THE USE OF AN ARTIFICIAL KIDNEY.[1] I. TECHNIQUE

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INTRODUCTION

The relative importance of the various retained metabolites in the production of the uremic syndrome has yet to be elucidated (1). Although in most instances uremia is the terminal evidence of irremedial kidney damage, the existence of a group of conditions leading to acute, reversible renal insufficiency necessitates a mechanism for maintaining life during the period of repair. This temporary compensation for renal failure has been attempted in several ways, the most important of which are:

(a) peritoneal lavage (2–4)
(b) intestinal lavage (5, 6)
(c) various types of "artificial kidneys."

Abel, Rowntree, and Turner in 1914 introduced the first "artificial kidney," dialyzing the blood of experimental animals through celloidin tubes, using hirudin as an anticoagulant (7). They realized the potentialities of this basic idea, but it has been only recently with the development of (*a*) effective anticoagulation with heparin, and (*b*) improved dialyzing membranes, that this same fundamental method has been of practical importance. It remained for Kolff to pioneer in the construction of a dialyzing apparatus proving to be successful in the therapy of uremia in man (8). This apparatus consisted of a long cellophane tube wound spirally about a large drum, which revolved horizontally in a bath of the dialysate. Blood was introduced into the tube from the radial artery and returned by a pump to an antecubital vein. Simultaneously with this important development in Holland, work was being carried out independently in Sweden by Alwall (9) and in Canada by Murray (10) on smaller apparatus, somewhat similar to each other. The cellophane tubing was wound spirally about a vertical, immobile cylinder or drum, fully immersed in a bath of dialysate, and used arterial pressure to advance the blood through the tubing. Newer models have been constructed by Rosenak (11), with the cellophane tubing wound concentrically in a horizontal plane, and by Skeggs and Leonard (12), with the flat sheet of cellophane between two longitudinally corrugated pads.

Some of the relative advantages and disadvantages of different methods will be discussed below. The basic similarity of all designs is evident. Overall, the practical ideals are (*a*) large dialyzing surface; (*b*) small volume of blood in the apparatus, *i.e.* "small deadspace"; (*c*) high diffusion gradient, *i.e.*, maintenance of low bath concentration of the metabolites; (*d*) optimum blood flow; (*e*) simplicity of design, construction, sterilization and immediate repair.

In theory such a system, made clinically safe and effective, might be applicable to problems of electrolyte and crystalloid imbalance other than acute reversible renal insufficiency. Such a possibility seemed to justify further experiment along these lines.

Our apparatus (Figures 1 and 2) is basically similar to that of Kolff. It consists of a rotating drum, on which the dialyzing membrane in the form of cellophane tubing,[3] is wrapped in a spiral fashion. Blood from the radial artery is conveyed into this tubing through a rotating coupling. The blood is then propelled by the rotation of the drum and the help of gravity through the cellophane to the distal end of the drum, where it leaves the machine by way of another rotating coupling. In its course along the drum, blood within the

[1] This study was supported in part by the John H. Harris Research Fund and the Medical-Surgical Research Fund of the Peter Bent Brigham Hospital.

[2] This work was done during the tenure of a Research Fellowship of the American Heart Association.

[3] "No Jax" seamless cellophane tubing, 23/32" inflated diameter is obtainable from Visking Corp., 6733 W. 65th St., Chicago, Ill.

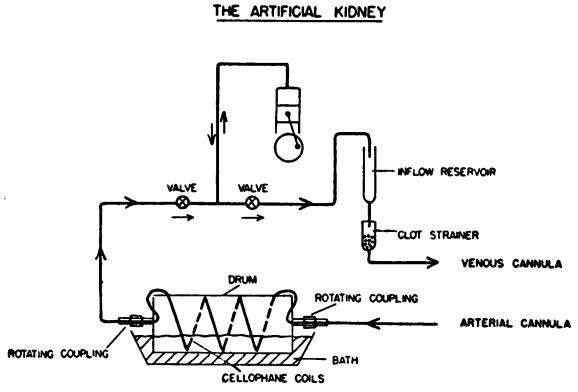

FIG. 1.

The valves allow blood to flow only in the direction of the arrows as indicated. The blood is aspirated into and expelled from the vertical tube between the valves with each cycle of the compressor and in this way is propelled to the inflow reservoir.

cellophane tubing is immersed in the bath fluid contained in the tank below, and dialysis is accomplished. On leaving the machine the blood is pumped into flasks which serve as air and clot traps and returned by gravity to the patient's vein.

In an attempt to overcome certain difficulties encountered in earlier trials with such an apparatus (8, 10, 13, 14), and to increase the safety and efficiency of the procedure for clinical use, we have made the following modifications. (Similar modifications have recently been reported by Vanatta [15] and Grollman [16] who have used the artificial kidney successfully in animal experimentation.)

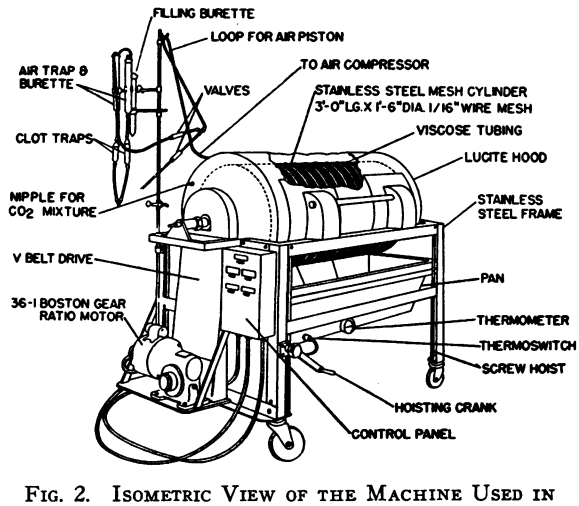

FIG. 2. ISOMETRIC VIEW OF THE MACHINE USED IN THESE STUDIES

GENERAL

Our machine has been constructed throughout of stainless steel.[4] The rotating drum is made of stainless steel wire mesh, with interstices fine enough so that a film of bath fluid is maintained over the drum even at the top of its circuit. This has the advantage of continuing dialyzing fluid contact with the blood film in the cellophane tube even though the top segment of the drum is not immersed. The drum is rotated at a constant speed of 25 revolutions per minute by a reduction-geared electric motor through a rubber V-belt drive. The operational noise of this arrangement is minimal. The bath is contained in a stainless steel pan, graduated to 100 L, which is raised or lowered by a motor driven hoist. The fluid is automatically maintained at a temperature of 101 degrees (F) by two thermostatically controlled heating units at the bottom of the pan. The elevation of the bath temperature above the physiological norm promotes ion exchange in the bath and returns the blood to the patient's vein at more nearly body temperature since some heat is lost in the circuit.

