ARTIFICIAL KIDNEY FUNCTION: KINETICS OF HEMODIALYSIS [1]

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(Submitted for publication April 9, 1951; accepted July 30, 1951)

Widening application of hemodialytic techniques in experimental medicine and therapy points up a need for data and theory which reflect the fundamental operations of these devices. The following study contributes to this subject.

METHODS

The artificial kidney of the Albany Hospital used in our experiments is a 1950 model built by Olson [2] according to the design of Merrill and his associates (1, 2). In all *in vitro* studies 26 turns of 23/32" cellophane tubing were used, providing a dialytic surface area of 21,000 sq. cm. When various prepared solutions were used in place of blood for the purpose of analysing rates of exchange of solutes and water between "blood" and bath fluid, a reservoir of 10 liters of "blood" was placed in series with the artificial kidney. The volume of bath fluid at the onset of dialysis was 100 liters in all studies and was maintained at 101° F. Essentially constant flow was maintained by adjusting the pump to a capacity for returning fluid to the reservoir which exceeded the actual "arterial" flow into the cellophane tubing while inflow was kept at a constant pressure head and regulated by an adjustable clamp.

Chemical analysis was as follows: urea (3), creatinine (4), non-protein nitrogen (5), uric acid (6), glucose (7), sucrose (8), amino acids (9, 10), chloride (11), bicarbonate (12), water (13), phenol red by photoelectric colorimetry, and sodium and potassium by flame photometry. Inorganic phosphate, inorganic sulfate, calcium, and magnesium methods are noted in a previous article (14).

SYMBOLS

A: concentration of a substance in arterial blood or other fluid entering natural or artificial kidney

a: minute rate at which arterial blood or other fluid enters natural or artificial kidney

α: a constant equal to $(B + b)/B$ for blood-to-bath transfer

B: volume of bath fluid

b: total volume of distribution of a substance in patient (or *in vitro*) and in artificial kidney, but excluding bath fluid volume

β: a constant equal to αk; the slope of the line relating ln (A–U) to time

C: clearance, equal to uU/A

γ: velocity constant of excretion for natural kidneys; equal to C/b for no-threshold substances

D: dialysance, equal to uU/(A–U)

d: relative dialysance, equal to D_x/D_{urea}

Δ: "change of"

e: base of natural logarithms, equal to 2.718

K: a constant representing the total solute content of the hemodialytic system, bA + BU; equal to bA_o for substances initially absent from bath fluid

k: a constant equal to D/b

n: number of changes of bath fluid during a hemodialytic procedure

R: concentration of a substance in renal venous blood or other fluid leaving natural or artificial kidney

S: average concentration of solute throughout the length of cellophane casing during flow

t: time in minutes unless otherwise specified

U: concentration of a substance in urine from natural kidneys, or in bath fluid of artificial kidney

u: minute rate of urine flow from natural kidneys; a value denoted by B/t in computing rate of solute exchange

V: volume of blood or other fluid contained in a given segment of artificial kidney excluding bath

x: "a given substance"

INTRODUCTION

During hemodialysis all substances freely filterable through the cellophane membrane have thresholds determined conjunctively by the volume and composition of the bath fluid and by the volume and composition of the blood and body fluids. If bath fluid is replaced at frequent intervals, any substance present in the plasma but not in virgin bath fluid acts as if it were a no-threshold substance, the more so as the frequency of replacement is greater. Equations which describe the kinetics of excretion in the human kidney have parallels in equations which describe the kinetics of the artificial kidney.

Under suitable conditions many no-threshold substances in man have rates of excretion which are proportional to their plasma concentrations, and the ratio of these variables is the clearance. In the artificial kidney, rates of excretion often are proportional to the concentration gradient between

[1] This work was supported in part by a grant from the U. S. Public Health Service.

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TABLE I

Comparative kinetics of human and artificial kidneys

Human kidney	Artificial kidney
1. Rate of excretion is proportional to blood concentration*	1a. Rate of excretion is proportional to difference between blood and bath concentrations
2. $C = \frac{uU}{A}$ (clearance)	2a. $D = \frac{uU}{A - U}$ (dialysance)
	2b. $C_t = D \cdot \frac{A - U}{A}$
3. Clearance is relatively constant with the passage of time	3a. Clearance decreases with time unless B is infinite and U = 0. Since if U = 0, C = D, then when the solute in question is not present in bath fluid, the dialysance is numerically equal to the dialytic clearance in the virgin bath at zero time
4. $C = a \cdot \frac{A - R}{A}$	4a. $D = a \cdot \frac{A - R}{A - U}$
5. $a = \frac{uU}{A - R}$	5a. $a = \frac{uU}{A - R}$
6. Diverse substances may have diverse clearances	6a. Diverse substances may have diverse dialysances
7. $A_t = A_0 e^{-\gamma t}$*	7a. $A_t = \frac{B}{B + b} \cdot A_0 e^{-\alpha k t} + \frac{b}{B + b} \cdot A_0$†
	7b. $(A - U)_t = (A - U)_0 e^{-\beta t}$
	7c. $Ab + UB = K$; $K = A_0 b$, when U = 0
8. $\gamma = \frac{C}{b}$	8a. $\alpha = \frac{B + b}{B}$; $k = \frac{D}{b}$; $\beta = \alpha k$
9. $\frac{U}{A} \gtreqless 1$	9a. $\frac{U}{A} < 1$ (for blood-to-bath transfer)

* Applicable to no-threshold substances such as inulin or urea.

