CLINICAL PROGRESS

The Artificial Kidney—Past, Present, and Future

By W. J. Kolff, M.D.

The name artificial kidney was first suggested by Abel, Rowntree, and Turner, and indicates perfectly the intended function of the apparatus. All currently used artificial kidneys remove retention products from the blood, by exchange through a semipermeable membrane.

Types of Artificial Kidneys

Blood Pumped Through Cylindrical Tubing. The dialyzer designed by Abel, Rowntree, and Turner utilized cylindrical collodion tubing through which the blood flowed while the rinsing fluid circulated outside. The same principle of design but with cellulose tubing was followed by Haas, and by Murray, Delorme, and Thomas. One of the disadvantages of these kidneys was the large volume of blood required to fill them as compared to the relatively small dialyzing area. The Murray artificial kidney has a blood volume of 560 ml. and a dialyzing surface of 0.88 M.², which is not too unfavorable because the tubing is small (1/4-inch diameter), but unfortunately it is too thick-walled for adequate dialysis. With thin-walled cellulose tubing the size of a drinking straw, the prospects for good dialysis are better. Rosenak has induced the American Viscose Company to make such tubing and he uses it in a counterflow arrangement with 2 concentric tubings. Blood runs through the inner cellulose tubing while rinsing fluid runs in the opposite direction through the outer tubing.

The rotating type of artificial kidney combines a large dialyzing area (2.4 M.²) with a small volume of blood (600 ml.). A thin film of blood is propelled by gravity through cellulose tubing wrapped around a slowly rotating drum. There is dialysis through the tubing but filtration does not occur because there is hardly any difference in hydrostatic pressures across the membrane. The rotating type of kidney was described in 1943 by Kolff and Berk, and detailed plans were published in 1946 and in 1947. To encourage their clinical use, 4 kidneys were made in Holland during World War II and subsequently were donated to several medical centers. One was sent to London, one to Montreal, one to New York, and the fourth one disappeared behind the iron curtain. Kidneys of this type have also been made by Allis-Chalmers and, with modifications, by the Peter Bent Brigham Hospital group, by Olsen.

The reverse of the usual system of dialysis is used by Guarino and Guarino: blood is outside the cellulose tubing and rinsing fluid is inside. This design in its present state of development, although very interesting, has a low clearance and no safeguard against air embolism or against overhydration of the patient if a leak should develop in the cellulose tubing.

To provide a limited space for blood but a large dialyzing area one can enclose the cellulose tubing or sheets between ridges or screens. As the blood is forced through the narrow space there is a hydrostatic pressure difference across the membrane and ultrafiltration as well as dialysis takes place. The most effective of this type currently used was designed by Skeggs, Leonards, and Heisler, who sandwiched sheets of cellophane between grooved rubber plates. Its assembly requires adequate training.

As early as 1923, Necheles designed a type

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of dialyzer in which "Goldschelegerhaut" (peritoneum) was compressed between screens. Alwall, in Sweden, used cellulose tubing wrapped around a screen and surrounded in turn by a second screen that was fitted very much the way a corset is fitted around a body (fig. 1). Why he changed from this to a system of stainless steel ridges, which must be expensive and difficult to make, is not altogether clear.

Von Garrelts made a stationary coil in which cellulose tubing and wire mesh are wound together, thus the volume of blood in the cellulose tubing is small, the dialyzing area is large, and the unit is compact (fig. 2).*

Inouye and Engelberg ingeniously used cheap, disposable plastic screen in a stationary coil that they fitted into a pressure cooker (fig. 3). Kolff and Watschinger have further developed this type of artificial kidney and have put it into a tin can, making a dialyzing unit that is cheap, disposable, and can be mass-produced (fig. 4).

Resin Artificial Kidneys. Some work has been done with resin artificial kidneys. That resins absorb, or rather exchange, certain ions is well known. Muirhead and Reid showed in animal experiments that certain resins also absorb urea. Di Marchi and Brönniman, in Switzerland, and Bonanome, in Italy, have used resin artificial kidneys in treating patients. The field has not been developed yet, but Zinsser has demonstrated the potentialities of resins in absorbing various retention products. Resins now are available in sheets.