1) Clotting

One of the major problems in circulating a large volume of blood through an extensive system outside the body is the prevention of clotting. This must be accomplished ideally with the use of a minimum of anticoagulant, since frequently patients suitable for dialysis have lesions, surgical or otherwise, which may give rise to hemorrhage. Our approach to the problem of clotting has been careful selection of materials for conducting the blood which will minimize clot formation. We have replaced the rubber tubing in our system with "Tygon," [5] an inert, non-wettable, translucent modified vinyl material. The clotting time of blood placed in this tubing is definitely prolonged, although for inconstant intervals, when compared with the same blood placed in new acid-cured rubber tubing of the same internal diameter. Two 3" sections of rubber tubing are used near the cannulae, for the purpose of withdrawing arterial and

[4] Fabricated by Edward A. Olson, 120 W. Central St., Natick, Mass.

[5] "Tygon" tubing is obtainable from Macalaster Bicknell Co., 34 Broadway, Cambridge, Mass.

venous samples, since the plastic tubing is not self-sealing once perforated by a needle. With this exception the entire non-dialyzing tubing circuit is composed of Tygon.

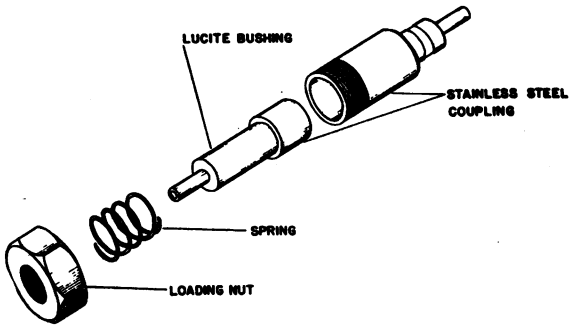

FIG. 3. THE ROTATING COUPLING

Exploded diagram of the rotating couplings. The Lucite bushing faces are normally in apposition within the steel jacket of the coupling.

The rotating couplings, which constitute an obviously vulnerable part and one in which clotting was frequently encountered by Kolff (8), have been redesigned in the form of a packless, spring-loaded butt box coupling (Figure 3). The box, loading nut, and shafts are made of a hardened stainless steel. The bore of the box, the ends and the exterior of the shafts are accurately ground to assure alignment. Each shaft is bored and countersunk to accomodate a highly polished Lucite bushing, the flange of which abutts its mate in the coupling. The sleeves of the bushings serve to conduct the blood through the shafts, one of which rotates with the drum, the other being keyed to the stationary box. One such coupling is at either end of the drum axle. Tygon tubing is attached to either end of the coupling to carry the blood.

A radial hole is drilled in the steel jacket of each coupling at the point of contact of the Lucite faces. This allows observation and cleansing of the periphery of the contact point, for, if considerable flow pressure is exerted by arterial inflow, a small amount of blood may exude from between the faces and must be removed. The coupling on the distal end of the axle is exposed to very little positive and to moderate negative pressure and no leakage is experienced at this point. A small piece of water-proof tape is placed over the radial hole to protect against influx of air into the system should the coupling become defective. No air leakage can be tolerated at any point if the run is to be successful.

Since turbulence in the blood circuit contributes to clotting, it was important that this factor be eliminated in so far as was possible. After considerable experimentation, a simple and effective pump was devised by suspending a loop of Tygon tubing in the shape of a narrow, inverted U. One limb of this U was connected to the pump while the other was attached to the center tube of a Y tube bearing one-way valves on either arm. In the negative phase, the blood rose in one limb of the U and in the positive phase was expelled from this limb. The height of the tubing was so adjusted that a safe margin remained between the highest position of the blood and the top of the inverted U. Thus in effect there was an air piston with the blood coming in contact only with the non-wettable surface of the Tygon tubing of an internal diameter of ¼". There is little observable turbulence in this system. A further modification has been to wind the pump tube spirally about a cylindrical form, thus diminishing the over-all height and dead-air space, but maintaining the same volume of effective displacement.

The source of alternating positive and negative pressure which acts on the blood is a modified refrigeration compressor with a displacement of 100 cc. running at 20 revolutions per minute. Under these conditions the system is capable of pumping about 400 cc. of blood per minute maximum. The modification of the compressor consisted of removing the valves and valve plate and plugging the oil return channel between the pressure port and the crank case. The cylinder head was then filled with babbitt to increase the compression ratio. The suction cock was closed tightly. The free end of the U tube was connected to the pressure port. The rate of pulsation is controlled by varying the speed of the ¼ H.P. motor which drives the compressor through a reduction-gear train. This modified compressor can be run continuously without overheating.

The construction of suitable valves was also a problem. Of necessity, to decrease hemolysis and clotting, these must be non-wettable, smooth-surface, have no projecting parts, and still meet the mechanical requirements of precise seating with no reflux. At present one type of valve meets those requirements as well as any of the many types we

have tried. This valve is constructed of polished Lucite (Figure 4).

The infusion burettes are made of Lucite, and the discharge from the pump is spilled down its side in a smooth stream rather than injected into the bottom of the blood column (8) with resultant fountaining, and turbulence.

