but his family refused.

Observations During Treatment with the Artificial Kidney

Removal of retention products with the artificial kidney requires no further discussion. This program was established as early as 1912 by Abel, Rowntree and Turner. In general, there is good correlation between the clinical improvement and chemical changes; however, in my experience, maximum improvement may not be evident for 24 hours following treatment. Furthermore, for reasons not evident dramatic clinical improvement may be noted which is out of proportion to the chemical changes.[39]

Electrolytes

After protracted dialysis the concentration of the electrolytes of the patient's blood plasma water approaches the concentration of these substances in the bath water. At present I use a composition of rinsing fluid which contains less sodium than that used by most investigators, with the exception of Palmer.[46]

NaCl	500 to 600 mg. per hundred ml.
$NaHCO_3$	200
KCl	40
$CaCl_2$	28
$MgCl_2$	10
Glucose	1000 to 3000

The regulation of the electrolytes might be called the tubular function of the artificial kidney. Hence **hyperchloremia** (e. g. from 750 to 660 in 1 case) or **hypochloremia** (e. g. from 462 to 528 in another case) can be corrected. A low NaCl may be adjusted while at the same time the total volume of the extracellular fluid may be reduced[39] by adding more glucose to the rinsing fluid.[56] In the patient with hypertension and convulsions previously discussed (case 3), we purposely reduced the serum **sodium** from 139 to 117 mEq/L.

The **high serum potassium** of the woman aged 67 was reduced from 55 to 21 mg. per hundred ml. Wener and de Leeuw[60] observed similar changes and the Boston investigators[39] currently report 5 cases in which they suggest that the artificial kidney may have been life-saving through the control of

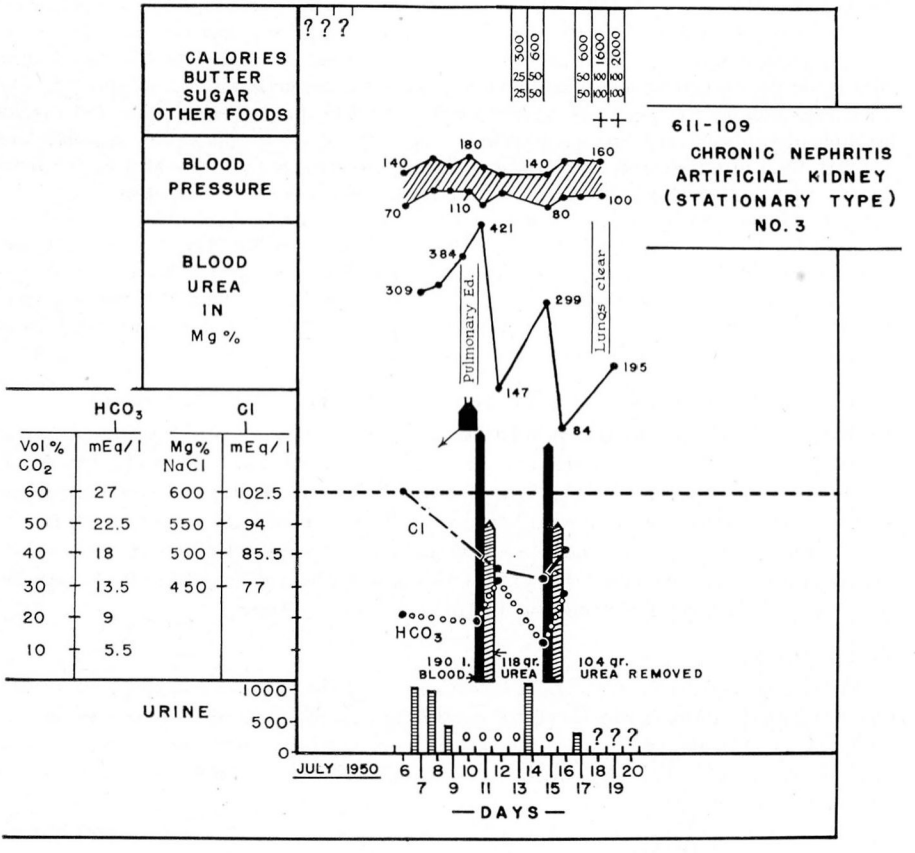

FIG. 6. Patient in terminal stage of chronic nephritis. Uremic condition improved, convulsions ceased, pulmonary edema disappeared, and congestive heart failure subsided after two treatments with the stationary type of artificial kidney. On discharge he resumed a high caloric diet. We cannot estimate how long urea balance may be maintained with the remaining fraction of kidney function.

hyperpotassemia. Reinecke[48] removed 1 to 2 Gm. of potassium from normal dogs by dialysis and found that this could be compensated although the serum potassium would drop, e. g. from 16 to 11.5 mg. per hundred ml. One of Vanatta's[55] experimental dogs developed a low serum potassium (it was quoted as 0.1 mEq/L after the dialysis but had this value been correct the dog probably would not have survived). If serum potassium levels are not measured repeatedly during dialysis it is dangerous to omit the potassium from the rinsing fluid because of the possibility of inducing hypopotassemia.[27]

Calcium may be kept in solution in the rinsing fluid in the presence of $NaHCO_3$ if a pH of approximately 7.4[26,39] is maintained or if the solution is kept in a cool tank and heated just before it is allowed to flow through the artificial kidney. If no calcium is added to the rinsing fluid, calcium gluconate must be given intravenously in order to replace that lost into the bath.