The ideal artificial kidney has not yet been built; usually a compromise is necessary to arrive at a usable unit, and one or more desirable qualities must be sacrificed. A good artificial kidney should have a large dialyzing area for adequate clearance, and continuous movement both of blood and of rinsing fluid. It must operate with a small volume of blood and maintain a constant volume of blood in the machine —causing no change in blood volume in the patient. It must have good visibility so that if a leak occurs in the dialyzing membrane it will be seen immediately. It must have controlled temperature of rinsing fluid. The rinsing fluid must be of the correct composition (10 per cent CO₂ in O₂ bubbled through it to maintain the pH at 7.4). The blood must not come in contact with glass or metal or materials that promote clotting and require the use of large doses of heparin. The dialyzing unit must be easy to assemble and to clean; it may be prefabricated and disposable. It must be sterilizable (preferably after assembling). The apparatus should be easy to operate.

If there is a pressure gradient across the dialyzing membrane it is preferable that the

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* It has been brought to my attention that S. S. Rosenak, G. D. Oppenheimer, and A. Saltzman exhibited a small stationary coil kidney at the Annual Meeting of the American Urological Society in Boston 1948, which may have been the first of this kind in this country.
pressure on the blood side be higher than that on the rinsing fluid side. The reasons are (1) in case of a leak, blood coming into the rinsing fluid can be seen, whereas rinsing fluid going into the blood is difficult to detect (infusion of rinsing fluid into the blood may lead to overhydration of the patient, and as the rinsing fluid is not sterile it may introduce bacteria) and (2) positive pressure on the blood side will cause some ultrafiltration, thus counteracting the colloid osmotic forces of the blood plasma that operate in the opposite direction.
The following considerations deserve attention: sedimentation in the apparatus and minimum clearance. When the blood flow is small, sedimentation of erythrocytes may take place in the apparatus, so that only plasma comes out. The settling out of red cells may occur in multiple-channeled dialyzers with parallel and consequently slow flow in each channel. It also occurs when dialysis is interrupted for a time.

There is a minimum clearance necessary for an artificial kidney to be clinically useful. It is a frustrating experience to remove 30 Gm. of urea during a day’s dialysis only to discover on the next day that the patient’s blood urea is the same as it was prior to dialysis: a gain of 1 day only has been obtained; whereas, with more efficient dialyzers 4 or 5 days may be gained.

If we express the efficiency of an artificial kidney in dialysance or clearance, we usually express it in urea dialysance or clearance. Wolf and co-workers have shown that the urea level provides the most favorable index of clearance (fig. 5). For example, with a urea clearance of 100, the clearance for phenol red is only 3. Artificial kidneys with clearances of 120 to 180 ml./min. are now available, and contraindicate use of less effective devices that require more time, longer supervision, longer heparinization, and offer greater hazard of hemorrhage.

Membranes with Greater Porosity. The possibilities of developing kidneys with membranes of greater porosity have hardly been explored. The rate of urea clearance probably would not be increased, inasmuch as the diffusibility of urea through the fluid layer coating the membrane, rather than the number or size of the pores of the membrane seems to be the limiting factor. The pore size in our present cellulose tubing is 25 angstrom units. By treating the tubing with zinc chloride solutions the pore size may be increased to 170 Å. Hemoglobin will pass through at 60 Å. By using membranes having greater porosity another category of products might be removed from the blood by dialysis. Unfortunately, treatment of membranes with zinc chloride seems to make them more brittle.
THE ARTIFICIAL KIDNEY

DAMAGE TO BLOOD AND UNFAVORABLE REACTIONS

Pyrogenic Reactions from Cellulose. Visking tubing is made from cotton linters. It is not a pure substance such as cellulose acetate, cellulose acetate butyrate, or ethyl cellulose, but is regenerated cellulose. According to the Visking Corporation, it contains glycerin, water, and 0.1 per cent sulfur. The inside of the roll of cellulose as it comes from the factory is sterile (although the factory does not guarantee this). If properly stored, it is unlikely that microorganisms will attack the tubing. Cellophane sheets and cellulose tubing have been considered as requiring chemical treatment or extensive boiling to preclude pyrogenic reactions in the patient. I have no personal experience with unboiled cellophane sheets, but am convinced that boiling of cellulose tubing is unnecessary. We have not boiled our tubing in the last 40 consecutive dialyses and we have had not a single pyrogenic reaction. With prolonged boiling or soaking the cellulose seems to lose some of its shininess and smoothness; the rough surface may injure the blood corpuscles.

