THE USE OF AN ARTIFICIAL KIDNEY.[1] II. CLINICAL EXPERIENCE

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The technique of construction and use of an artificial kidney modified from the basic design of Kolff (1) has been described elsewhere (2). This paper describes our clinical experience in 60 instances in which this procedure has been employed in the treatment of 43 patients (Table I). It is not possible at the present time to draw definite conclusions as to the efficacy of such a procedure in the general treatment of renal disease, but our results seem to indicate: (1) that the use of an artificial kidney is a feasible method for the removal of specific diffusible substances from the circulating blood; (2) that it can be accomplished without excess hazard to the patient; (3) that it can be repeated if necessary; (4) that its use should not be postponed so that it is offered to the patient as a last resort because other methods of treatment have failed; and (5) that in addition to nitrogen metabolites it is possible to remove other diffusible substances which may be toxic in high concentrations, such as the barbiturates and sulfonamides. It is also possible selectively to remove sodium, potassium, calcium, and water. In patients with specific mineral depletion these substances may be restored without the addition of other electrolyte or water. In anuric, sodium-depleted patients this last function may be extremely valuable.

In essence the principle of application of the artificial kidney is as follows: Blood is led from the radial artery by means of an inlying glass cannula through a rotating coupling to the surface of a revolving metal drum. Here it passes through a length of cellophane tubing wound spirally around the drum, and is carried by the motion of the drum to the distal end. During its course, the blood-filled tubing is passed through a rinsing fluid (2) maintained at a constant temperature of 101 degrees F in a 100 L container. Into this medium diffusion from the blood takes place through the cellophane membrane. Distally, the blood is passed through a second rotating coupling, and pumped to inflow flasks, whence it is fed by gravity to a vein in the forearm through another inlying cannula (2). The conducting tubing is Tygon, a plastic non-wettable material which can be autoclaved. The glass cannulae and connecting tubes are coated with silicone (3) and other parts in contact with the blood, including valves, couplings, and inflow flasks are made of Lucite, another type of plastic material which materially reduces clotting difficulties.

METHODS

The following methods were used to determine the values under consideration in this study. The blood urea nitrogen was determined by the method of Archibald (4); blood non-protein nitrogen and non-protein nitrogen of the bath by the method of Daly (5); serum chloride by the method of Schales and Schales (6); serum CO_2 combining power by the manometric method of Van Slyke ([7], p. 269); total serum base by the method of Sunderman (8); potassium and sodium were determined by the flame photometer using the internal lithium standard (9); determination of the uric acid of the serum and the dialysate was done by the method of Kern and Stransky (10); and the urea nitrogen of the bath was determined by the method Van Slyke ([7], p. 490). The serum and bath inorganic phosphate was determined by the method of Fiske and Subbarow (11) and serum calcium was done by the method of Clark and Collip (12). Hematocrits were estimated by the method of Wintrobe (13), while clotting times were performed by the tube method of Lee and White (14). The heparin tolerance test was done according to the method of de Takats (15).

As a guide to adjustment of the tonicity of the bath fluid, we use the estimation of the serum melting point (2). As close to the time of dialysis as is practical, 25 cc. of blood are drawn from the patient and the serum melting point determined by

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TABLE I

Analysis of cases subjected to dialysis

No.	Patient	Sex	Age	Diagnosis and complications	Procedure No.	Duration of dialysis	Hypertensive response	Living one mo. after dialysis	Result
						hrs.			
1	G. S.	M	25	Chronic glomerulonephritis with uremia	1 2	2 2	No No	No —	Good immediate results. Died 1 wk. later.
2	P. P.	M	25	Chronic glomerulonephritis with uremia	3 4 5	¾ 1½ 1	No No No	Yes — —	Good clinical result. Condition stabilized on discharge.
3	M. A.	F	34	Diabetes mellitus, arteriolar nephrosclerosis, uremia	6	5	No	No	Died 2 days after dialysis. ? as a result of hypoglycemia.
4	D. C.	M	65	Lower nephron nephrosis due to intravascular hemolysis. P.O. choledochostomy, septicemia	7 8 9 10 11	6 5½ 3 3 1	No No Sl No No	No — — — —	Died of septicemia with recovering renal function.
5	J. B.	M	20	Acute anuria type undetermined	12	5	Yes	Yes	Complete recovery.
6	F. M.	M	79	Lower nephron nephrosis, P.O. transurethral prostatectomy	13 14	4 6	Yes Yes	No —	Died of cardiac failure 2 days after dialysis.
7	L. G.	F	25	Bilateral cortical necrosis of the kidneys following premature separation of placenta	15	1	?	No	Died 3 days post-dialysis. P.M. showed also infarction of pituitary and hypothalamus.
8	J. L.	M	59	Arteriolar nephrosclerosis, uremia	16	4	No	No	Little improvement. Died 20 days after dialysis.
9	J. C.	M	48	Embolic glomerulonephritis S.B.E.; potassium intoxication	17 18	3 3	Yes Yes	No —	Potassium intoxication relieved. Died in uremia and potassium intoxication 5 days after dialysis.
10	C. P.	M	32	Chronic glomerulonephritis with uremia	19	5	Yes	No	Poor subjective improvement. Died 3 wks. after dialysis.
11	J. Be.	F	35	? Cortical necrosis after premature separation of placenta; acute potassium intoxication	20	7	No	Yes	Full recovery.
12	R. M.	M	47	Lower nephron syndrome due to carbon tetrachloride intoxication	21	5	Yes	Yes	Full recovery.
13	D. B.	M	56	Chronic pyelonephritis and uremia	22	5	Yes	Yes	Well stabilized with mild azotemia.
14	J. M.	M	56	Diabetes mellitus, nephrosclerosis, uremia	23	5	Yes	Yes	Improved. Died of coronary 3 mo. later.
15	M. L.	F	52	Arteriolar nephrosclerosis, uremia	24	5	Yes	No	Transiently improved but died 3 days later in uremia.
16	R. S.	M	35	Anuria, cause? hypotension, P.O. subtotal gastrectomy	25 26	7 1	Yes No	No —	Excellent immediate response but died in shock next day. P.M. showed pulmonary infarcts.
17	A. McL.	F	54	Hematemesis, episodes of hypotension and shock with later hypernatremia and hyperchloremia	27	3	No	Yes	Immediate improvement with full recovery.