† For substances not present in bath initially; otherwise, $A_t = \frac{B}{B + b} \cdot (A - U)_0 e^{-\beta t} + \frac{b}{B + b} \cdot A_0 + \frac{B}{B + b} \cdot U_0$. When U = 0 this equation reduces to 7a; when B = infinity and U = 0, equation 7a reduces to 7.

the plasma and the bath fluid at any instant. This implies that, at constant blood flow in the artificial kidney, the clearance of a substance tends to fall with time and is thus not useful as a hemodialytic parameter in the same way as it is in describing natural kidney function. The rate of excretion per unit concentration gradient between plasma and bath fluid is a parameter functionally equivalent to the clearance in natural kidneys, and is called here the *dialysance,* D. It is defined specifically as the minute rate of net exchange of a substance between blood and bath fluid per unit blood-bath concentration gradient. Although it varies with blood flow and surface area of cellophane (1) its value is relatively characteristic for different molecular and ionic species.

Table I compares the kinetics of excretion in natural and artificial kidneys. In spite of similar mathematical formulations for certain aspects of both human and artificial kidneys, their principles of excretion differ. In the human kidney, excretion depends primarily upon a filtration process coupled or not with tubular influence; in the artificial kidney, excretion is primarily by diffusion coupled perhaps with some filtration. It is unnecessary to elaborate the derivations of the equations indicated in the table. Some of these have been considered elsewhere (15). The basic assumptions include: *1*) the differential $dA/dt = -k(A-U)$ which is justified by most of our experimental findings, and *2*) the statement of constant solute content in the system, $bA + BU = K$. We shall not note here equations which describe the effects of steady inputs of material into the system, as exampled by urea formation. Omission of this factor, which has often a high degree of uncertainty, actually makes little difference to the results to be described, although its consideration serves to account in some measure for the discrepancy observed (2) between the amount of urea recovered from the

bath fluid and the corresponding drop in plasma concentration in the course of therapy.

While some information concerning dialysance may be obtained from hemodialysis in patients, much is precluded because the bath fluid contains materials, *e.g.*, sodium, in substantially the same concentration as in plasma. In this case accurate determination of extraction fraction, excretion or retention, or dialysance is not practicable. Thus, a series of *in vitro* experiments have been performed in which prepared solutions were dialysed against water or other prepared solutions, and advantage taken of analytically large gradients. It has been found that different materials have different characteristic dialysances; and the concept of the *relative dialysance,* or the ratio of the dialysance of a given substance to that of urea measured at the same time, has been introduced (Table II; Figure 3). The relative dialysances of electrolytes are influenced by the requirements of electroneutrality and Donnan equilibria, as well as by the diffusion-accelerating and diffusion-retarding influence of other solutes, but useful facts can be discovered notwithstanding.

TABLE II

Average dialysances (D) and relative dialysances (d) obtained from in vitro *experiments at a "blood" flow (a) of 500 cc./min.*

A dialysance listed here may be plotted as a point on the graph of Figure 3 and a curve drawn between the origin and this point in conformity with the other curves. The drawn curve approximates to the actual dialysance-flow curve for that substance. The ratio D_x/a, either from this table or from any point on a dialysance-flow curve, is numerically equal to C_x/a at zero time after bath fluid contacts cellophane and therefore to the extraction fraction, $(A - R)/A$, which would be found for x when it is absent from a virgin bath ($U_x = 0$). D/a varies with a. For all substances freely diffusible through the cellophane, D/a as well as d approaches unity as a approaches zero.

The number of determinations includes "instantaneous" values of D_x and d_x obtained from the relations $D_x = a(A_x - R_x)/(A_x - U_x)$ and $d_x = D_x/D_{urea}$, as well as from $D_x = D_{urea}(\beta_x/\beta_{urea})$. From these, dialysance-flow curves as in Figure 3 were constructed and the values of D at a = 500 cc./min. were taken for this table.