Leukopenia and Thrombocytopenia. De Leeuw and Blaustein1 made microscopic studies of blood passed through the rotating type of artificial kidney, and observed that the cellulose tubing was coated with leukocytes. This explains the transient leukopenia observed during vividialysis. Transient thrombocytopenia may be similarly produced. De Leeuw and Blaustein’s experiments were performed with cellulose tubing that was boiled. Whether the unboiled cellulose attracts the leukocytes equally is not known. In the construction of artificial lungs, although polyethylene and cellulose are equally permeable for oxygen and carbon dioxide, polyethylene is preferred, since it is less likely to induce adherence of leukocytes and thrombocytes.

Hemolysis. With the rotating type of artificial kidney, hemolysis cannot always be avoided, but it is less often encountered with unboiled cellulose. Some patients with uremia have very fragile cells, and hemolytic anemia occurs without using the artificial kidney. Hemolysis should be avoided if it is at all possible, but there is no proof that it further impairs renal function in kidneys already severely damaged.

Change in Blood Pressure. Falls in blood pressure may be due to changes in blood volume or to substances comparable with the pyrogens. In the author’s experience falls in blood pressure are rare.

When the blood flow through the apparatus is 200 ml./min. or more, a rise in blood pressure frequently is observed; with lower flow rates it is unusual. This rise in blood pressure probably occurs with all types of artificial kidney. Usually the blood pressure returns to its previous level during the night after treatment. In patients in whom electrolyte disturbance can be ruled out, it seems most likely that some pressor substance has been formed in the blood during handling outside the body. Serotonin may be the substance. Page and McCubbin16 showed that serotonin infused in patients with hypertension is pressor.

Hemorrhage. The use of siliconized glass and plastic tubing has greatly reduced the need for heparin; consequently, the danger of hemorrhage usually is negligible. The problem still exists, however, in some patients who are referred to the artificial kidney as a last resort. A nasal hemorrhage or the trickle of blood from a fresh tracheotomy, running down the trachea, may be a fatal complication. At the end of dialysis, protamine sulfate (1 mg. for each mg. of heparin used) may immediately return the clotting time to normal. It should be given very slowly.

Experimental work is needed to learn how to eliminate the dangers of heparin. Several possibilities may lead to this goal. For example, heparin might be continuously administered through an automatic syringe on the arterial side, with protamine sulfate simultaneously being administered in the outflow end of the artificial kidney. Heparin might be removed by an anionic resin. Since heparin consists of a high percentage of ester sulfate, its affinity for certain resins might be greater than that of any other substance in the blood. The use of sodium citrate to bind calcium in the blood has been suggested as a means to prevent clotting, but
no practical way has yet been found. A calcium-binding resin might bind the calcium ion in the blood, as described by Clark, Gollan, and Smith. It might be used at the entrance to the artificial kidney. Calcium can be restored to the patient easily through another vein.

Postdialytic Oliguria. In patients with chronic uremia, urinary output may diminish on the day of, and on the day after, treatment with the artificial kidney. Merrill, Legrain, and Hoigne added urea to the rinsing fluid to maintain the blood urea while removing retention products other than urea. They observed no reduction in volume of urine and concluded that diminished diuresis is due to reduction of blood urea levels. This may not be the only explanation, since diuresis usually is restored before the blood urea has returned to its former level.

Overloading with Sodium from the Rinsing Fluid. The electrolyte content of the patient's blood plasma should not be restored to normal in the course of a single dialysis. Overloading with fluid and electrolytes of bilaterally nephrectomized dogs resulted in their developing a malignant type of hypertension, and a similar course is conceivable and must be carefully avoided in the virtually renoprival patient. Table 1 gives a suitable composition for the rinsing fluid.