TABLE I—*Continued*

No.	Patient	Sex	Age	Diagnosis and complications	Procedure No.	Duration of dialysis	Hypertensive response	Living one mo. after dialysis	Result
						hrs.			
18	O. B.	M	75	Obstructive jaundice with hepatorenal syndrome P.O. Choledochostomy	28 29	5 2	Yes Yes	Yes —	Good response in all respects. Recovered.
19	L. B.	F	43	Anuria, P.O. rt. nephrectomy for renal calculi, hyperparathyroidism	30	5	Yes	Yes	Immediate improvement with full recovery.
20	R. R.	F	71	Anuria, c.v. thrombosis, arteriolar nephrosclerosis	31	7	Yes	No	Good chemical result. Remained comatose and died 8 hrs. later.
21	M. R.	F	63	Anuria, cholecystitis, cholangitis with jaundice	32	6	Yes	No	Diuresed after dialysis, improved though liver function poor.
22	T. S.	M	3½	Nephrotic syndrome	33	4	Yes	Yes	Mod. improvement but for short duration.
23	K. B.	F	35	?Cortical necrosis following pre-eclamptic delivery; acute potassium intoxication	34	6	Yes	Yes	Immediate improvement with full recovery.
24	J. Z.	F	23	Subacute yellow atrophy of liver	35	6	No	No	No change in downward course.
25	A. S.	F	39	Chronic pyelonephritis and uremia	36	6	Yes	No	No clinical improvement. Died 4 days later.
26	T. R.	M	45	Chronic glomerulonephritis and uremia	37 53	6 7	Yes Yes	Yes No	Good response. Stabilized well for 4 mos. Good clinical result. Died in uremia 2 wks. later.
27	F. B.	M	34	Chronic glomerulonephritis	38 55	6 6	Yes Yes	Yes No	Good response. Improved for 3 mos. Died in uremia 1 wk. later.
28	A. L.	M	63	Gout, severe	39	4	No	Yes	No change.
29	M. F.	F	35	Anuria following pre-eclamptic delivery of stillborn infant; acute potassium intoxication	40	5	No	Yes	Immediate improvement and full recovery.
30	M. L.	F	29	Edema of undetermined cause	41	5	No	Yes	Wt. loss of 3.6 kg.
31	F. G.	M	70	Lower nephron syndrome following cystectomy	42	5	No	No	Diuresed. Died of P.O. complications.
32	M. K.	F	43	Diabetes with K-W syndrome	43	6	Yes	No	Good chemical response. Died in uremia.
33	M. O'H.	M	51	Pyelonephritis with renal calculi bilaterally	44	6	Sl.	No	Died 2 days later in shock. P.M. pyelonephritis with hepatic necrosis.
34	G. E.	M	67	Lower nephron syndrome after TUR; potassium intoxication	45	6	Yes	Yes	Slow to diurese but full recovery.
35	J. R.	M	63	Sulfathiazole intoxication with CNS damage	46	6	Yes	No	No improvement. Died 1 day later.

TABLE I—*Continued*

No.	Patient	Sex	Age	Diagnosis and complications	Procedure No.	Duration of dialysis	Hypertensive response	Living one mo. after dialysis	Result
						hrs.			
36	J. L.	M	65	Lower nephron syndrome, acute colitis, salmonella	47	5½	No	Yes	Moderate improvement.
					49	6	Sl.	Yes	Good improvement and full recovery.
37	G. H.	M	51	Lower nephron syndrome. P.O. sympathectomy, shock, Bronchiectasis	48	6	Sl.	No	Died of bleeding duodenal ulcer. P.M. showed amyloid kidneys.
38	D. O'L.	M	65	Chronic glomuleronephritis and pyelonephritis	50	6	Yes	No	Improved.
					54	6	Yes	No	Died 2 wks. later with septicemia.
39	J. C.	M	43	Subacute glom. nephritis	51	6	Yes	No	Improved but died 4 days later.
40	W. F.	M	24	Subacute glom. nephritis	52	6	Yes	No	Improved. Died 2 days later of coronary occlusion.
41	M. McA.	M	54	Acute dehydration P.O. P.G.E.	56	*	*		
42	L. Go.	F	42	Lower nephron syndrome due to transfusion, RHD with M.I. and M.S.	57	*	*		
					58	5½	Sl.	Yes	Full recovery.
43	K. W.	F	54	Diabetes, pyelonephritis, P.O. nephrectomy	59	6	Mod.	Yes	Slow recovery.
					60	6	Sl.	Yes	Gradual improvement in general status.

* Unable to secure adequate blood flow. Inadequate dialysis.

means of a Beckman thermometer and an ice-acetone bath. Since depression of the serum melting point bears a direct relationship to its osmotic activity, we have a clinically accurate and reasonably simple method for determining and matching the bath fluid with the patient's serum osmotic pressure. Thus, knowing the melting point depression of the standard bath solution, and further depression produced by addition of each 100 mg.% of glucose, a calculated quantity of the latter is added until the bath is isotonic or hypertonic with respect to the patient's serum, as the situation warrants. Since glucose diffuses into the blood from the hypertonic bath, the judicious use of regular insulin may help to maintain the proper gradient across the membrane by reducing the blood sugar level.