Substance	D	d	D/a	Number of determinations
Chloride	310	1.03	0.61	13
Urea	300	*1.00*	0.60	16
Potassium	300	1.00	0.60	13
Sodium	235	0.78	0.47	15
Creatinine	169	0.56	0.34	15
Bicarbonate	168	0.56	0.34	2
Tryptophane	150	0.50	0.30	1
Alanine	148	0.49	0.30	6
Uric acid	135	0.45	0.27	12
Glucose	120	0.40	0.24	13
Calcium	60–152	0.21–0.51	0.12–0.30	8
Magnesium	100	0.33	0.20	10
Glutamic acid	96	0.32	0.19	1
Sulfate	96	0.32	0.19	9
Inorganic phosphate	92	0.31	0.18	7
Sucrose*	67	0.22	0.13	7
Phenol red	33	0.11	0.07	5

* In calculating transfers of material from bath to blood by means of equations of the type in Table I (7a, 7b), substitute U in place of A, b in place of B, and B in place of b, obtaining for example,

$$U_t = \frac{b}{B + b} \cdot U_0 e^{-\frac{B+b}{b} \cdot \frac{Dt}{B}} + \frac{B}{B + b} \cdot U_0.$$

With $D_{sucrose}$ = 67 cc./min., b = 14,000 cc., B = 100,000 cc., and U_0 = 1.000 per cent sucrose in the bath at zero time, we find at t = 60 min. that U_t = 0.965 per cent. This means a movement from bath to blood of 35 grams of sucrose in one hour.

The formula $D = a(A - R)/(A - U)$ for dialysis in the bath-to-blood direction reduces to $D = aR/U$ where A = 0. R/U for bath-to-blood transfer corresponds to the extraction fraction, $(A - R)/A$, for blood-to-bath transfer.

The dialysance of water is not considered here. Of more importance to considerations of water balance is the positive or negative clearance of water when specified quantities of osmotically effective materials are contained in bath fluid and blood, but no means at our disposal provided accurate measurement of absolute water exchange.

PROCEDURES AND RESULTS

I. Volume of blood, rate of flow, and circulation time in the artificial kidney. The quantity of fluid contained in the cellophane casing depends in steady state on its rate of flow and, when the blood balance is positive or negative, upon the relation between rates of intake and output. We set our pump to operate at its maximum capacity for drawing blood from the venous side of the kidney and adjust the arterial inflow by means of a clamp, assuring a given rate of passage through the machine at any given arterial pressure. Sucking the cellophane loops to their minimal possible volume at all flows stabilizes the blood content of the patient during treatment and permits valid estimates to be made of the blood volume contained in the casing and of the average time required for the blood to pass from the proximal end of the arterial coupling to the distal end of the venous coupling. To determine extraction fractions, blood samples are drawn from these sites with proper allowance for this *circulation time.* Figure 1 relates circulation times and blood volumes in the artificial kidney to blood flow.

II. Recirculation experiments in vitro. With a reservoir containing 10 liters of solution ("blood") in series with the artificial kidney, the "blood" concentrations, extraction fractions, dialysances, etc. were determined at a given "blood" flow. The results of several studies of this type are found in Tables II and III and Figures 2–4.

III. Dialysance-flow experiments in vitro. From a reservoir containing either water alone or a prepared solution, fluid was allowed to flow at a fixed rate through the artificial kidney. Immersion of cellophane loops in a bath containing either a prepared solution or water alone was established at a determined time. Bath fluid was sampled before contact. "Arterial" fluid was sampled immediately after maximal immersion, and "venous" fluid after the appropriate "circulation time" (Figure 1). Thus, extraction fractions, either (A–R)/A or R/U, and dialysances could be calculated for "zero" time at a given flow. The results of these experiments are summarized in Tables II and III and Figure 3.

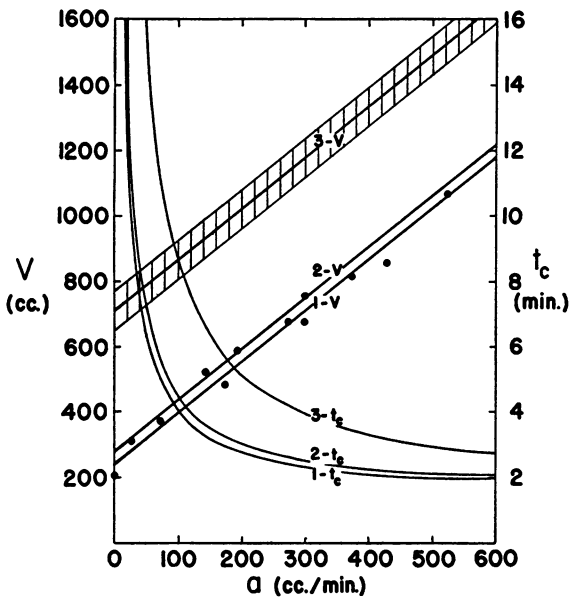

FIG. 1. RELATION OF FLUID VOLUMES, V, CONTAINED IN VARIOUS SEGMENTS OF THE ARTIFICIAL KIDNEY AND OF CORRESPONDING CIRCULATION TIMES, t_c, TO RATE OF FLOW THROUGH THE MACHINE, a

