

## Interaction of Sodium Ion With Serum Protein<sup>1,2</sup>

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### INTRODUCTION

The interaction of sodium ion with blood proteins (2-7), other proteins (8-13) and with cellular content (14-19), is extensively dealt with in current literature. In the evaluation of the dialysis-perfusion system developed in this investigation, <sup>22</sup>Na ion was used as a test substance. This dialysis perfusion system allows the monitoring of unidirectional diffusion of a gamma emitting isotope from a dialysis cell. This cell is equipped with teflon end plugs and stopper, permitting the repeated use of the same cellulose membrane for serial dialysis experiments. (1)

### METHOD

Using the continuous monitored flow dialysis chamber, the rate of escape of <sup>22</sup>Na was determined in physiologic sodium chloride solution under buffered (Phosphate buffer) and non-buffered conditions. The steady state was maintained where possible; it was compromised by the presence of serum electrolytes other than sodium within the dialysis cell. Studies of washed and unwashed serum protein indicated that this deviation did not significantly influence the studies. The rate of escape of <sup>22</sup>Na was determined under standard conditions and as influenced by temperature, pH, serum protein concentration and the presence of potassium ion. In addition, the Donnan effect and the relation of distance of diffusion to diffusion characteristics were studied.

The serum protein was obtained from pooled specimens drawn from normal adult male laboratory workers. The pool was divided into aliquots for daily use and stored under frozen refrigeration. Each aliquot was thawed on the day of use. Freezing had no apparent effect upon sodium interaction.

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The interaction was determined by comparing the rate of elution of  $^{22}\text{Na}$  from the saline solution with the rate of elution from a saline solution of the serum protein in static condition. Half times and rate constants were determined by the described method (1). For the sake of brevity, the data is tabulated as half time. All determinations were made at a flow rate of 10 ml per minute. In each of the series of determinations, the same membrane was used throughout. Each elution curve was determined in triplicate.

## RESULTS

*Effect of Temperature*

The effect of temperature upon elution of  $^{22}\text{Na}$  was determined between  $4^\circ\text{C}$  and  $37^\circ\text{C}$ . These results are tabulated (Table I) and graphically represented (Figures 2 and 3). The rate of elution is related to absolute temperature (Figure 3). Interaction is indicated by an impedance to diffusion of 35% not influenced by temperature.

A calculation was made of the apparent activation energy of sodium ion diffusion based upon the Arrhenius equation. In logarithmic form  $\ln k = \ln A - E_a/RT$ , the experimental plot of  $\ln k$  against  $1/T$  should yield the slope equivalent to  $E_a/R$ . (See table 1a).

TABLE I.

THE EFFECT OF TEMPERATURE UPON THE OBSERVED AVERAGE HALF-TIME OF  $^{22}\text{Na}$  ELUTION FROM A 3.17 MM DIAMETER DIALYSIS CELL.

Tem- perature ( $^\circ\text{C}$ )	Half-Time <sup>1</sup> (min)				Half-Time Ratio		
	NaCl-NaCl $t_0$	3.5% $t_1$	Serum-NaCl $t_2$	$t_r$	$\frac{t_2}{t_0}$	$\frac{t_2}{t_1}$	$\frac{t_2}{t_r}$
4.0	33.80	33.90	46.00	9.05	1.36	1.36	5.08
9.0	28.60	29.60	39.30	9.37	1.37	1.33	4.19
18.5	21.51	21.72	29.20	6.61	1.36	1.34	4.42
28.0	17.60	17.55	23.70	6.21	1.35	1.35	3.82
37.0	16.19	14.03	18.88	4.58	1.17	1.35	4.12

<sup>1</sup> $t_1$ ,  $t_2$ , and  $t_r$  are the half time of first, second and resolved phases

TABLE IA.

APPARENT ACTIVATION ENERGY OF SODIUM ION DIFFUSION

Dialysis Cell Content		Dialysate	Activation Energy Kcal/mole
Non-permeable	Permeable		
—	NaCl 0.85%	NaCl 0.85%	4.40
Serum 50%	NaCl 0.85%	NaCl 0.85%	4.41
Serum 50%	NaCl 0.85%	NaCl 0.85%	5.01

*Effect of pH*

The effect of pH upon elution of  $^{22}\text{Na}$  was determined between pH 5.4 and 8.0. These results are tabulated. (Table II) Interaction was not significantly influenced by pH.

*Effect of Protein Concentration*

The effect of serum protein concentration upon elution of  $^{22}\text{Na}$  was determined between 1.75 grams per cent and 7.0. A relationship may exist between concentration and apparent binding; this trend may be seen in Table III.