To date we have undertaken 60 clinical applications of the artificial kidney on a widely differing and complex group of patients (Table I). Out of this experience, reasonably consistent patterns of response have emerged. Our earlier attempts were fraught with many technical difficulties, but these, at present, have been for the most part eliminated and the applicability of the procedure widened to the point where it has been possible to employ it on a three and one-half year old child (T. S.) without difficulty. Other problems and aspects of the clinical course are to be discussed below.

CLINICAL COURSE OF THE PATIENT DURING DIALYSIS

Body temperature

Since the bath fluid is kept at a constant temperature of 101 degrees F, the blood returning to the body, after passing through some 12 feet of tubing exposed to room temperature, is at appoximately normal body temperature. During the change of bath, at which time the entire cellophane membrane is exposed to room temperature, the patient

may complain of some sensations of chilliness which straightway disappear when the cellophane is re-immersed in the bath. Pyrogen reactions have been stressed by earlier investigators (1, 16) and the elimination of pyrogens has been important in modifying our feeling about safety in the clinical application of the artificial kidney. To date we have had only one questionable reaction. This virtual absence of pyrogen reactions we ascribe mainly to the use of disposable tubing, and utmost attention to sterile technique (2). Since the cellophane is impervious to molecules larger than and inclusive of serum albumin, contamination of the blood by the entry of virus or bacteria is not a problem.

Effects on the cardiovascular system

By controlling the rate of blood flow (2) we have had no difficulty with vascular collapse. The ability to control this factor, however, as well as to regulate hydration, only serves to stress the need for extremely careful evaluation of the patient's clinical status prior to the dialysis since dehydrating procedures may induce shock in patients with initially small plasma volumes. One such patient (D. B.) with a history of recurrent pulmonary edema following transfusion, was dehydrated during dialysis with the loss in five hours of 1.6 kg. of weight. Following the procedure his blood pressure dropped to 40/0, but was promptly elevated to normal levels by transfusion of 700 cc. of whole blood. His blood pressure remained normal thereafter and the remainder of his hospital course was uneventful. In retrospect, this normotensive patient had been in negative water balance for some ten days prior to dialysis and had lost 4.2 kg. in the five days preceding. He had had no peripheral edema and presumably his plasma volume was normal or decreased at the time of dialysis, thus explaining his reaction to dehydration.

On the other hand, the dehydration of patients with pulmonary edema has resulted not only in their ability to tolerate the procedure well, but in actual improvement in their congestive failure. Patient L. G. showed a decrease in plasma volume of 500 cc. following dialysis against a hypertonic bath with resultant clearing of clinical signs of congestive failure although the patient remained anuric.

A consistent finding is the gradual elevation of both systolic and diastolic blood pressure beginning one hour to 1½ hours after the onset of blood flow through the machine. Of 45 dialyses lasting more than three hours and conducted with a blood flow of better than 125 cc./min., 32 were accompanied by a rise in systolic pressure of 40 or more mm. of mercury. Diastolic pressure rise in these cases was of less magnitude but present in all 32 which showed the pressor response. This rise in blood pressure is unaccompanied by a rise in pulse rate of similar degree. More important, it does not appear to be accompanied by evidence of left ventricular overloading. Four patients with chronic congestive failure and three patients with acute pulmonary edema showed improvement in physical findings as evidenced by clearing of rales, increase in vital capacity and decrease in venous pressure, in spite of significant elevation of both systolic and diastolic pressure.

This phenomenon does not appear to be a response to the opening of an arterio-venous fistula. Unlike an a-v fistula the diastolic pressure rises at the same time, while the pulse shows proportionately little change. The hypertensive response does appear to be related to some extent to the speed of flow (maximum, 350 cc./min.) and the clearance, since this rise can be prevented and to some slight extent decreased, once established, by reducing the flow through the machine (Figure 1).

There is a less definite correlation with the glucose content, and thus the hypertonicity of the bath fluid. Segers (17) has reported increase in cardiac output following the infusion of hypertonic glucose which is attributed to direct stimulation of the myocardium. This was not, however, accompanied by a rise in the blood pressure. Alwall (18) reports a rise in both systolic and diastolic pressure in one of his patients during the course of dialysis, but does not comment further on it. Since flow rate is correlated in a linear fashion with the removal of diffusible substances from the blood (2), it is possible that the excessive removal of some substance which plays a role in circulatory homeostasis may be responsible. At the present time, the explanation for this reaction is conjectural. Since larger amounts of metabolite are removed with greater flow, the resultant pressor response to the greater flows is a detriment to adequate clearance by necessitating a decrease in flow rate. Re-