INDICATIONS FOR TREATMENT WITH THE ARTIFICIAL KIDNEY

Acute Anuric Uremia

Treatment with the artificial kidney may be indicated during acute uremia due to any one of the following conditions.

1. Acute Tubular Necrosis (erroneously called "lower nephron nephrosis"), also called "acute tubular degeneration," "necrotizing nephrosis," and, in its most severe expression, "symmetrical cortical necrosis." Conditions favoring the occurrence of this type of tubular necrosis have in common a shocklike state (or impaired renal blood supply) and trauma. The shocklike state may be caused by extensive hemorrhage, especially retroplacental or postpartum hemorrhage. The trauma may be represented by massive, crushing wounds or multiple fractures. Additional factors may be severe fluid loss as in intestinal obstruction, or diarrhea, severe infection, especially peritonitis, and severe anoxia, as with carbon monoxide poisoning. Acute tubular necrosis often coincides with, and often is inseparable from, the conditions to be discussed later.

2. Hemoglobinuric and Myohemoglobinuric Nephrosis. The most frequent cause of free hemoglobin in blood plasma is a transfusion accident. Myohemoglobin from dead or crushed muscles forms casts similar to those of hemoglobin in the renal tubules. The causes of hemoglobinuric nephrosis include mismatched transfusions, overheating of bank blood, long storage at room temperature; bacterial growth during storage of bank blood, and subcutaneous instead of intravenous infusion of blood. Intra-vascular hemolysis may be caused by burns, heat (stroke), hemolytic anemia, icterus neonatorum, sickle cell crisis, intoxications, eclampsia, or various infections. Free hemoglobin also may appear when distilled water enters the veins, either when given accidentally instead of an isotonic solution, or in the course of transurethral prostatectomy.

3. Specific Renal Toxins. The damage previously discussed occurs focally in any part of a nephron, but renal poisons, such as bichloride of mercury, damage those specific parts that are concerned with handling the poison. The basic lesion is tubular necrosis without tubular rhesis. Unfortunately, large amounts of these poisons not only produce the specific changes but, because of fluid loss and circulatory collapse, also the lesions of focal ischemia. The toxic agents include the heavy metals and organic compounds such as carbon tetrachloride, diethylene glycol (antifreeze), alloxan, cresol,
mushroom poison, black widow poison, and serine. Other chemical toxins include phosphorus, chlorate ion, bichromate, tartrate, roentgen contrast media (especially after the high dosages used in angiokardiography21), and, rarely, the sulfonamides. Bacterial toxins of the staphylococcus, meningococcus, or typhoid bacillus may also cause acute anuria.

4. **Acute Glomerulonephritis.** Acute glomerulonephritis and septicemia with hemorrhagic glomerulitis may produce uremia and may be difficult to differentiate.

5. **Acute Obstruction of the Ureters.** Acute obstruction of the ureters may simulate tubular necrosis so closely that it is mentioned here, although other surgical obstructions are not discussed. An encroachment on the ureter from cancer of the bladder, uterus, or colon is a rather frequent occurrence. There may be no pain and the onset of renal shutdown may be acute. Acute obstruction of the ureters also may occur in pyelitis or in renal tuberculosis when a caseous mass blocks the ureter. Rarely, it is a complication of severe hematuria.

Sulfonamides may cause acute renal failure by allergic or toxic action with tubular necrosis, obstruction of the tubules with crystals or, most frequently, obstruction of the ureters with crystals. Only rarely, if ureteral catheterization does not lead to diuresis, will dialysis be indicated in patients with acute obstruction.

6. **Acute Pancreatitis.** In pancreatitis, oliguria of 600 to 700 ml./day is more common than is complete anuria. The tendency to improvement is slight.

7. **The Hepatorenal Syndrome.** This is not an entity. During severe hepatocellular damage, renal tubular necrosis often is found, either following the liver cell necrosis or following the primary damaging factor. Certain poisons, such as carbon tetrachloride, damage both the kidney and the liver. Cholangioliitis with icterus may be followed by glomerulonephritis.