Black dots represent experimentally determined fluid volumes contained in 26 cellophane threads of the Archimedes' screw at different measured flows, after balance had been obtained in a recirculation system *in vitro*. From curve 1-V, a straight line fitting the points shown, was calculated the curve 1-t_c, since $V/a = t_c$. From measured "dead spaces" beyond the cellophane casing it was possible to estimate the intercoupling volume and intercoupling circulation time (curves 2-V and 2-t_c, respectively), and the total extracorporeal volume and extracorporeal circulation time (curves 3-V and 3-t_c, respectively). The vertically hatched region about 3-V indicates the variation in extracorporeal volume which may occur during measurement of blood flow by means of the buret ordinarily used for that purpose. Curve 2-t_c is useful in choosing the time which must elapse after sampling A, before sampling R, in the determination of extraction fractions, etc.

The equation of curve 1-V is $V = 1.6a + 240$ which indicates that for every change of flow of 100 cc./min., there is a corresponding change in casing volume of 160 cc.

TABLE III

Comparison between D, d, and D/a values from in vitro *experiments and from a patient*

Substance	a	*In vitro*			In patient (M. B.)		
		D	d	D/a	D	d	D/a
Urea	296	212	1.00	0.72	204	1.00	0.69
Non-protein nitrogen	296				177	0.87	0.60
Creatinine	296	143	0.67	0.48	123	0.60	0.42
Glucose	296	108	0.51	0.37	82	0.40	0.28
Inorganic phosphate	296	82	0.39	0.28	77	0.38	0.26

In the patient (see lower part of Figure 2 for additional information) blood flow was maintained close to and averaged 400 cc./min.; plasma flow, 296 cc./min.; b = 52,000 cc. for urea; and B = 100,000 cc. *In vitro*, b = 10,000 cc. and B = 100,000 cc. Since 25 coils of cellophane were used during the patient's run, and 26 in the other experiments, the actual D values of the patient should be increased by a small factor to be comparable (1). It is uncertain, particularly for urea, as to what value of "a" corresponds to a given total flow where whole blood is being dialyzed, since that substance so freely crosses red cell membranes.

IV. Water exchange. Without means for accurate weighing of the patient during hemodialysis it is difficult to estimate absolute water exchanges across the cellophane membrane. We attempted, however, to approximate the critical concentration gradient of glucose between plasma and bath at which no net water exchange occurred. During two hemodialyses on the same patient the glucose content of the bath was varied. A, R, and U samples were drawn at appropriate times and plasma and bath fluid were analysed gravimetrically for water content and chemically for glucose. No pyknic or osmotic corrections for transferred solute were made. Figure 5 shows how different glucose gradients cause the water content of the plasma to vary in its passage through the artificial kidney. An apparent water balance is indicated when

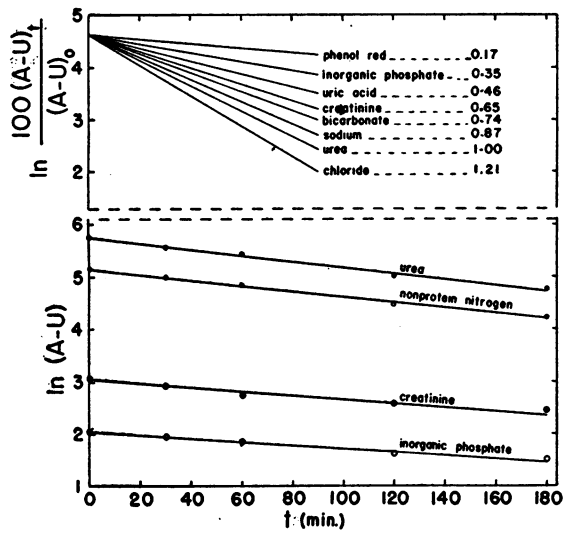

FIG. 2

Upper: In vitro results of a single experiment at a flow of a = 300 cc./min. The A-U gradient at time t was first expressed as a per cent of the gradient at zero time, giving all substances the same value of $\ln \frac{100(A-U)_t}{(A-U)_0}$ at zero time. This permits readier visualization of the varied slopes of their curves. D_{urea} = 220 cc./min.; β_{urea} = 0.0242 min.$^{-1}$; b = 10,000 cc.; B = 100,000 cc. Numerical values in graph are relative dialysances.

Lower: Actual values of ln (A-U) plotted against time, t, for a single hemodialysis in a 70 kg. man (M. B.). Slopes are β_{urea} = 0.00595, "β_{NPN}" = 0.00472, $\beta_{creatinine}$ = 0.00378, and $\beta_{phosphate}$ = 0.00367 min.$^{-1}$ The volumes of distribution of these materials in man (unlike the above *in vitro* experiment) are not identical so that the dialysance is in fixed relation to the β value only for a given material. Since

$$\beta = \alpha k = \frac{B + b}{B} \cdot \frac{D}{b},$$

we may solve for b = Db/(Bβ − D). Taking the average "instantaneous" D_{urea} (from Table III, containing additional data on this patient) as 204 cc./min., and β_{urea} as 0.00595 min.$^{-1}$, we calculate b = 52,000 cc., an expected magnitude. Analytical concentrations were in mg. per cent except for phosphate which was in mEq./l.