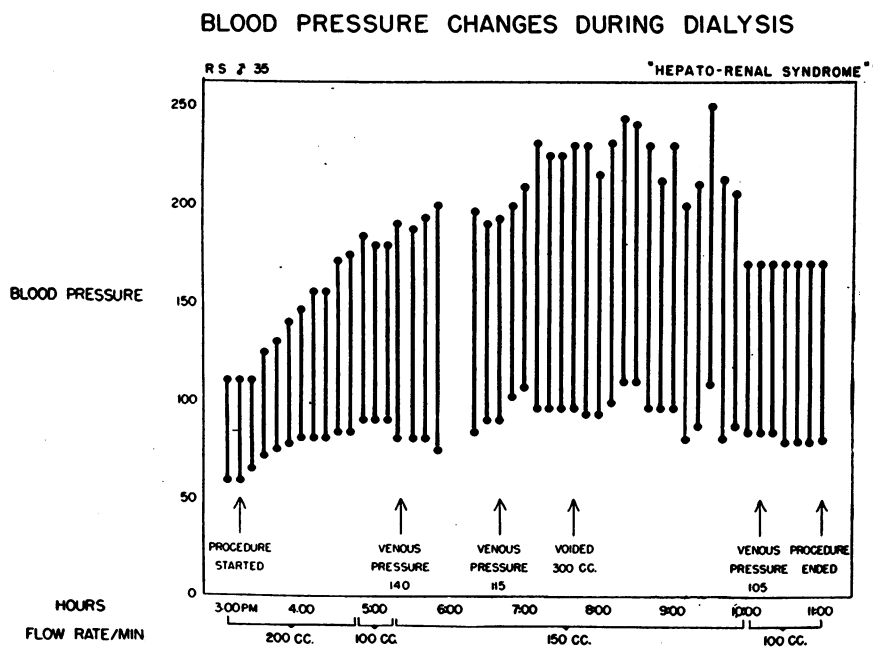

FIG. 1. BLOOD PRESSURE RECORD OF PATIENT R. S. DURING DIALYSIS

It will be noted that the blood pressure fell moderately but remained stable after the flow was slowed during the last hour.

cent evidence has indicated that the blood pressure may be lowered in spite of high flow rates by the intramuscular administration of small doses of veratrum alkaloids (Veratrone) (19).

Cardiac outputs determined by the direct Fick method, catheterizing the right auricle in one patient in this laboratory, showed no significant change during the hypertension induced by dialysis. Both systolic, diastolic, and mean arterial pressures rose approximately 35% with a comparable rise in peripheral arteriolar resistance and cardiac work. This preliminary observation thus suggests a peripheral arteriolar constriction as the mechanism of hypertension during dialysis (20).

Hemolysis

Hemochromogen values before and after dialysis have varied (21). In general, the changes have been insignificant. In two cases levels increased by 7.8 mg.% and 19.8 mg.% respectively following a six hour dialysis. In four cases measured there has been either no change or a slight decrease. Since the renal threshold for hemoglobin is above the visible range and since hemolysis which is slight enough to be invisible probably does not represent clinically significant blood destruction (22), we have abandoned routine hemochromogen determinations.

Clinical response to dialysis

The patient's clinical response to dialysis has varied, as would be expected, with a number of factors. Among these are (*1*) the original degree of intoxication, (*2*) complicating conditions such as hepatic failure, hypertensive encephalopathy, as well as (*3*) the length of dialysis, and (*4*) the amount of retained metabolite removed. In all uremic patients whose treatment has lasted two hours or more with a flow rate of over 100 cc./min., there has been definite clinical improvement as manifested by increased level of awareness, cessation of vomiting, increase in appetite, etc. This improvement has often appeared during the procedure, although in some instances it has been delayed for six to eight hours after its termination. Its duration is determined by the status of renal function. In general, hypertensive and arteriosclerotic patients and those with hepatic failure show less clinical change in proportion to their chemical improvement than do patients without

these complications. Untoward reactions take the form of vomiting which may occur toward the end of the procedure, but usually disappear in two to three hours following dialysis. The pressor response during dialysis has been described. The blood pressure returns to previous levels in five to six hours following the procedure. There have been no fatalities attributable to the procedure.

In general there is good correlation between the clinical improvement and chemical changes, particularly the correction of acidosis. In this small series, however, we have seen dramatic clinical improvement out of proportion to the chemical change, and, in one case, unexplained death three days following dialysis in a patient whose blood chemistries had reverted to nearly normal values.

CLINICAL SITUATIONS IN WHICH THE USE OF THE ARTIFICIAL KIDNEY MAY BE OF VALUE

1) *Acute Anuria*

Improved medical management of acute reversible anuria has decreased the number of such cases in which artificial removal of metabolites may be deemed a life-saving measure (23). It is difficult to imagine, however, that conservative measures could have availed for long in a clinical situation such as that of D. C. This patient was comatose on admission, with a non-protein nitrogen of 328 mg./100 cc., and a carbon dioxide combining power of 13.1 mM/L. Although death from septicemia occurred on the 30th hospital day, some return of renal function had occurred as evidenced by a urinary output on the 27th hospital day of 1600 cc. with a specific gravity of 1.017. It was possible to use the artificial kidney five times in this case with clinical benefit.

The risk of our procedure at the present time, however, is small enough to warrant its use earlier and in less critically ill patients than we had heretofore thought justified. The increased alertness, sense of well-being and appetite usually seen following an effective dialysis greatly facilitate the conservative management of both reversible and chronic renal disease, and these changes have been constant enough so that they constitute an effective argument for earlier use of the artificial kidney in appropriate cases.