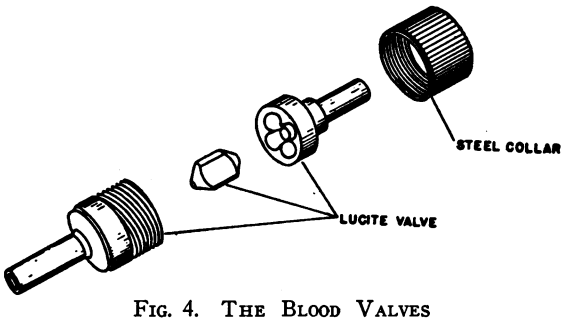

FIG. 4. THE BLOOD VALVES

The steel collar fits over the valve parts compressing the Lucite faces into an airtight seal.

The clot catcher is suspended directly beneath the infusion burettes. We found the metal bolting cloth and the perforated glass tubes unsatisfactory filters. Our present filters are small glass cylinders containing 6 mm. glass beads at the bottom and a thin layer of 4 mm. beads at the top. The flow through such an arrangement is as rapid as necessary, and the spacing seems to prevent additional clot formation. The tilting of the tubes at a 45 degree angle gives free flow over the upper edge, while small clots are removed and settle to the lower portion. As with all glass used in the system, those tubes are previously coated with silicone [6] (17, 18), an extremely effective non-wettable coating which has been found to prolong the clotting time of normal blood in tubes prepared in this way to six or eight hours (19).

With such precautions we have been able to carry out successful dialysis on a 72 kg. patient with a slow rate of blood flow through the machine (100 cc./min.) over a period of six hours using only 150 mg. of heparin. This compares favorably with the amount used in routine anticoagulant therapy.

2) Hemolysis

Coincident with turbulence is trauma to the red cells and resulting hemolysis. Blood used for filling the apparatus prior to dialysis should be as fresh as possible to increase the resistance of cells to mechanical trauma (20). The factors mentioned in connection with prevention of clotting combine to obviate hemolysis as well. The regulation of the osmotic pressure of the bath, described below, may play a role, in that the blood is brought in contact only with an isosmotic or hypertonic bath. In 60 clinical trials we have never observed gross hemolysis attributable to the apparatus. Hemochromogen values (21) for control and post-dialysis blood samples have on only two occasions shown increases above normal figures. In one a level of 12.8 mg.% (normal is 10 mg.%) was found after six hours of dialysis. The other, a patient with hepatitis and intravascular hemolysis started with a high initial level (41.8 mg.%) and rose to 61.6 mg.% over a period of six hours. In a subsequent dialysis on the same patient a high initial level fell slightly.

3) Pyrogen reactions

Pyrogen reactions of undetermined etiology have been a source of difficulty to investigators using *in vivo* dialysis (22). Pyrogens can enter the blood stream either from within the closed circuit itself, or by diffusion into it from the bath water. Naftulin, Wolf and Levinson (23) report that pyrogens do not cross the barrier imposed by heavy Viscose tubing, but the tubing employed by these authors was not intended for use as a dialyzing membrane. We, therefore, employed measures aimed at eliminating pyrogenic material both from within the circuit of tubing and from the bath itself.

Sterilization of the glass parts, rubber, and Tygon tubing is accomplished in saturated steam at 121 degrees (C) for 30 minutes. The Lucite burettes and valves are disinfected by immersion in 1 : 1000 aqueous Zephiran solution for at least 24 hours prior to the procedure. The same solution is instilled into the couplings, the ends of which are then occluded by clamps and left for a like period. The cellophane tubing is wound on a wooden reel and boiled for 30 minutes before use. In addition to sterilization this procedure serves to remove the glycerine coating with which the cellophane is prepared. After removal of glycerine coating, care must be taken to prevent drying of the cellophane, which, without its coating,

[6] "Dri-Film" No. 9987, General Electric Corp., Schenectady, N. Y.

will become excessively brittle when dry. The tubing, thus prepared, is fixed in place and after a small amount of saline has been washed through, about 100 cc. of matched bank blood is run into the machine and the cellophane observed closely for leaks which are quite easily detectable by this method. If all is in order, the system is then flushed with 10 L of sterile saline. With this method of preparation cultures taken from the extreme venous end of the circuit have been consistently negative for bacterial growth at the end of four days' incubation on both blood agar and thioglycolate. At the end of the dialysis the Tygon and cellophane tubing are discarded and the glass and Lucite parts thoroughly cleaned with detergent. The glass is then autoclaved and the Lucite immersed in Zephiran.

The bath constituents are made up in dry form save for $CaCl_2$ and $MgCl_2$, which, being deliquescent must be kept in solution. These solutions are sterilized after preparation to insure no bacterial growth during storage. The quantities are made up in such a fashion to allow for necessary variation of bath composition.

The tank is scrubbed with detergent after each procedure and its bottom constantly kept covered by a shallow layer of 1 : 1000 aqueous Zephiran to which sodium nitrite has been added as an antirust agent. Before dialysis the tank is rinsed with tap water.

Although we have not tested directly for pyrogens in the bath, the quantitative estimation of bacterial growth (Table I) does not seem significant following such preparation. To substantiate this clinically is the fact that to date we have not had a frank pyrogen reaction in any patient under treatment. Pyrogens in all likelihood do not pass the cellophane barrier and the lack of reaction is probably due to the care of the closed circuit and the use of disposable tubing (24–27).

4) Leaks

Occasional leaks in the cellophane tubing have been encountered. These can be repaired in a matter of minutes by cutting out the defective loop and splicing the adjacent coils over a small piece of rubber-covered glass tubing. Twenty cc. of blood are easily detectable in the 100 L bath, both by color change and by foaming. Since the pressure within the loops is always higher than that in the bath, and since the cellophane is collapsible, leaks are always from within out, and there is no danger of an infusion of bath water. We have made large rents in the tubing and found that particulate matter placed in the bath will not pass into the circulating fluid.