$(A - R)_{H_2O} = 0$. No claim is made that this point represents true water balance in the artificial kidney because no satisfactory analysis has been made of fluid shifts in the tri-phasic osmotic system consisting of fluid of blood cells, plasma, and bath fluid. In view of the difficulty in sampling whole blood and analysing it accurately for water, in view of the variable colloid osmotic pressure of plasma in different patients and at different times during a single hemodialysis, and in view of the variable effective osmotic pressure of plasma crystalloids and of those in bath fluid, these data have only relative value in suggesting glucose contents of bath fluid conducive to hydration or dehydration of the patient.

In Figure 5 apparent exchanges of water across the membrane are shown as a function of the average bath-plasma gradient of glucose concentration, $(U-S)_{glucose}$. This value is found from

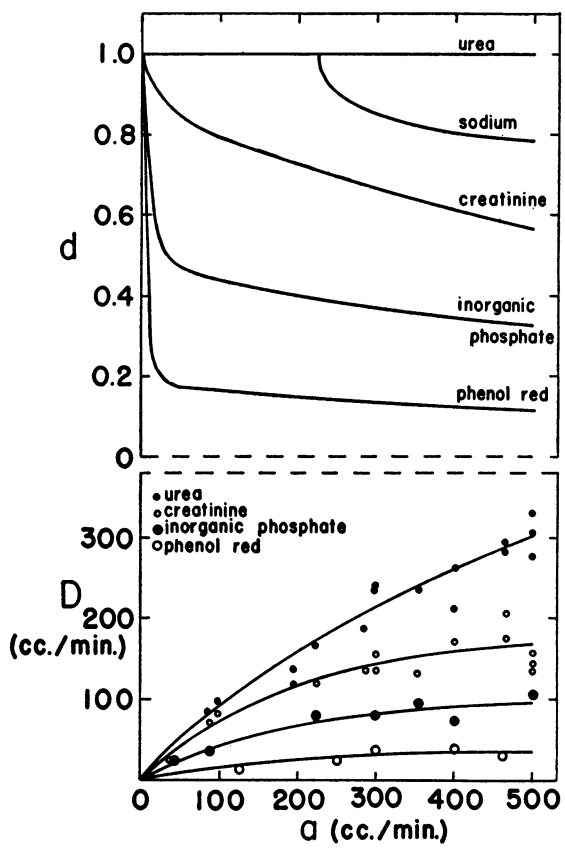

FIG. 3

Upper: Relative dialysance, d, as a function of "blood" flow, a. These curves are based upon the values of D_x/D_{urea} obtained from the lower curves. Limiting values for d are not obtainable at flows as small as here employed. The sodium curve included here but not among the lower curves points up the fact that intrinsically different dialysances may not be disclosed until relatively high flows are reached.

Lower: Dialysance, D, as a function of "blood" flow, a. These curves are based upon determinations as described in the caption of Table II. Limiting (maximal) values for D are not generally obtainable at flows as small as here employed, but for substances of low dialysance, *e.g.*, phenol red, they are approximated.

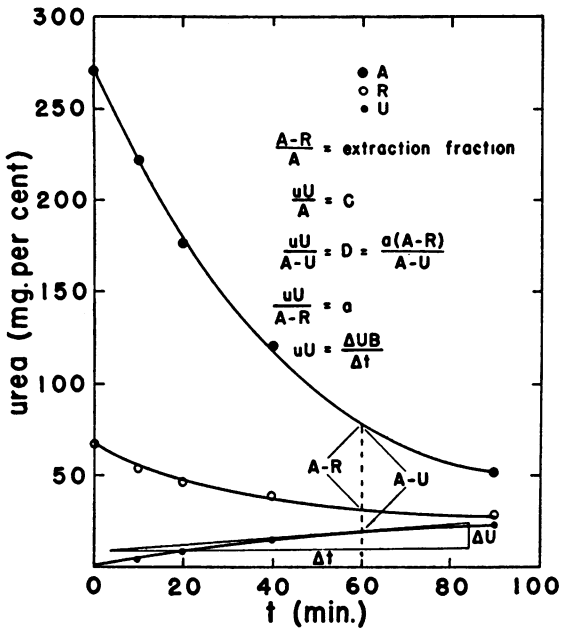

FIG. 4. RELATION OF UREA CONCENTRATION IN "BLOOD" ENTERING ARTIFICIAL KIDNEY, A, LEAVING THE KIDNEY, R, AND IN BATH FLUID, U, TO TIME, t