An example of our present feeling is patient R. M. (Figure 2). In this patient, although diuresis appeared imminent, the nausea, vomiting, high serum potassium level, and the expectation that for the first few days of diuresis azotemia would actually increase, led to the use of the artificial kidney to hasten the loss of retained metabo-

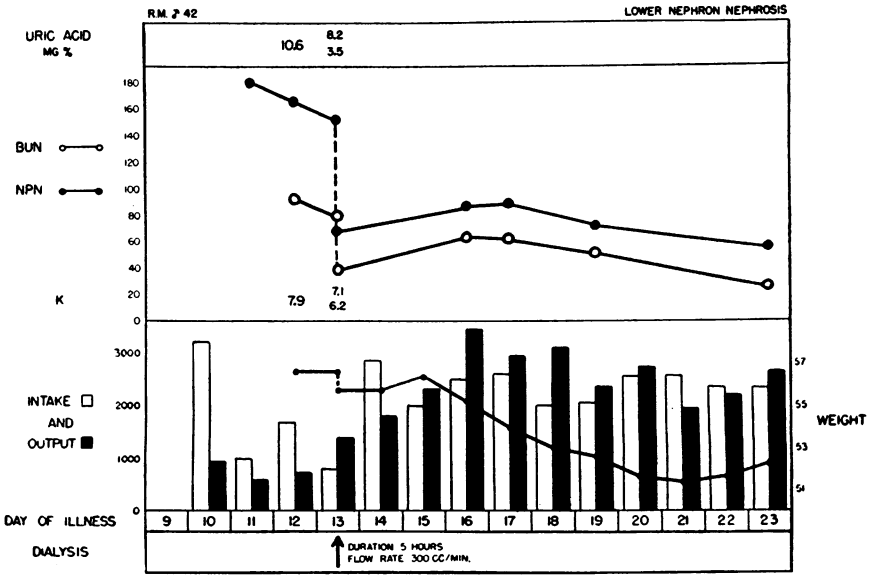

FIG. 2. CLINICAL COURSE OF A PATIENT WITH LOWER NEPHRON SYNDROME

Patient R. M. received an intravenous pyelogram on the tenth day of his illness and was admitted on the 11th day with more marked oliguria.

lites. The use of the artificial kidney in this case was probably not life-saving. On the other hand, this patient's clinical situation was so improved following dialysis that all doubt of the outcome was immediately dispelled. The onset of diuresis cannot be predicted in these cases, and once it has occurred, the azotemia may increase in the face of a rising volume of poorly concentrated urine for a week or more, with the necessity of parenteral feedings because of apathy and nausea. The ability to ingest calories and fluids facilitates medical management. In patient R. M. the incipient danger of potassium intoxication was a real one, and this possibility could be dismissed following dialysis. There is some logic, therefore, in the concept that the artificial kidney may be used, not as a last resort when other methods of treatment have failed, but as an effective adjunct to more conservative methods of therapy. Since there is evidence, too, that the correction of chemical abnormalities, particularly acidosis, may speed the onset of diuresis, there is added reason for earlier use of such a procedure. In two patients (K. B. and M. R.) diuresis followed correction of severe electrolyte imbalance closely enough to suggest a causal relationship.

2) *Hyperkalemia (acute spontaneous potassium intoxication)*

Six cases of spontaneous potassium intoxication associated with uremia have been treated with the artificial kidney. The development of this syndrome in the anuric patient represents a serious medical emergency. By omitting potassium in the bath fluid, it is possible to remove it rapidly from the patient's extracellular fluid. In five of our patients (J. C., J. Be., K. B., M. F., and G. E.) it appears that the removal of potassium by dialysis was a life-saving measure, since conservative methods of therapy for this situation do not produce results lasting enough to support life in the face of the subsequent slow recovery of renal function (24, 25). It is probable that the amelioration of acidosis and nitrogen retention in these cases corrects a toxic situation which facilitates abnormal cell shifts of potassium as well as sodium ion.

3) *Hyponatremia*

The role of low concentrations of extracellular sodium in potentiating potassium intoxication and acidosis is important (26). In the anuric patient who is already overhydrated the problem of raising the serum sodium without expansion of extracellular fluid volume and danger of pulmonary edema is difficult. In such a situation it is possible by making the bath hypertonic to the patient's serum to add sodium at the same time as water is removed, as evidenced by increase in hematocrit and weight loss (Table II).

TABLE II

Changes in blood constituents during dialysis

K. B. 35 yrs.	Anuria ? Cortical necrosis (Post-partum)	
	Initial	Final
Hematocrit	32	33
Sugar (mg.%)	151	165
Serum Na (mEq/L)	108	130
Serum K (mEq/L)	7.3	5.1
Serum Cl (mEq/L)	76	106
CO_2 (mM/L)	16.1	19.7
Ca (mEq/L)	3.7	5.1
NPN (mg.%)	162	64
BUN (mg.%)	72	48
Uric acid (mg.%)	18.7	6.7
Serum inorganic P(mM/L)	3.8	1.9
Total NPN removed	35.1 Gm. (six hours)	
Total urea N removed	28.3 Gm.	

4) *Hypernatremia*

In patient A. McL., the ability specifically to remove sodium ion by diffusion was utilized. This patient, with oliguria and hypernatremia following gastrointestinal hemorrhage (27) was treated with the artificial kidney. The bath in this case contained only 120 mEq/L of sodium. Five and six tenths Gm. of sodium were removed in a three-hour period, in spite of extremely poor blood flow through the machine, with a drop in serum level from 182 to 163 mEq/L. This patient went on to diurese and her sodium and chloride levels were restored to normal with accompanying clinical recovery. The feasibility of sodium removal suggests the possibility of application of this technique to other problems where the removal of sodium and/or water may be advantageous.