8. **Acute Renal Failure Supernovening on Existing Renal Disease.** Chronic glomerulonephritis, pyelonephritis, or polycystic renal disease may deteriorate quite suddenly into an oliguric phase because of intercurrent infection, excessive vomiting, or other metabolic disturbances. Multiple myeloma with slightly impaired renal function, suddenly may produce acute anuria for unknown reasons. Acute renal failure supervening in these conditions should be treated as any other acute renal failure, in the hope that the previous state of equilibrium may be restored.

When should treatment with the artificial kidney begin during acute uremia? When an artificial kidney and team are available, dialysis should be used early in the course of uremia. The dangers of such treatment are negligible, and the clinical course of the disease is much milder if uremia is relieved early. This is especially true in aged patients prone to pulmonary and other complications that follow prolonged bed rest. Salisbury22 has pointed out that treatment with the artificial kidney should not be postponed until the patient is semicomatose and respiratory complications have appeared. It should not be postponed when the blood urea level is between 300 and 400 mg./100 ml.,* the serum potassium level is higher than 7 mEq./L., or the CO2-combining power is less than 12 mEq. I tend not to wait so long; I am guided largely by the clinical conditions of the patients, which may differ immensely at identical levels of retention products. Potassium intoxication can be relieved promptly by using the artificial kidney; the electrocardiogram returns to normal during the dialysis.

**Chronic Uremia**

Goldner, Gordon, and Danzig1 reported that of 20 patients with chronic uremia who had been previously treated conservatively and had shown little improvement, 7 showed remissions that lasted an average of 2 months. This clinical change often was longer than the "chemical" improvement.

In chronic uremia a single dialysis may break the spell of continuous vomiting and misery. Six hours of dialysis may be the equivalent of 6 weeks of difficult, frustrating, medical management. Some patients, seemingly in the terminal stage of uremia, have been restored to several months of useful living. If it is believed that the treatment will be worthwhile, the family of the patient must be told that the expected favorable results will be only temporary.

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* The blood urea level is expressed here in milligrams of urea, which is 2.14 times the blood urea nitrogen.
The combination of chronic uremia with malignant hypertension usually resists all attempts at improvement.

Other Indications for Treatment with the Artificial Kidney

1. Intoxications without Primary Nephrotoxic Actions. Some intoxications may be treated with the artificial kidney. According to Wolfe, bromide is more effectively removed by the artificial kidney than by the human kidney. The tubule is unable to distinguish between Cl and Br; the clearance of Br thus becomes a fraction of the total halide clearance and consequently is small. The artificial kidney clears bromide according to its own concentration gradient across the cellulosc membrane. Salicylates are removed well by dialysis. Of the barbiturates, some are dialyzable (pheno-barbital), some are slightly dialyzable (pentobarbital), but others are almost undialyzable while bound to plasma proteins (secobarbital), and amobarbital.

2. Dialysis as Preoperative or Postoperative Measure. Hemodialysis occasionally is of value in preparing a patient with uremia for surgery, especially if the objective of the operation is removal of the cause of the urinary suppression. In less critical cases, surgery may be performed first, and then dialysis may be undertaken if recovery is not prompt.

3. Intractable Edema as Indicator for Treatment. Intractable edema may occur in many clinical conditions and often complicates acute or chronic uremia. The artificial kidney designed by Skeggs, Leonards, and Heisler, when used as a dialyzer-ultrafilter, can remove 1000 to 1200 ml. of ultrafiltrate/hr. from a patient. Other types of filtering and dialyzing kidneys are less effective, according to Lunderquist, but they can be used. Hematocrit determinations must be made during treatment for recognition of too rapid dehydration. During the ultrafiltration we found it useful to maintain the circulating plasma volume with dextran. Since some oliguria may occur after treatment with ultrafiltration, it is necessary to restrict the patient’s fluid intake the following days. Sometimes diuresis follows a single treatment with a filtering-dialyzing artificial kidney. The purely dialyzing, nonfiltering types of artificial kidneys are less effective in removing edema but, by the addition of extra glucose (1.5 to 5 per cent) to the rinsing fluid considerable amounts of fluid may be removed from the patient. In this way, Lewis and associates induced a 4 Kg. loss in weight in 6 hours of dialysis.

Contraindications to Treatment with the Artificial Kidney

Active bleeding formerly was thought to be the only absolute contraindication to treatment with the artificial kidney, but even this concept has been shown to be unfounded according to the wartime experience of Meroney and Hendon in Korea.