5) Flow control

The estimation and regulation of blood flow through the machine is of importance for a number of reasons. First, the total amount of metabolite extracted per unit time has a linear relationship to the rate of blood flow through the machine (Figure 5). This has a clinical analogue in the direct relationship between renal blood flow and urea clearance (30). However, preliminary observations have led us to believe that there is a flow limit in a system such as this, beyond which increased cardiac output is a result. Of 45 dialyses lasting more than three hours and conducted with a flow rate of better than 125 cc./min., 32 were accompanied by a rise in systolic pressure of 40 mm. or more of mercury. Diastolic pressure rise in these cases was of less magnitude but present in all 32 which showed the pressor response. The nature of the increase in blood pressure is not typical of arterio-venous shunt and may represent a response to a rapid inflow of high glucose content or removal of a vasodepressor substance. This will be discussed in detail in a later publication. Our clinical findings suggest that the limit of such flow is in the neighborhood of 200 cc./min. when blood is taken from the radial artery and returned to the brachial vein. Below this limit we have run without difficulty 15 patients with moderate degree of left heart failure. Such a flow limit must vary with the condition of the vascular system, but 200 cc./min. has seemed a safe approximation in our experience to date. It is possible that a circuit complete from vein to vein might obviate this difficulty. We have not attempted to cannulate the inferior vena cava, and the difficulty in obtaining adequate flow from other venous channels has limited our source to the radial artery. Since the rotary motion of the drum propels the blood to the distal end of the dialyzing tube, all excess blood in the system accumulates in the distensible terminal loop of cellophane. If this distention is

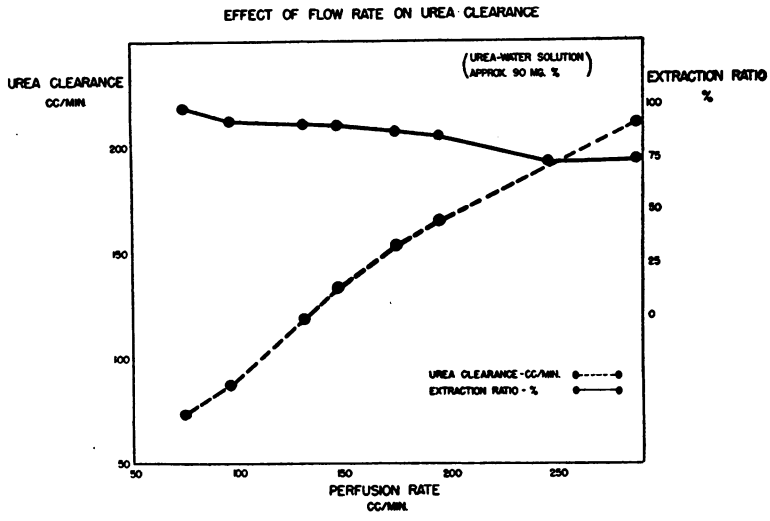

FIG. 5.

Urea clearance is expressed in terms of Van Slyke (28), *i.e.*, cc. of perfusate completely cleared of urea per minute. Extraction ratio indicates percentage of urea removed in one passage through the machine or

$$\frac{\text{arterial level} - \text{venous level}}{\text{arterial level}}.$$

As would be expected, the amount of urea extracted on one passage decreases with increased flow rate and thus briefer exposure to the bath of each unit of blood. This decrease, however, is slight, whereas the increase in total amount of urea removed per unit time has almost a linear relationship to increased flow. This is in accord with the findings of Alwall (29) in similar *in vitro* experiments dialyzing urea against water. The surface area of our dialyzing membrane is approximately three times as great as that used by Alwall in his stationary apparatus. At the optimum flow rates (about 200 cc./min.) the extraction ratio of the rotating apparatus is slightly less than twice as much. Thus, with flows of 215 cc./min. and a urea level of 125 mg.% and 250 mg.% Alwall (29) finds an extraction ratio of 40%. For similar flow rates at a concentration of only 90 mg.% the extraction ratio of the rotating apparatus is 76%.

constant, and the level in the inflow flask is maintained, it follows that the amount of blood in the system must be constant. Thus changes in the arterial flow are reflected by increasing retrograde distention of the terminal loop, while venous flow excess is quickly apparent in the dropping level of the burette reservoir. The flow is balanced by adjusting metered clamps on arterial and venous sides of the system, and, once balance is reached, it may be maintained without further adjustment for hours. It is thus possible by noting the rate of flow through the graduated burette to calculate the total rate of flow through the machine. With the present apparatus blood can either be added to or taken from the inflow flasks during the procedure. It is also possible temporarily to withdraw it from the patient's circulation by constricting the tubing proximal to the pump and pooling the blood in the distensible cellophane.

6) *Fluid exchange*

The problem of control of fluid balance has been approached by attempting to balance the osmotic pressure of the bath against that of the patient's serum. Estimation of the serum osmotic pressure may be made by determining the melting point depression. The simplified melting point method as suggested by Dr. R. H. Gordon, at that time a fourth year Harvard medical student, is presented in detail.

The apparatus consists of a Beckman freezing point thermometer and a metal stirring rod held in

a 30 mm. × 150 mm. test tube by a rubber stopper. The ice-acetone bath is prepared by finely chipping ice and covering it with acetone.

The solution of which the melting point is to be determined is placed in the test tube in sufficient amount to cover the mercury bulb of the thermometer. The test tube is then immersed in the ice-acetone bath and the solution continually agitated until a finely divided suspension of ice crystals is obtained (with protein solutions it is necessary to add one drop of caprylic alcohol to prevent foaming).

The ice-acetone bath is then removed and readings on the thermometer are taken every 30 seconds until the rate of increase in temperature seems uniform and then for every 15 seconds as the rise continues. A constant rate of agitation is necessary during this period.

On trial it will be seen that the temperature rises at uniform rate for a certain period. Then a rapidly increasing rate of warming begins to take place, continuing until the solution has completely melted.