Results are of a recirculation experiment *in vitro* where a = 300 cc./min., b = 10,000 cc., and B = 100,000 cc. Illustrated is the basis for calculation at t = 60 min. of "instantaneous" urea excretion rate, extraction fraction, clearance, dialysance, and flow. $\Delta U/\Delta t$ is the slope of the U curve at t = 60, and $\Delta UB/\Delta t$ is the minute rate of excretion (units conforming to those of A and R) for which the term uU may be substituted. All curves approach a common asymptote. At zero time the clearance, whose value falls with time, is equal to the dialysance whose value is independent of time.

the formula

$$(U - S)_{glucose} = \frac{(R - A)_{glucose}}{\ln \frac{(U - A)_{glucose}}{(U - R)_{glucose}}}$$

based upon the exponential decrease of the glucose gradient along the cellophane path. Evidence for this type of decrease is afforded in information given by Merrill and his colleagues (1) on the relation between the extraction fraction and the number of coils of cellophane. U–S may also be found by using an "A bar" table (15). S is approximated for poorly extracted materials by $(A + R)/2$ or $\sqrt{AR}$.

A precise theoretical and practical solution to this problem of water balance seems remote so long as we deal with materials like glucose in the bath. Sucrose, having a smaller dialysance, offers possibilities which have not been examined therapeutically but it is far from ideal.[8] The cryoscopic method of Merrill and his associates (1) for adjusting fluid balance has no theoretical validity since the osmotic pressures in blood and bath do not reflect the fugacity of the fluids in these phases (15).

The relationship between the water clearance and blood flow at given U–S gradients of osmotically effective materials has not been carefully studied. Presumably where large U–S gradients exist, the water clearance is proportional to flow when flow is extremely small, *i.e.*, when the maximum possible clearance of water from plasma occurs. Where flow (ignoring colligated pressure effects) considerably exceeds the water clearance the two

[8] We find glucose solutions to be only ca. 0.75 times as effective as isosmolar sucrose solutions in causing osmosis at intermediate flows. Presumably this relates to the greater relative dialysance of glucose.

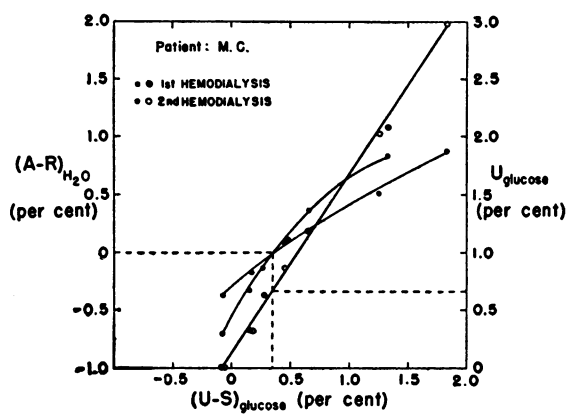

FIG. 5. EFFECT OF GLUCOSE IN BATH FLUID ON WATER CONTENT OF PLASMA DURING HEMODIALYTIC TRANSIT

$(A\text{-}R)_{H_2O}$ is the difference between the water concentration (g. water per 100 g. plasma) of plasma entering and plasma leaving the artificial kidney. $(U\text{-}S)_{glucose}$ is the average bath-plasma concentration gradient of glucose determined as indicated in section IV of the text. $U_{glucose}$ is the bath concentration of glucose. The curved lines fitting small circles relate $(A\text{-}R)_{H_2O}$ to $(U\text{-}S)_{glucose}$. The straight line fitting large circles relates $(U\text{-}S)_{glucose}$ to $U_{glucose}$. The point of apparent water balance, where $(A\text{-}R)_{H_2O} = 0$, is thus found on the interrupted line at $(U\text{-}S)_{glucose} = 0.36$ per cent and at $U_{glucose} = 0.66$ per cent. Plasma protein at t = 0 ranged from 4.9 to 5.3 per cent. Blood flow: first hemodialysis, 130–158 cc./min.; second hemodialysis, 188–240 cc./min. Water concentration in acalcic, aglycic bath fluid: first hemodialysis, 99.1147 per cent; second hemodialysis, 99.1455 per cent. Hematocrit: ca. 0.26.