Acidosis may be corrected by dialysis since acids that are retained in uremia are removed. Furthermore, $NaHCO_3$ passes through the cellophane membrane into the blood. If the patient's alkali reserve is especially low it may be wise to give extra $NaHCO_3$ intravenously. Alkalosis can be corrected since the concentration of $NaHCO_3$ of 200 mg. per cent in the rinsing fluid corresponds to an alkali reserve of 53 volume per cent. Blood levels in excess of this amount will loose the ions to the rinsing fluid.

Morphologic changes and hemolysis in the blood during dialysis have been carefully studied by de Leeuw,[13] using the unmodified, unimproved rotating kidney. Figure 6 demonstrates coating of the cellophane with granulocytes. If leukopenia occurs it is corrected within a few hours after dialysis. Hemolysis, which may be evident in dogs, can be avoided in human beings[26] even when the original rotating kidney is used with its original pump, when there is a fair flow of blood. However, the yellowish color of uremic plasma often becomes more intense. No increases in bilirubin values have been evident in such cases; nor were they observed by Merrill and his co-workers.[39]

Earlier in our investigation we observed some hemorrhages due to overdosages of heparin; in the same period Bywaters and Joekes[11] lost a patient from a subdural hematoma. The cerebral petechia in elderly people treated with the artificial kidney at Mount Sinai in New York[16] may also be attributed to excess of heparin. However, since plastic tubing can be used in place of rubber[38] and since all glassware can be coated with dry film[38] or DC* 1107 and less heparin used, such hazards may be avoided. One hundred and fifty to 300 mg. of heparin should be sufficient for one treatment in adults, unless an artificial kidney is utilized with a relatively small clearance which requires a long time for the dialysis. Heparin is instantly neutralized by intravenous injection of protamine.

A so-called toxicity of the cellophane tubes in dog experiments is described by Vanatta, Muirhead and Grollman.[55] Leonards and Skeggs observed the same reaction when using sheets of cellophane. It apparently is of little importance in humans when the cellophane is boiled and rinsed as indi-

Supplied by Dow Corning, Midland, Michigan.

cated.[26,38] Should it become a problem, however, the material can be detoxicified by boiling for a period of 12 hours.[33]

Effects on Arterial Blood Pressure

Transient arterial hypertension was noted by the Boston group in most cases where there was sufficient flow of blood through the kidney.[39] Although I have observed it on occasion, removal of 200 or 300 ml. of blood from the circulation usually has been sufficient to reduce it. In my experience, vasoconstriction may also occur in experiments with the artificial heart. This may be due to the manipulation of blood outside of the body. Further investigation will be necessary to determine whether a lowering of the sodium of the rinsing fluid will reduce the occurrence of this pressure effect.

Indications for Treatment with the Artificial Kidney

Patients with anuria are treated along conservative lines for as long as possible. A patient, however, who has been overtreated with water, salt, diathermy, splanchnic blocks and decapsulation, may be in such condition that immediate treatment with the artificial kidney is imperative. In any patient critically ill with acute or chronic uremia, whatever the cause, dialysis may be attempted. Should dialysis be tried as a last resort in a moribund patient, there is little hope of recovery. In experienced hands, however, treatment with the artificial kidney appears to impose extremely little risk.

There is some logic in the concept that the artificial kidney may be used, not as a last resort when other methods of treatment fail, but as an effective adjunct to more conservative methods of therapy.[39]

Congestive heart failure with pulmonary edema may constitute an additional indication for prompt dialysis in the presence of uremia. The blood necessary to fill the artificial kidney will act as a venesection and the removal of fluid with hypertonic glucose solution into the rinsing fluid will, in many cases, greatly improve pulmonary edema. I can confirm[25] completely the observations of the Boston investigators[39] on this point.

Summary

There are three types of artificial kidneys. 1. Purely dialyzing (Kolff rotating type). 2. Purely filtrating (Malinow and Korzon). 3. Dialyzing and filtrating (all other types).

Vivo dialysis can replace all known excretory functions of the kidney. Moreover it can regulate the electrolyte pattern of the blood plasma water inasmuch as this approaches the composition of the rinsing fluid.

Clinical improvement has been convincing in cases of acute or chronic uremia. In experienced hands treatment with the artificial kidney imposes little risk. It may be an effective adjunct to other methods of treatment. Congestive heart failure in the presence of uremia may be an additional reason for prompt dialysis.

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