Each determination requires that the stem error of the thermometer be calibrated by determining the melting point for distilled water. This value is variable depending greatly upon environmental conditions of temperature and air currents and should be made as close as possible to the time of freezing point determination of the unknown solution.

In calculating the freezing point it is necessary to graph the points obtained for both the stem error calibration and the unknown. Then the slopes of those curves at their most constant rates of change are determined by drawing a line through as great a number of points as possible before and after the change in velocity has taken place. By extrapolating these lines to a point where they intersect, a point is found which is assumed to represent the rate of greatest change of temperature gradient and hence is a fairly accurate approximation of the melting point of the solution after correction for the error of the thermometer by the values obtained using distilled water.

As close to the time of dialysis as possible blood is drawn from the patient and a serum melting point determined. Based on this figure, at the time of dialysis, a pre-calculated amount of glucose is added to the standard bath mixture such that its freezing point and thus its total osmotic pressure matches that of the patient's serum. The elimination of the effect of the fibrin difference between serum and plasma does not affect this calculation materially (31). In actual practice the bath is made slightly hypertonic to the patient's serum, since slight dehydration is easier to correct than excess of water. Hydremia can be corrected by making the bath markedly hypertonic.

7) Composition of the bath

The bath fluid contains the following constituents in 100 L of tapwater:

Gm./100 L of Tapwater			*Concentration (mEq/L)*
NaCl	660		113 (Na+)
KCl	30		4.0 (K+)
$NaHCO_3$	225		26.8 (Na+)
$CaCl_2$	40		7.2 (Ca++)
$MgCl_2$	10		2.1 (Mg++)
Glucose	200		6.2
		Total Na+	140.0
		Total Cl−	126.0

Total osmolarity 308 mOS/L

The melting point depression of the bath thus constituted is − 0.57 degree (C). The addition of each additional 100 Gm. of glucose depresses the melting point approximately − 0.01 degree. Thus the osmolarity of the bath can be matched with that of the patient's serum. Since glucose is diffusible through the membrane, it would seem advantageous to employ a substance which yields osmotic pull without passing the cellophane barrier. Of the several substances considered, gelatin seemed most suitable. However, gelatins available for medical use vary considerably in their molecular weight (32). The undegraded form, which would be necessary for our procedure, has an average molecular weight of 100,000. Comparison with the weight of the glucose molecule, 180, indicates that roughly 550 times as much gelatin as glucose is required to give equal osmotic effect. This fact, besides the difficulty of handling gelatin and other colloids, makes the use of such substances impractical.

The pH of the bath as constituted, is approximately 8.65 as determined by the Beckman pH meter. It is impossible to keep adequate amounts of calcium ion in solution since at this pH the solubility product of calcium carbonate is exceeded and the insoluble salt precipitated, particularly

with the addition of inorganic phosphate from the blood. At Kolff's suggestion we have enclosed the drum with a plastic hood, the bottom of which makes a waterseal with the liquid in the bath. Into this space enclosed by the hood, CO_2 or a mixture of CO_2 and oxygen is introduced at a flow of 3–4 L a minute and it is possible, thus, to saturate the bath with CO_2, reducing the pH and enabling the calcium ion to remain in solution. Saturation with 5% CO_2, 95% air or oxygen mixture reduces the pH to 7.6 while use of 100% CO_2 lowers it to 7.1. Our present practice is to use the 5% CO_2 mixture, and to change the bath frequently enough to prevent accumulation of prohibitive phosphate levels. In contrast to the observations of MacLean and his associates (13), we have observed in every case of acidosis a rise in the CO_2 combining power of the blood during dialysis.

PREPARATION OF THE PATIENT FOR DIALYSIS

Certain fundamental observations must be made prior to use of the artificial kidney. In cases where time is of an essence these need not necessarily be as complete as listed below, but it must be stressed that we feel that a complete and painstaking preparation has been a major contributing factor in decreasing the risk and possible complications of the procedure.

In the complete history and physical examination of a patient, emphasis is placed on previous history of renal or cardio-vascular disease. Detailed and explicit information on previous therapy, and fluid balance in the period immediately prior to admission is of paramount importance. Since it is possible to remove water as well as retained metabolites, evidence of over-hydration should be sought.

TABLE I

Cultures of bath fluid

Hours	Thio-glycolate	Pour plates	Blood agar streak
0	No growth in four days	One colony gram-positive spore-forming bacillus per cc.	No growth in four days
1	Growth in 48 hours	One colony gram-positive spore-forming rods per cc. in 48 hrs.	No growth in four days
2	Gram-positive	Three colonies gram-positive coccobacilli in 48 hours	No growth in four days

This should be corroborated by determinations of the venous pressure and circulation time, as well as by physical signs of peripheral or pulmonary edema. An electrocardiogram may serve to demonstrate evidence of underlying cardiac disease and, equally important, may give the first clue to early potassium intoxication (33).

Evidence by history or physical examination of bleeding is important in relation to the use of heparin during dialysis. In our experience, recent surgery or even hematemesis has not been a contraindication when the procedure was deemed to be life saving, and in one case who vomited 300 cc. of dark blood one-half hour prior to heparinization, no further bleeding was encountered. Protamine sulphate (34), which rapidly counteracts the action of heparin, is available, if necessary, and has been used prophylactically in three patients following the dialysis, with no ill effect.

CHEMICAL DETERMINATION

Essential determinations made on the blood include values for blood urea nitrogen, non-protein nitrogen, total serum protein, serum chloride, carbon dioxide combining power and serum sodium or total base. In the anuric or oliguric patient a determination of the serum potassium value is of great importance. A complete blood count is done on admission, although in following the progress of a patient, changes in hematocrit are most valuable. Prior to the procedure, but not essential to evaluation of the patient, blood is taken for determination of uric acid, phosphate and creatinine content. A clotting time is done before the administration of heparin. In some cases a heparin tolerance test (35) may be of value. It should be stressed, however, that patients with liver disease and prolonged prothrombin times in our experience require as much or more heparin than do patients with normal liver function to prevent clotting in the extravascular circuit.