5) *Chronic uremia*

In the acute exacerbation of chronic glomerulonephritis where there is reason to believe that the acute situation may be ameliorated to some degree with healing of the acute lesions, the artificial kidney may be used for the same reason as in lower

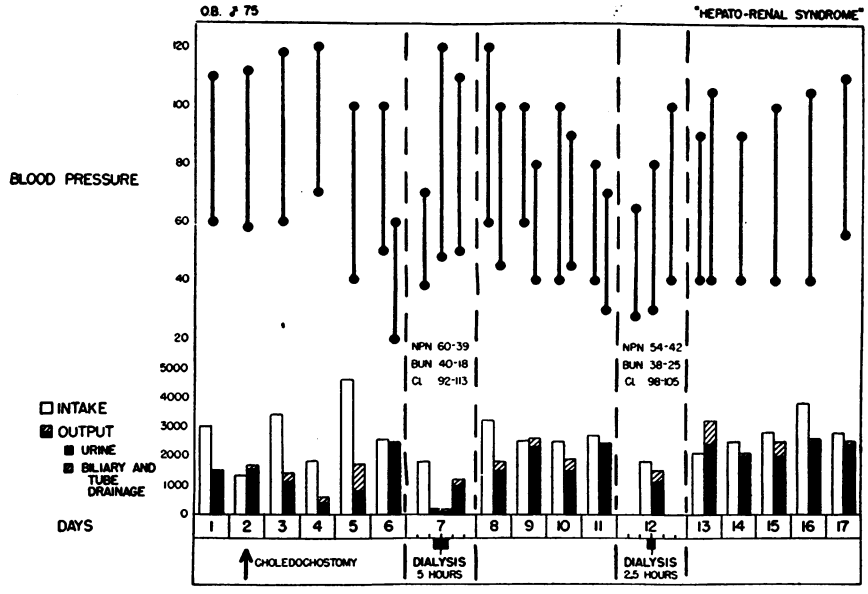

FIG. 3. BLOOD PRESSURE RESPONSE IN POST-OPERATIVE "HEPATO-RENAL" SYNDROME
The clinical course of patient O. B. who showed repeated episodes of hypotension unresponsive to the usual therapy.

nephron nephrosis (patient P. P.). In selected cases of chronic renal insufficiency with uremia, proper dietary management may be impossible because of apathy, anorexia, and nausea. In such a patient subjective improvement following dialysis may enable him to take adequate dietary measures which may maintain him in more favorable nitrogen and electrolyte balance (patient J. M.).

Patient D. B. suggests the possibility that the procedure may be valuable in severly toxic uremic patients whose renal disease may be amenable to surgical procedure. This patient who was comatose when dialyzed responded well to the procedure and was able to tolerate surgical measures which led to eventual rehabilitation.

6) Shock-like states

The pressor response elicited has had therapeutic application in two cases of severe hypotension following major surgery (Figures 1 and 3). Following biliary surgery, patient O. B. (Figure 3) developed a shock-like syndrome which did not respond to the usual measures including adequate blood and plasma therapy. This patient showed a rise in blood pressure during dialysis carried out specifically for this pressor response. Normal blood pressure levels were maintained for four days, after which hypotension again developed. This again responded to treatment with the artificial kidney and convalescence thereafter was uneventful.

7) Congestive heart failure and pulmonary edema

In patient C. P., although the primary indication for the use of the artificial kidney was uremia, consideration was given to the presence of congestive heart failure. Following dialysis against a hypertonic bath objective evidence of improvement in vital capacity and pulmonary engorgement was obtained. In patient L. G. who showed evidence of pulmonary edema, there was a decrease in plasma volume, as measured by the Evans Blue technique (28), of 500 cc. with clinical evidence of improvement in pulmonary congestion. In 11 instances dialysis has been undertaken in patients with congestive heart failure and/or pulmonary edema. In no case has difficulty attributable to the cardio-vascular system been encountered. The measurement of the serum melting point depression as a guide to adjusting the tonicity of the bath fluid is a valuable adjunct in such cases. In one anuric patient (L. Go.) with mitral stenosis, pulmonary edema developed in spite of rigid fluid restriction and marked dehydration. This did not respond to digitalis in adequate dosage over

a period of four days. Following dialysis on the 11th day of anuria, the lung fields became clear, and dyspnea and orthopnea disappeared. During the run the patient gained 0.2 kg. in weight, so that the result cannot be attributed to further dehydration. It is interesting that Fishman and his associates (29) have reported an instance (Case V) in which pulmonary edema in a uremic patient cleared following application of an artificial kidney. Blood volume reassessed by the Evans Blue technique showed no change after dialysis. These patients suggest the possibility that decrease in plasma volume may not be the only factor involved in pulmonary edema in these instances and that improvement in myocardial function attendant upon correction of chemical imbalance may play a role.

8) Miscellaneous

The value of the artificial kidney as an investigative tool in animal experimentation has been clearly demonstrated by the recent reports of Vanatta, Muirhead, and Grollman, (30, 31). The decreased risk of the procedure has enabled us to use it as an investigative tool in such unrelated clinical states as acute yellow atrophy and gout (patients J. Z. and A. L.). *In vitro* clearances have shown that barbiturate salts diffuse well through the cellophane membrane, and the removal of barbiturates by dialysis has obvious therapeutic possibilities in the patient whose toxicity has progressed to the stage of shock and oliguria.

Removal of such substances by diffusion obviously depends for its efficacy upon the concentration in the plasma of the substance to be removed. The greater the level, the more rapidly it is removed. Thus, morphine which is fixed in the tissues soon after assimilation, and which is not found in the circulating blood in any quantities, would not be removed effectively by dialysis.

CHEMICAL CHANGES

Tabulation of the chemical changes occurring during dialysis and analysis of such figures are difficult because of the numerous factors involved in determining each value. For instance, drop in blood urea nitrogen concentration depends on duration of dialysis, initial level, flow rate through the machine and, as will be discussed later, upon the underlying pathological condition of the patient. Since not all of these factors are consistent in any two patients, the interpretation of such values is difficult without relating them to each such factor. The same objections may be raised to changes in serum uric acid, phosphate, and nonprotein nitrogen concentrations. In the analysis of changes in serum chlorides or carbon dioxide combining power, additional difficulties arise. Thus, in patient J. L., who had depleted his serum chlorides by vomiting, dialysis was accompanied by a fall in his already low normal level carbon dioxide combining power due to increase in chloride content of the serum. This fall occurred in spite of removal of acid metabolites and a rise in total base from 130 to 140 mEq/L.