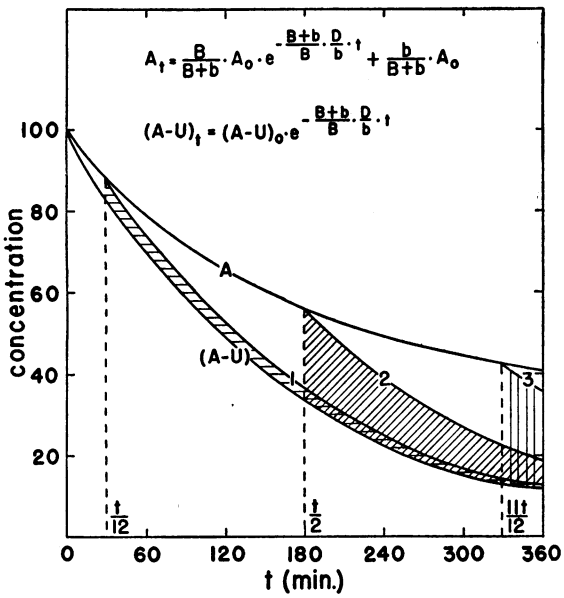

FIG. 6. GRAPHIC DETERMINATION OF OPTIMAL TIME FOR CHANGING BATH FLUID

The curves A (uppermost) and A-U (lowermost) were plotted from the equations in the graph using the following constants: D = 200 cc./min.; b = 50,000 cc.; B = 100,000 cc.; and A_0 = 100 concentration units. In a given time period, *e.g.*, 360 minutes, with no change of bath fluid, the quantity of material removed from blood to bath (containing none of the material at t = 0) is proportional to the area under the curve A-U. If at time t/12 we replace the bath with fresh fluid, A-U is increased from its value with respect to the first bath to a higher value, $(A\text{-}U)_{t/12} = A_{t/12}$, since for the second bath, U = 0 at t/12. A new A-U curve, 1, now bounds an increment of area denoted by horizontal hatching which measures the augmentation of excretion in 360 minutes. Instead of changing the bath at t/12, we might have changed at 11t/12 obtaining curve 3 and the vertically hatched area would have measured the augmentation of excretion. The obliquely hatched area under curve 2 derived from a bath change at t/2 is the maximal possible, hence t/2 is the optimal time for changing the bath once during a hemodialytic run whose total operating time is t.

variables become dissociated, the latter becoming essentially dependent only upon the U–S gradient. Evidence for this is suggested in the dissociation of the dialysances (and, therefore, the clearances) of other poorly extracted materials (*e.g.*, phenol red) from flow (Figure 3).

V. Dialysances in man. The effect of hemodialysis on urea, non-protein nitrogen, creatinine, and inorganic phosphate in a three hour period is shown in Table III and Figure 2.

VI. Optimal time for change of bath fluid. In order to augment the exchange of hemodialyzable solutes in the artificial kidney during a total operating time, t, the bath may be drained and refilled with fresh fluid at an intermediate time, t_1, increasing thereby the A–U gradient. Where dialytic blood flow is kept constant, the removal of urea from blood to bath follows closely an exponential curve (Figures 2, 4, and 6). It can be shown graphically (Figure 6) that the maximal removal of urea (ignoring its rate of formation) with a single change of bath fluid occurs when $t_1 = t/2$. All operating time intervals, t_i', between n changes should therefore be equal,[4] and $t_i' = t/(n+1)$. This holds regardless of the values of A and U at t = 0. For a total operating time, t = six hours, it was estimated (16) that with one bath change at three hours the urea removal from the body is ca. 16 per cent above that which would have occurred with no bath change. With two changes (two and four hours) the increment is ca. 20 per cent. With an infinite number of changes the calculated increment is ca. 31 per cent. These particular approximations were for a system having a bath volume of 100 liters, a 70 kg. man, and a urea dialysance of 175 cc./min.

[4] We are indebted to Dr. Ralph A. Beaver for providing a general mathematical solution for the problem.

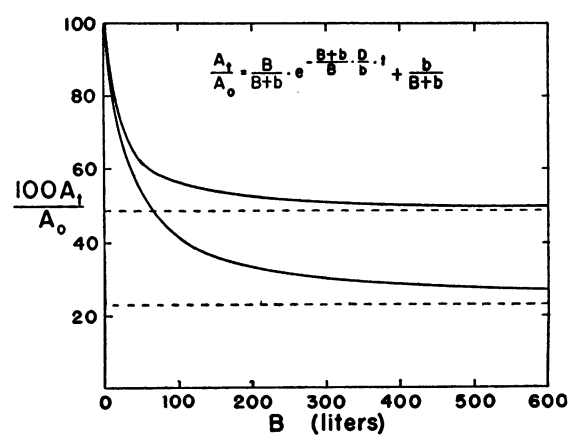

FIG. 7. THE PER CENT OF SOLUTE REMAINING IN THE BLOOD, $100A_t/A_0$, AS A FUNCTION OF THE VOLUME OF BATH FLUID, B

Arbitrary constants for the indicated equation in the graph are t = 360 min.; b = 50,000 cc.; upper curve, D = 100 cc./min.; lower curve, D = 200 cc./min. The upper and lower horizontal lines denote the value of $100\ A_t/A_0$ when B is of infinite volume for the upper and lower curves, respectively.