These determinations having been completed, the patient on the day of dialysis is carefully weighed so that following the procedure, reweighing may yield information about fluid loss or gain. Mild sedation may be administered, if necessary, though it is frequently obviated by the somnolence of the uremic patient. If barbiturate is used, it

should be one of the short-acting drugs which is detoxified by the liver, although *in vitro* clearances have proved that all barbiturate salts easily pass the cellophane barrier of the artificial kidney and thus should be cleared from the blood during the course of the dialysis. Morphine or demerol, dosage to be gauged by clinical evaluation of the patient, may be used. However, the uremic patient is prone to vomit and since such vomiting may be aggravated during the latter part of dialysis, the role of morphine in potentiating this vomiting should be considered. Dramamine®, 100 mg. by mouth one hour before dialysis and every three hours during the procedure, has minimized nausea and vomiting in many cases. The discomfort incident to the cut-down and cannulation of the vessels requires little analgesia other than local procaine infiltration and for a reason as yet not completely clear, the patient, whose rinsing bath contains high concentrations of glucose, frequently becomes drowsy toward the end of a six or seven hour procedure. On the other hand, it is not unusual to have a semi-comatose patient become alert enough during the dialysis to become mildly anxious about his surroundings. In any case, since one does not wish to confuse the clinical issue with heavy sedation, it is wiser to employ only small dosages, repeated frequently, if necessary. There is no subjective sensation other than slight discomfort from the cannulae, once the procedure has been established.

During the procedure hourly hematocrits are drawn for further check on hydration and hemolysis. A 15 minute chart of pulse, respiration, blood pressure, and temperature is kept during dialysis, and at half-hourly intervals thereafter for four hours. Complete blood chemistries are drawn from the arterial tube at the beginning and end of the procedure, and as frequently between these periods as necessary. Penicillin, 200,000 units intramuscularly, is given before and after the procedure to minimize risk of infection in the cut-down wounds.

TECHNIQUE OF ATTACHMENT

The apparatus, having been tested for leaks in the cellophane, is flushed with saline. The arm on the side selected for cannulation is surgically prepared and draped, and the vessels exposed and cannulated under local procaine infiltration. It is wise to have selected a suitable vein and request that this vessel be spared the risk of thrombosis incident to hypertonic glucose infusions in the days preceding dialysis. The vein should be as large as possible since adequate clearance of metabolites has a linear relationship to blood flow through the machine (Figure 5) and thus the vein must be capable of handling a flow of at least 200 cc./min.

We employ silicone-coated glass cannulae tied into the radial artery and into any adequate-sized forearm vein. The venous cannula is placed first, heparin administered through this, and then the arterial cannula tied in place. The precaution of palpating the ulnar artery should be taken, since the radial artery is tied off on removal of the cannulae, and an adequate anastomotic channel should be present. Our patients have experienced no circulatory difficulty following ligation of the radial artery. The arterial cannula is inserted as far distally as possible and with this technique, we have been able to cannulate the same artery three times at intervals of approximately one week, the cannula at each procedure being inserted about 1 cm. higher than the previous position. No signs or symptoms of circulatory difficulty were encountered. Retrograde thrombosis extends proximally about ½ cm. in the artery. When extreme thickening of the intima and narrowing of the lumen is encountered it is necessary either to cannulate the vessels higher in the arm, or to connect both radial arteries by a Y tube in order to obtain adequate flow. An inadequate vein may also be supplemented by such a Y connection to another vein.

The problem of oozing from incisions in the heparinized patient is a real one. As suggested by Alwall (9), this may be minimized by exposing the vessels an hour or two before the cannulae are inserted and the patient heparinized. The small vessels thus have time to clot before anticoagulant is given, the wound being kept moist with sterile saline packs until ready. This, however, is inconvenient, and we have found bleeding to be well controlled by the topical application of thrombin and a matrix such as fibrin foam or Oxycel. Pressure bandaging around the cannula provides additional hemostasis. Placing and fixing skin ties under tension facilitates such pressure control.

Initiation of Flow

The "dead space" in the cellophane and plastic tubing is eliminated by filling with banked blood. This should be freshly drawn (not more than 48 hours old) to insure maximum stability of red blood cells (20). The amount used is approximately 500 cc. The arterial and venous tubes are connected to the apparatus and the clamps constricting them opened simultaneously. Thus, as the first portion of blood passes from the patient's radial artery into the machine, an equal portion of banked blood from the inflow flasks enters the patient's vein. This balance of flow can be so adjusted that there is no change in the pulse rate or blood pressure with the institution of blood flow through the artificial kidney. Since the distensible cellophane and the 200 cc. inflow flasks constitute potential reservoirs, a predominance of either arterial outflow or venous inflow may be temporarily established by appropriate adjustment of the clamps on the tubing.

EFFICACY

The efficacy of the apparatus in removing metabolites is dependent mainly on three factors: *1*) rate of flow through the cellophane, *2*) load of metabolite in the infused blood, and *3*) dialyzing area (Figures 5 and 6). This is in keeping with factors affecting clearance in the human kidney, and should be taken into account in any comparison of the efficacy of methods for extracorporeal dialysis (30, 36). To a lesser extent there is some dependence on temperature of the bath, and on frequency with which the bath is changed and thus a new diffusion gradient established. We have found that differing sizes of cellophane tubing give approximately equal clearance when maximal amounts are used on the drum. We employ tubing with inflated diameter of 23/32", having found that smaller tubing is not adequately flattened by the motion of the drum, while larger tubing wrinkles, in both cases decreasing efficiency per unit of contained blood. In addition, tubing with larger internal diameter has greater thickness, and thus decreased permeability.