*Effect of Potassium Concentration*

The effect of potassium ion concentration upon the elution of  $^{22}\text{Na}$  was determined (Table IV). The impedance to diffusion of sodium by serum pro-

TABLE II.

THE EFFECT OF pH UPON THE OBSERVED AVERAGE HALF-TIME OF  $^{22}\text{Na}$  ELUTION FROM A 3.17 MM DIAMETER DIALYSIS CELL AT 37°C

pH	Half-Time <sup>1</sup> (min)				$\frac{t_2}{t_0}$	$\frac{t_2}{t_1}$	$\frac{t_2}{t_n}$
	NaCl-NaCl	3.5% Serum-NaCl					
	$t_0$	$t_1$	$t_2$	$t_4$			
5.4	16.19	14.03	18.88	4.58	1.17	1.34	4.12
6.5	14.81	13.81	19.15	4.88	1.29	1.38	3.92
7.4	14.87	13.99	17.67	4.64	1.19	1.26	3.82
8.0	14.52	13.54	17.61	4.68	1.21	1.30	3.75

<sup>1</sup> $t_1$ ,  $t_2$ , and  $t_4$  are the half time of first, second and resolved phases

TABLE III.

THE EFFECT OF SERUM CONCENTRATION UPON THE OBSERVED HALF-TIME OF  $^{22}\text{Na}$  ELUTION FROM A 3.17 MM DIAMETER DIALYSIS CELL AT 10°C pH 5.4.

Sample	Serum Protein Concentration (%)	Half-Time <sup>1</sup> (min)		Serum-NaCl	Half-Time Ratio	
		NaCl-NaCl			$\frac{t_2}{t_0}$	$\frac{t_2}{t_1}$
		$t_0$	$t_1$	$t_2$		
NaCl	0	29.0	—	—	—	—
Unwashed Serum	1.75	—	28.5	34.5	1.19	1.21
Unwashed Serum	3.50	—	27.5	33.0	1.14	1.20
Unwashed Serum	7.00	—	27.0	36.5	1.26	1.35
Washed Serum	1.75	—	28.5	33.5	1.16	1.18
Washed Serum	3.50	—	29.0	37.0	1.28	1.28
Washed Serum	7.00	—	31.0	38.0	1.31	1.23

<sup>1</sup> $t_1$  and  $t_2$  are the observed half-time of first and second phases

tein was not influenced by the presence of potassium. The level remained constant at 35 per cent.

The control curve determined for  $^{22}\text{Na}$  in sodium chloride solution indicated a half time ( $t_0$ ) which in almost every instance was nearly identical with the half time ( $t_1$ ) of the first phase of the sodium chloride-serum protein curve.

#### *Effect of Fluid Thickness upon the Dialysis Rate*

The relation of the thickness of fluid in the dialysis cell, to the elution rate of  $^{22}\text{Na}$  was determined. The thickness of fluid was altered by placing cylindrical teflon cores of various displacement within the dialysis cell. The membrane area and external configuration of the cell remained unchanged. Dialysis cells having three fluid thickness values were employed in this study.

The permeability constant of the membrane for  $^{22}\text{Na}$  and  $^{131}\text{I}$  was determined by flow dialysis for conditions of isotopic exchange, diffusion and exchange plus diffusion. In each instance the area of diffusion cross section was  $5.38 \text{ cm}^2$ . The diameter of the core, the fluid thickness and cell volume are indicated on the pertinent tables. The permeability constant is obtained from the following formula:  $k = \frac{0.693 V}{A t_{1/2}}$  where  $V$  is cell volume,  $A$  is the area of membrane and  $t_{1/2}$  is the half time of elution. In the curves observed, first order kinetic prevailed. As anticipated, the permeability of the membrane was unchanged and unrelated to fluid thickness. The results are charted in Table V.

Using the one ml capacity, 3.17 mm radius, dialysis cell, the effect of serum protein upon the elution of  $^{22}\text{Na}$  is graphically illustrated in the two-phase curve in Figure 1. The first phase is equal to the rate of elution obtained from a  $\text{NaCl}:\text{NaCl}$  system in water solution, and the second phase has a slower rate by a factor of approximately 35 per cent. This phenomenon is verified by the information in Tables I, II and IV and Table VI—lines 7 to 9.

Use of teflon cores resulted in dialysis cells with reduced capacity and a cylindrical layer of fluid between the teflon core and the Visking membrane, but with an unchanged membrane area and external dimensions. Two such cells were

TABLE IV.

THE OBSERVED HALF-TIME OF  $^{22}\text{Na}$  ELUTION FROM A 3.17 MM DIAMETER DIALYSIS CELL AT VARIOUS RATIOS OF K TO NA AT  $38^\circ\text{C}$  AND pH 5.4.