VII. The effect of bath fluid volume on total exchange. In Figure 7 is plotted the percentual decrements calculated to occur in the plasma concentration of a substance at two different dialysances (flows) after six hours of dialysis against an unchanged bath of given volume. Increasing the volume of the bath fluid beyond certain limits carries no clear advantage to total removal (which bears upon theoretical aspects of counterflow dialysis systems which may keep U close to zero, and which effectively create a bath of semi-infinite volume). It can be shown, for example, that a single change of a 100 liter volume of bath fluid at the optimal time may, in a certain total operating time, have as good an effect in lowering blood concentration of urea as if a 300 liter volume had been used without change in the same operating time.

DISCUSSION

The fact that the circulating fluid volume in the cellophane casing is proportional to the rate of flow has practical importance to the technique of hemodialysis. If one seeks to minimize fluctuations in a patient's blood volume during treatment he will bear in mind that rapid changes of flow through the cellophane cause rapid changes in blood volume. An increment in flow of 100 cc./min. causes approximately 160 cc. of blood to leave the patient for the machine; vice versa for a decrement in flow.[5] Further, proper attention to volume-flow relations enables one to reduce the likelihood of pulmonary edema which may occur if, for example, at the end of a run at 400 cc./min., the arterial inflow to the machine is stopped and the machine allowed to disgorge its contained blood rapidly into the patient. Even in the absence of excessive dilation of terminal loops a sudden plethora of 720 cc. of blood could be produced in less than two minutes. If terminal loops are dilated, much more blood than this can be forced on the patient. Watching a machine with no arterial inflow, but with dilated loops, return blood to a patient gives the illusion that it is only the swollen loops which are being drained off. Actually the engorged loops are being fed constantly until the casing proximal to them has become relatively empty. Operation of the artificial kidney without unnecessary dilation of terminal loops greatly assists the operator in stabilizing and regulating volumes and flows.

Although solutions containing several ions with concentrations up to 150 mEq./l. for sodium and chloride, and lesser values for other ions, have permitted reasonably reproducible determinations of dialysances, it is realized that different conditions engender other results. For example, Table II suggests that potassium is a highly diffusible and highly permeable ion ($d_K = 1.00$) and phosphate a poorly diffusible and/or permeable one ($d_{phosphate} = 0.31$). But where KH_2PO_4 was the only electrolyte in the "blood" in one test, it was found initially that $d_K = 0.65$ and $d_{phosphate} = 0.40$. This points up the interdependence of ions in a system where their freedom of movement is limited by coulomb forces and by the paucity of other ions whose presence could serve to increase the freedom of the inherently more mobile ones. The dialysance of one ion, in a mixture of several, has occasionally been observed to change appreciably as dialysis proceeded. And pH changes, which could be expected to occur under these conditions, have been observed. Nevertheless the study of dialysance is fruitful. It enables us to appraise potential transfers of materials in physiological and clinical tests; it points up the dialytic process as one of true "separation" not merely between colloids and crystalloids, but among diverse ionic and molecular species; and it enables us to make estimates of rates of tranfer as a function of molecular weight[6, 7] and electric charge.

SUMMARY

1. An artificial kidney (Brigham-Kolff type) has been used to study kinetics of hemodialysis *in vitro* and in man. Its operation has been described quantitatively and parallels to human renal excretion have been formulated.

2. The concept of dialysance, or the minute rate of net exchange of a substance between blood and

[5] The practice of hemodialysis lays the basis for a study of the effects of "varivolemia" on the circulatory function.

[6] Relative dialysances of non-electrolytes obtained from the range of flows used here are not definitive in the sense of being limiting values. However, they generally decrease with increase of molecular weight.

[7] That transfers of substances of higher molecular weight are relatively independent of blood flow (Figure 3) suggests a possibility of inferring the nature of the "causative" agents of uremia by the way in which hemodialytic relief of uremic symptoms may vary with rate of blood flow.

bath per unit blood-bath concentration gradient, is introduced as a parameter in artificial kidney function corresponding to the clearance in natural kidney function. Its value is relatively characteristic for different molecular and ionic species although for any one species it increases with blood flow and cellophane surface area. Using the urea dialysance as a reference, relative dialysances have been determined under various conditions for several non-electrolytes and ions.

3. The volume of circulating fluid contained in the cellophane casing is proportional to the rate of flow. From this relation have been deduced circulation times through the machine. A method is presented for stabilizing a patient's blood volume during therapy and reducing the likelihood of occurrence of pulmonary edema.

4. The effect of various concentrations of glucose in the bath fluid on fluid balance in the artificial kidney has been studied quantitatively.

5. In order to augment maximally the exchange of hemodialyzable solutes during some total operating time, the bath may be drained and refilled with fresh fluid at an intermediate time. It is concluded that, for any given total operating time and any chosen number of changes of bath fluid, operating time intervals between changes are optimum if equal.

6. The effects of dialysance, blood flow, and bath volume on the exchange of material during hemodialysis are quantified.

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