Because of the high extraction ratio with the 23 coils employed, the possibility arose that some of the terminal coils might be unnecessary, since they might be carrying blood from which so much metabolite had been removed that the diffusion gradient was relatively ineffective. Figure 6, however, shows that the clearance drops rather sharply with reduction of surface area below the maximum for our apparatus. Table II shows amounts of nitrogen metabolite removed for given

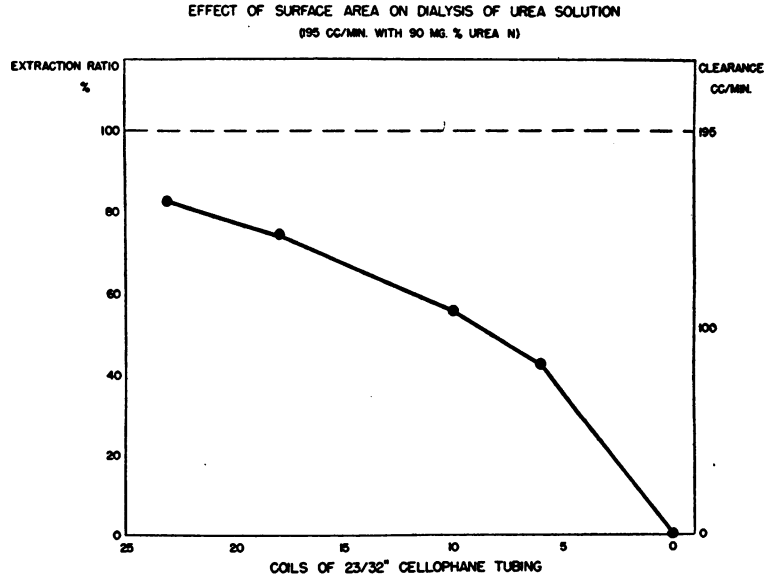

FIG. 6.

The effect of diminishing surface area (*i.e.*, coils of cellophane) on the efficiency of the machine during an *in vitro* experiment.

TABLE II

Patient	Dialysis		BUN		NPN		Total urea N removed	Total NPN removed
	Blood flow	Duration	Initial	Final	Initial	Final		
	cc./min.	*hours*					*Gm.*	*Gm.*
G. S. (*1*)	50	1.5	98	94	190	154	12	24
G. S. (*2*)	50	2	83	83	168	124	23	28
P. P. (*1*)	50	0.5	75	68	112	108		
P. P. (*2*)	50	1	75	71	127	102	4	4
M. A.	125	5	64	44	114	69	18	27
D. C. (*1*)	200	6	121	89	317	139		
D. C. (*2*)	250	5	100	95	271	191	67	
D. C. (*3*)	200	3	115	102	250	159	36	
D. C. (*4*)	200	3	99	92	267	197		
J. B.	200	5	86	50	161	95	31	31
F. M. (*1*)	225	4	80	45	173	105	23	28
F. M. (*2*)	225	6	60	30	150	74	29	40
J. L.	200	4	92	42	114	66	24	28
J. C. (*1*)	150	3	111	101	186	128	24	28
J. C. (*2*)	200	3.5	97	78	184	130	29	32
C. P.	250	5	92	63	162	93	36	
J. B.	125	7	95	32	155	62	31	39
R. M.	300	5	79	38	151	68	24	38
D. B.	200	5	93	41	145	53	24	40
J. M.	150	5	64	33	94	58	18	19
M. L.	175	5	99	77	281	125	50	56
R. S.	200	7	102	60	268	80	45	49
A. M.	50	3	43	41				
O. B.	125	5	40	18	60	39	11	
L. B.	200	5	84	24	116	54	19	25
R. R.	125	7	87	48	228	82	29	38
M. R.	250	6	97	65	222	83	54	63
F. S.	75	4	74	31	99	50	5	10
K. B.	200	6	72	48	162	64	29	35
A. S.	130	6	88	67	200	100	36	38
T. R.	220	6	60	22	86	36	19	25
F. B.	250	5	38	20	66	34	16	18
M. F.	200	5	81	39	200	78	25	33
Alwall (27)								
1		6			418	320		45
2		8			235	182		18*
3 (*1*)	100	5			346	182		34
(*2*)	100	8			200	77		28
Murray (10)								
1		8+			120	105		6.6
		6½			100	100		6.0

* Only 60% cellophane surface employed.

Not infrequently large amounts of urea may be removed without a corresponding drop in the blood urea nitrogen. This is particularly true when there is an initial elevation of total non-protein nitrogen out of proportion to the urea nitrogen fraction. In such cases drop in serum non-protein nitrogen correlated more closely with the non-protein nitrogen recovered in the bath fluid.

serum level and flow rate in the first 33 clinical cases. Values are compared with those reported by other observers. In addition, sulfonamides and barbiturates are dialyzable, and such procedures may find clinical or experimental application. Preliminary results on the removal of alpha amino acids in patients with normal and inadequate liver function have contributed data of physiologic interest (*37*).

SUMMARY AND CONCLUSIONS

The technique for use of an artificial kidney of the Kolff type has been described.

The use of plastic materials and the treatment of glass parts with an anti-wetting agent has decreased the hazard of clotting and reduced the amount of heparin necessary to within the usual therapeutic range.

Modifications of the rotating couplings and a

new type of blood pump have been described. These have minimized trauma to red blood cells and decreased turbulence in the blood circulating through the apparatus.

The use of disposable plastic tubing, and careful attention to sterile technique has eliminated pyrogen reactions as a cause of concern.

Methods for estimating and controlling flow through the apparatus have been described. Careful adjustment of this factor decreases stress on the cardio-vascular system and has enabled us to employ this technique safely in patients with congestive heart failure.

By enclosing the drum and bath in a hood, the rinsing fluid can be saturated with 5% CO_2. This lowers the pH of the bath fluid and permits calcium to remain in soluble form, thus preventing its removal from the blood.

With such modifications the artificial kidney has proved to be a safe and efficient method for the removal and addition of diffusible substances in the blood.