Elimination of one of these varying factors, the duration of dialysis, may be accomplished by computing average removal per hour, but it should be stressed that such figures represent varying blood flows and initial levels and that to some extent the duration of dialysis influences the amount removed per unit time, since this amount decreases with the decreasing blood levels incident to longer dialysis. In general with flow rates of 200 cc./min. or better, dialysis of a patient with a blood urea nitrogen of 90–100 mg.% will effect the removal of roughly 10–12 Gm. of urea per hour. Table II illustrates representative changes during dialysis. It should be stressed that the correction of acidosis, both by the removal of acid metabolites and the addi-

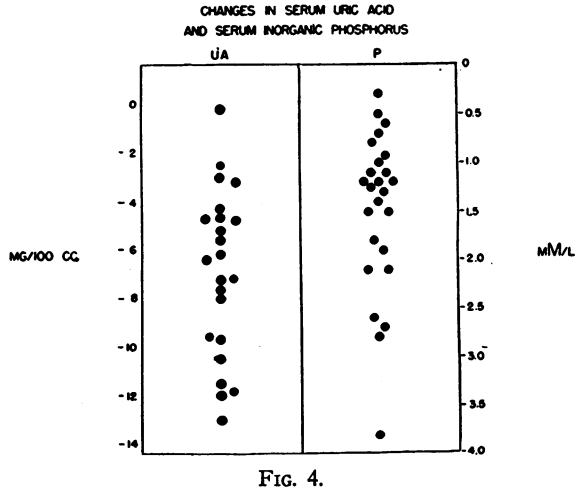

FIG. 4.

As in Figures 5 and 6, each point represents the change in serum uric acid and inorganic phosphate caused by dialysis.

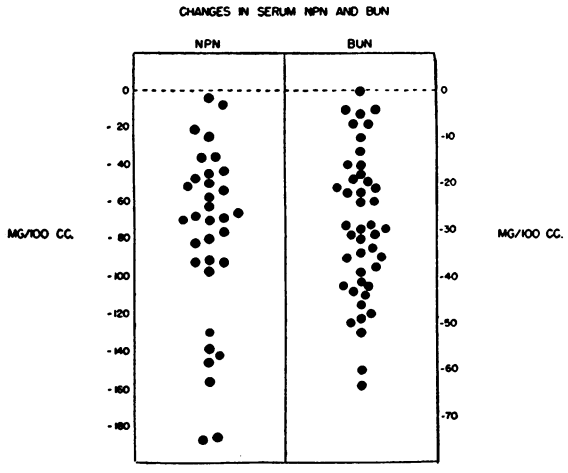

FIG. 5.

The position of each point denotes the degree of change in serum values of BUN and NPB as a result of dialysis. Not all patients are represented since some cases had normal blood values before the procedure. These are not included.

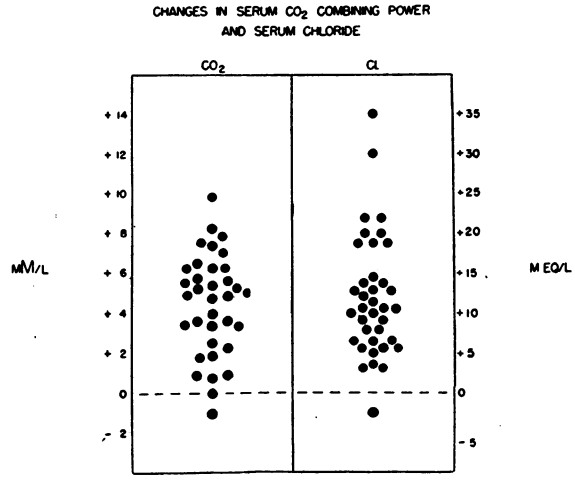

FIG. 6.

Each point represents the change in CO_2 combining power and serum chlorides after dialysis. As would be expected the nearer to normal the original values were the less change was obtained by dialysis.

tion of base, is a constant and important therapeutic factor. Figures 4–6 show the magnitude and direction of changes for patients in whom these serum values were measured before and after dialysis.

AMINO ACID STUDIES

We have had the opportunity of observing the effect of dialysis on the removal of alpha amino acids in four instances (Table III). Determinations were done in the laboratory of Dr. Halvor Christensen by the manometric ninhydrin procedure at pH 2.5 (32). Urea was removed with urease. Measurements were made on the plasma of four patients before and immediately after dialysis. In addition, the amount of alpha amino acid nitrogen removed in the bath fluid was directly measured. From Table III it is seen that patient F. M. with normal liver function had an initial normal plasma value (4 mg.%). Patients D. C. and M. R. with hepatic insufficiency had elevated values. On the basis of extracellular fluid volume calculations and measured decrease in plasma values, it is possible to estimate the amount of alpha amino nitrogen which must have been removed from the extracellular fluid to give such a result. In patient F. M., with normal liver function, a far greater amount was recovered in the dialysate than was calculated from the plasma value decrease. In patient M. R. (hepatic insufficiency) the discepancy is less, while in patient D. C. (also hepatic insufficiency) on two successive occasions the amount removed coincides well with the amount calculated from decrease in concentration in the extracellular fluid. Dr. Christensen's interpretation of these results was, "The quantities of amino acids extracted appear to be of small nutritional importance. In the case where the plasma amino acid level was normal at the beginning of dialysis (patient F. M.) the decrement of amino acids (calculated for the whole extracellular fluid)