<i>KCl : NaCl Ratio</i>	<i>Half-Time (min)</i>			<i>Half-Time Ratio</i>	
	<i>NaCl-NaCl</i>	<i>3.5% Serum-NaCl</i>		$\frac{t_2}{t_0}$	$\frac{t_2}{t_1}$
	$t_0$	$t_1$	$t_2$		
0 : 100	14.3	14.2	19.1	1.34	1.34
5 : 95	14.6	14.2	18.4	1.26	1.29
12.5 : 87.5	14.2	14.3	19.2	1.35	1.34
25 : 75	14.1	13.9	19.0	1.35	1.36
50 : 50	13.9	14.3	19.4	1.40	1.36
95 : 5	13.9	14.7	19.8	1.42	1.35

used, one with a capacity of 0.6 ml and a fluid thickness of 1.15 mm, the other with a capacity of 0.4 ml and a fluid thickness of 0.74 mm. The elution rate of  $^{22}\text{Na}$  from these altered cells may be seen in Tables VII and VIII. The second phase is not seen in either the presence or absence of serum protein or methyl cellulose. The rate of elution is a single constant rate phenomena; the rate of elution in conditions of sodium exchange in the presence or absence of serum protein (Table VII—lines 2 and 9) shows no significant difference; the rate of elution in a heteroionic system using KCl as the dialysate shows a decreased rate of elution of  $^{22}\text{Na}$ , but the rate is identical in the presence or absence of serum protein (Table VII—lines 3 and 10 and lines 6 and 14). The rate is also unaffected by serum protein in the non-steady state system using 0.85% NaCl: 8.5% NaCl (Table VII—lines 5 and 13). The rates of  $^{22}\text{Na}$  elution is little influ-

TABLE V

*Permeability calculation**Na-isotopic exchange (0.85% NaCl-0.85% NaCl)*

<i>Volume</i>	<i>Half-time</i>	<i>P</i>
0.4 ml	330 sec. ( 5.5 min.)	$1.56 \times 10^{-4}$ cm/sec.
0.6	516 ( 8.6 )	1.49
1.0	840 (14.0 )	1.53
<i>average</i> = $1.53 \times 10^{-4}$		

*Na-diffusion (0.85% NaCl-H<sub>2</sub>O, \*8.5% NaCl- H<sub>2</sub>O)*

<i>Volume</i>	<i>Half-time</i>	<i>P</i>
0.6 ml	450 sec. ( 7.5 min.)	$1.72 \times 10^{-4}$
1.0	732 (12.2 )	1.76
0.6*	408 ( 6.8 )	1.89
<i>average</i> = $1.79 \times 10^{-4}$		

*Na-exchange + diffusion (8.5% NaCl — 0.85% NaCl)*

<i>Volume</i>	<i>Half-time</i>	<i>P</i>
0.6 ml	444 sec. ( 7.4 min.)	$1.74 \times 10^{-4}$
1.0	660 (11.0 )	$1.95 \times 10^{-4}$
<i>average</i> = $1.84 \times 10^{-4}$		

*I-isotopic exchange (2.2% NaI — 2.2% NaI)*

<i>Volume</i>	<i>Half-time</i>	<i>P</i>
0.6 ml	150 sec. ( 2.5 min.)	$5.15 \times 10^{-4}$
1.0	252 ( 4.2 )	5.11
<i>average</i> = $5.13 \times 10^{-4}$		

*I-diffusion (2.2% NaI — H<sub>2</sub>O)*

<i>Volume</i>	<i>Half-time</i>	<i>P</i>
0.6 ml	252 sec. ( 4.2 min.)	$3.07 \times 10^{-4}$
1.0	408 ( 6.8 )	3.16
<i>average</i> = $3.12 \times 10^{-4}$		

enced by the nature of the non-permeable substance, serum protein or methyl cellulose or its concentration or combination over a wide range of viscosity (Table VIII). In the 1 ml capacity, 3.17 mm radius cylinder, the second phase is very prominent when methyl cellulose is employed as the non-permeable substance (Table IX). The first phase becomes less obvious and this phase disappears as concentration increases.