Experimental Use of the Artificial Kidney

Experimentally, the artificial kidney deserves to become more widely used. It often has been used in the study of electrolyte changes. As early as 1926, Lim and Necheles used the artificial kidney to demonstrate a hormone, a gastric secretory excitant, in circulating blood. Skeggs and associates used it for the detection of angiotonin. Most important is that the artificial kidney in the hands of Grollman, Muirhead, and Vanatta prolonged the life of nephrectomized dogs, and led to the discovery of renoprival hypertension, which has revised thinking about the etiology of renal hypertension.

Conclusion

It may be asked whether the artificial kidney has justified the expectations expressed in its name. I believe that it has, and cite 5 reasons: 1. The artificial kidney can restore the electrolyte composition of the blood plasma more rapidly than can the natural kidney. 2. The artificial kidney can reverse the clinical picture of severe, acute uremia within 24 hours; in chronic uremia it often takes 2 to 4 days to obtain optimum improvement. 3. The artificial kidney displays its ameliorating effect in patients whose serum electrolytes are not disturbed or whose serum electrolytes are not changed by dialysis. Thus, the improvement
must depend upon the removal of retention products. 4. The artificial kidney prolongs the lives of experimental animals and of human beings devoid of renal function. 5. The artificial kidney does not duplicate some of the metabolic functions of the natural kidney, but none of those functions is indispensable for the maintenance of life in the acute conditions for which the artificial kidney originally was designed.

Summario in Interlingua
Le question es si le ren artificial ha justificate le espetationes exprimite in su nomine. Mi responsa personal es affirmative, e io lista cinque rationes pro mi attitude.
1. Le ren artificial succede plus rapidemente que le ren natural a restaurar le composition electrolytic del plasma sanguineum.
2. Le ren artificial es capace a revertir le configuration clinic de sever formas de acute uremia intra 24 horas. In cases of chronic uremia, meliorationes optimal es frequentemente obtenite in 2 a 4 dies.
3. Le ren artificial exerce su effectos meliorative in patientes sin disturbance o alteration dialytic del electrolutos seral. Ergo le melioration affectuate per le ren artificial debe resultar del ablation de productos de retention.
4. Le ren artificial prolonga le vita de animales experimental e de humanos sin functionamento renal.
5. Le ren artificial non exerce certe del functiones metabolic del ren natural, sed nulle de ille functiones es indispensable pro le preservation del vita sub le conditiones acute pro le quales le ren artificial escesse originalmente construite.

References
2 Rosenak, S. S.: Proceedings of the First Meeting of the American Society for Artificial Internal Organs, Atlantic City, New Jersey, June 5, 1955. Mimeographed copies available from Dr. Peter Salisbury, Cedars of Lebanon Hospital, 4833 Fountain Avenue, Los Angeles, California.
16 Page, I. H., and McCubbin, J. W.: Arterial pressure response to infused serotonin in normoten-
18 Orrison, J. L., Christian, C. L., and Peters, E.: Studies on experimental hypertension and cardio-
21 Miller, G. M., Wylie, E. J., and Hinman, F.,

Nine of a series of 44 hypertensive patients who came to necropsy after methonium or pentolinium therapy had dissecting aneurysm. Of the 44, 34 had malignant hypertension. Of the 34, dissecting aneurysm occurred in 6 (the other 3 cases were instances of benign hypertension). Among 89 cases of malignant hypertension not treated with the drugs mentioned only 1 case of dissecting aneurysm occurred. Among 200 control cases of benign hypertension were 6 of dissecting aneurysm. Therefore, use of the drugs was accompanied by an increase of the total incidence of dissecting aneurysm from 2 per cent (7/289) to 20 per cent (9/44)!

Review of the literature appears to confirm the impression that dissecting aneurysm is ordinarily relatively rare in malignant hypertension. As a basis of the observed increase with therapy the authors suggest the following possibilities: 1. Prolongation of life permits time for development of this complication. 2. Fluctuation of blood pressure encourages the development of dissecting aneurysm. 3. These hypotensive agents have a specific biochemical effect on the aorta.

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