TABLE III

Removal of alpha amino acid nitrogen

Patient		Normal liver	Hepatic insufficiency		
		F. M.	D. C.	D. C.	M. R.
Plasma level mg.%	Initial	3.99	6.35	5.19	5.60
	Final	3.61	4.23	4.17	3.74
	Decrease	.38	2.12	1.02	1.86
Total removed (mg.)	Calculated from E.C. fluid	76	403	193	364
	Found in dialysate	590	420	210	633
	Fraction from E.C. fluid	12%	96%	92%	41%

N.B. The reciprocal of the "fraction from the extracellular fluid" represents the amount of alpha amino acid nitrogen formed or released from body stores during dialysis.

was very small compared to the quantity removed by dialysis, suggesting that a homeostatic replacement of plasma amino acids occurred. But when the level of plasma alpha amino acid nitrogen was abnormally high as in patients D. C. and M. R. comparatively little replacement of the extracted amino acids was evident until the plasma levels fell below average normal values."

This same homeostatic tendency has manifested itself in the maintenance of normal serum potassium levels in dogs during removal of potassium by dialysis with an artificial kidney (33) and has been observed in our patients with hyperkalemia during the course of potassium removal (26).

UREA RECOVERY

Table IV illustrates a consistent and as yet unexplained phenomenon connected with the removal of urea. If it is assumed that urea is completely diffusible throughout total body water, the amount of urea recovered from the bath fluid should be commensurate with the amount calculated to have been removed from the patient derived on the basis of drop in blood urea concentration multiplied by total body water (estimated at 70% of body weight at time of dialysis). Errors in the chemical method and in the estimation of body water might account for a discrepancy of 20–25% in these calculations. In certain cases, however, we have observed discrepancies of 70–80%; the blood urea nitrogen concentration dropping in these cases only 20–30% of the amount calculated from the amount of urea removed in the bath fluid. This discrepancy has been reported by other observers (16, 34). The total non-protein nitrogen fraction drops more nearly as expected in most cases. Failure of the BUN to drop as expected does not seem to be associated with lack of clinical improvement. The improvement seems to bear a direct relation to total metabolite removed in the bath and to correction of acidosis. The discrepancy between observed and calculated drop in BUN has some correlation with the duration of uremia, occurring more frequently in chronic renal failure than in acute renal insufficiency. It has, however, its more precise correlation with the clinical state of toxicity and the ultimate prognosis regardless of the duration of the disease. The explanation for this phenomenon is not clear at the present time. The more predictable drop in NPN as compared to unpredictable fall in BUN with dialysis suggests that urea is being formed from precursors in the NPN fraction at a rate rapid enough to maintain the level in spite of removal by dialysis.

TABLE IV

Decrease in blood urea nitrogen and total non-protein nitrogen values following dialysis

Patient	BUN	NPN	BUN Observed / Calculated	NPN minus BUN	NPN / BUN
	mg. %	*mg. %*	%		
M. A.	20	45	62	25	2.0
D. C.	13	91	22	78	7.0
J. C. (*1*)	10	58	21	48	5.8
(*2*)	19	54	35	35	2.8
J. L.	49	48	81	0	1.0
F. M. (*1*)	35	68	109	33	1.9
(*2*)	30	76	75	46	2.5
C. P.	29	69	46	40	2.3
P. P.	4	25	28	21	6.2
G. S. (*1*)	4	36	27	32	9.0
(*2*)	18	44	38	26	2.4
J. Be.	63	93	108	30	1.4
J. B.	36	66	64	30	1.8
R. M.	41	83	69	42	2.0
D. B.	52	92	88	40	1.7
J. M.	31	36	97	5	1.0
M. L.	22	156	22	134	7.0
R. S. (*1*)	42	188	42.5	146	4.5
(*2*)	6	35	27.4	29	5.9
D. B.	22	21	80	0	1.0
A. M.	2	35	21.7	33	17.5
L. B.	60	61	122	1	1.0
M. R.	32	139	34	105	3.3
T. S.	43	49.9	112	6	1.1
K. B.	24	98	37	74	4.0
M. S.	21	100	29.6	79	3.8
T. R.	38	50	88	12	1.3
F. B.	18	32	64	14	1.8
M. F.	42	122	73	80	2.9

The figures given in the first two columns are the difference between initial and final values. Column three represents correlation between observed drop in BUN and that calculated from the urea nitrogen recovered from the dialysate. The last two columns represent difference between NPN and BUN decrease and ratio between these decreases. It will be seen that where this ratio is greatest the discrepancy in BUN change is greatest.

SUMMARY AND CONCLUSIONS

Clinical experience with an artificial kidney of the Kolff type has been obtained in 60 instances (43 patients). Methods of controlling tonicity of the bath fluid and the virtual elimination of problems of clotting, hemolysis, and pyrogen reaction have added greatly to the efficacy and safety of the procedure. The apparatus is an effective means for removing specific diffusible substances from the blood by continuous dialysis, and the risk

of its application is small enough so that it is of clinical importance in the management of acute, reversible renal insufficiency, particularly when complicated by spontaneous potassium intoxication. Preliminary trials suggest its value in other clinical conditions in which the removal or addition of diffusible substances may be indicated.

Observations which have been made incident to dialysis on urea and amino acid metabolism, and on circulatory homeostasis suggest that this apparatus may prove to be an important investigative tool in elucidating physiological mechanisms.

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