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BIBLIOGRAPHY

1. Harrison, T. R., and Mason, M. F., The pathogenesis of the uremic syndrome. Medicine, 1937, **16**, 1.
2. Fine, J., Frank, H. A., and Seligman, A. M., The treatment of acute renal failure by peritoneal irrigation. Ann. Surg., 1946, **124**, 857.
3. Frank, H. A., Seligman, A. M., and Fine, J., Treatment of uremia after acute renal failure by peritoneal irrigation. J. A. M. A., 1946, **130**, 703.
4. Goodyear, W. E., and Beard, D. E., The successful treatment of acute renal failure by peritoneal irrigation. J. A. M. A. 1947, **133**, 1208.
5. Maluf, N. S. R., Urea clearance by perfusion of the entire intact small intestine in man. Federation Proc., 1948, **7**, 77.
6. Odel, H. M., and Ferris, D. O., Continuous lavage of the small intestine as a means of treating renal insufficiency: report of a case. Proc. Staff Meet. Mayo Clin., 1948, **23**, 201.
7. Abel, J. J., Rowntree, L. B., and Turner, B. B., On the removal of diffusible substances from the circulating blood of living animals by dialysis. J. Pharmacol. & Exper. Therap., 1914, **5**, 275.
8. Kolff, W. J., New Ways of Treating Uremia; the Artificial Kidney, Peritoneal Lavage, Intestinal Lavage. J. & A. Churchill, Ltd., London, 1947.
9. Alwall, N., On the artificial kidney. I. Apparatus for dialysis of the blood *in vivo*. Acta med. Scandinav., 1947, **128**, 317.
10. Murray, G., Development of an artificial kidney: experimental and clinical experiences. Arch. Surg., 1947, **55**, 505.
11. Rosenak, S., Personal communication.
12. Skeggs, L. T., Jr., and Leonard, J. R., Studies on an artificial kidney. I. Preliminary results with a new type of continuous dialyzer. Science, 1948, **108**, 212.
13. MacLean, G., Ripstein, C. B., de Leeuw, N. K. M., and Miller, G. G., The use of the artificial kidney in the treatment of uremia. Canad. M. A. J., 1948, **58**, 427.
14. Muirhead, E. E., and Vanatta, J. C., Use of the artificial kidney. Am. J. Med., 1948, **4**, 467.
15. Vanatta, J., Muirhead, E. E., and Grollman, A., Improvements on the artificial kidney: an experimental study of its application to dogs bilaterally nephrectomized or otherwise deprived of renal function. Am. J. Physiol., 1949, **156**, 443.
16. Grollman, A., Muirhead, E. E., and Vanatta, J., Role of the kidney in pathogenesis of hypertension as determined by a study of the effects of bilateral nephrectomy and other experimental procedures on the blood pressure of the dog. Am. J. Physiol., 1949, **157**, 21.
17. Jaques, L. B., Fidler, E., Feldsted, E. T., and Macdonald, A. G., Silicones and blood coagulation. Canad. M. A. J., 1946, **55**, 26.
18. Moloney, W. C., Murphy, A. S., and Harrington, W. J., Prolongation of the coagulation of whole blood by dicoumarol in man. Am. J. Med., 1948, **5**, 40.
19. Moloney, W. C., Personal communication.
20. Rapoport, S., Dimensional, osmotic, and chemical changes of erythrocytes in stored blood. I. Blood preserved in sodium citrate, neutral, and acid citrate-glucose (ACD) mixtures. J. Clin. Invest., 1947, **26**, 591.
21. Flink, E. B., and Watson, C. J., Method for the quantitative determination of hemoglobin and related heme pigments in feces, urine and blood plasma. J. Biol. Chem., 1942, **146**, 171.
22. Kolff, W., Personal communication.
23. Naftulin, H., Wolf, A. M., and Levinson, S. O., Viscose tubing for transfusions. J. A. M. A., 1943, **123**, 321.
24. Walter, C. W., Preparation of safe intravenous solutions. Surg., Gynec. & Obst., 1936, **63**, 643.
25. Walter, C. W., Aseptic Treatment of Wounds. Macmillan Co., New York, 1948.
26. Lewisohn, R., and Rosenthal, N., Prevention of chills following transfusion of citrated blood. J. A. M. A., 1933, **100**, 466.
27. Hartman, F. W., Elimination of rubber tubing on intravenous sets; new system for administration of intravenous solutions. Ann. Surg., 1940, **111**, 498.

28. Van Slyke, D. D., The urea clearance as a measure of renal function. Am. J. M. Sc., 1936, **2**, 42.
29. Alwall, N., and Norviit, L., On artificial kidney. II. Effectivity of apparatus. Acta med. Scandinav., 1947, Supp. 196, 250.
30. Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A., The relationship of the urea clearance to the renal blood flow. Am. J. Physiol., 1934, **110**, 387.
31. Findlay, A., Physical Chemistry for Students of Medicine. Longmans, Green & Co., New York, 1938.
32. Oncley, J. L., and Brown, A., Dimensions of certain plasma components and of suggested "blood substitutes." Memoranda and Reports on Physical Chemical Studies of Gelatin and Other Blood Substitutes, O.S.R.D., Washington, D. C., 1944.
33. Merrill, J. P., Levine, H. D., Somerville, W., and Smith, S., III, Clinical recognition and treatment of acute spontaneous potassium intoxication. To be published.
34. Jorpes, E., Edman, P., and Thanning, T., Neutralization of action of heparin by protamine. Lancet, 1939, **2**, 975.
35. de Takats, G., Heparin tolerance, test of clotting method. Surg., Gynec. and Obst., 1943, **77**, 31.
36. Gamble, J. L., Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. Harvard University Press, 1947.
37. Merrill, J. P., Smith, S., III, Callahan, E. J., III, and Thorn, G. W., The use of an artificial kidney. II. Clinical experiences. J. Clin. Invest., 1950, **29**, 425.