#### *Donnan Effect upon $^{22}\text{Na}$ Elution*

When  $^{22}\text{Na}$  in 0.85% and 8.5% NaCl is allowed to diffuse into distilled water, the rate of elution is constant until very low concentration is reached (Table VI—line 1 and Table VII—lines 1 and 4). When serum protein is added to the dialysis cell content, the elution rate against distilled water is initially identical to the rate without protein, as the sodium concentration decreases the rate of elution decreases until a virtual asymptote is reached at 10 to 12 per cent residual  $^{22}\text{Na}$  for 0.85% NaCl and 1.3% for 8.5% NaCl (Table VI—line 6 and Table VII—lines 8 and 12). Addition of NaCl to the dialysate restores the original rate of elution, as does KCl. The addition of 1.4% ethanol has no effect upon the  $^{22}\text{Na}$  retention by serum protein (Table VII—line 11). The rate of diffusion of an anion  $^{131}\text{I}$  from serum protein solution into distilled water is not significantly altered from the rate observed during exchange with NaI dialysate (Table X). The employment of equilibrium dialysis indicates a binding of  $^{22}\text{Na}$  by serum protein; the relative amount retained on the protein is inversely proportional to the NaCl concentration. Iodide was not retained in a similar equilibrium dialysis experiment (Table XI).

#### *Effect of Membrane*

Sorption phenomena does not appear to be significant. The membrane is

TABLE VI  
ELUTION OF  $^{22}\text{Na}$  FROM DIALYSIS CELL #1

Dialysis Cell Content		Dialysate	Half Time		Retained Non-Dialyzable $^{22}\text{Na}$
Non-permeable	Permeable		1st	2nd	
1. ———	NaCl 0.85%	H <sub>2</sub> O	12.0 min	—	1%
2. ———	NaCl 0.85%	NaCl 0.85%	11.0	—	
3. ———	NaCl 0.85%	KCl 1.08%	15.0	—	
4. ———	NaCl 8.5%	NaCl 0.85%	11.0	—	
5. ———	NaCl 8.5%	KCl 1.08%	10.3	—	
6. Serum	—	H <sub>2</sub> O	12.8		12%
7. Serum	—	NaCl 0.85%	14.0	19.0	
8. Serum	—	KCl 1.08%	14.3	20.3	
9. Serum	NaCl 8.5%	KCl 1.08%	11.7	18.7	

apparently not altered by previous experiments with protein solution. Very superficial rinsing and refilling of the dialysis cell allow nearly identical repetition of the observed elution curves. Some slight residual membrane charge may be observed in dialysis of NaCl against distilled water. The frictional impedance of the membrane to the diffusion of  $^{22}\text{Na}$  has special significance which is discussed below.

## DISCUSSION

The retention of residual  $^{22}\text{Na}$  in serum protein solution when dialyzing against distilled water is adequately explained by the Donnan membrane effect. The trapping of sodium with immediate release when additional sodium or potassium ion is furnished and the lack of anion trapping, as exemplified by iodide, all indicate a residual negative charge upon the protein molecule with a retention of  $^{22}\text{Na}$  to satisfy conditions of electrical neutrality.

Several tentative explanations for the two-phase curve observed when  $^{22}\text{Na}$  exchanges from serum protein solution had been considered. The identical rate observed in the  $t_0$  and  $t_1$  phase under all conditions would cast considerable doubt on the existence of two independent simultaneous first order reactions

TABLE VII  
ELUTION OF  $^{22}\text{Na}$  FROM DIALYSIS CELL #2

Dialysis Cell Content		Dialysate		Half Time		Retained Non- Dialyzable $^{22}\text{Na}$
Non-permeable	Permeable			1st	2nd	
1. ———	NaCl 0.85%	H <sub>2</sub> O		7.5 min	—	
2. ———	NaCl 0.85%	NaCl	0.85%	8.6	—	
3. ———	NaCl 0.85%	KCl	1.08%	9.2	—	
4. ———	NaCl 8.5%	H <sub>2</sub> O		6.8	—	
5. ———	NaCl 8.5%	NaCl	0.85%	7.4	—	
6. ———	NaCl 8.5%	KCl	1.08%	7.2	—	
7. ———	( $^{22}\text{Na}$ ) KCl 1.08%	KCl	1.08%	9.7	—	
8. Serum	———	H <sub>2</sub> O		7.8		10%
9. Serum	———	NaCl	0.85%	8.7	—	
10. Serum	———	KCl	1.08%	9.2	—	
11. Serum		Ethanol	1.4%	8.1		10%
12. Serum	NaCl 8.5%	H <sub>2</sub> O		6.8		1.3%
13. Serum	NaCl 8.5%	NaCl	0.85%	7.4	—	
14. Serum	NaCl 8.5%	KCl	1.08%	7.2	—	
15. Serum	( $^{22}\text{Na}$ ) KCl 1.08%	KCl	1.08%	9.6	—	

which may be identified as  $t_r$  (the resolved rate) and  $t_2$ . In the above circumstance, the resolved rate ( $t_r$ ) is always more rapid than  $t_2$ , implying the application of energy, thus making the transport of sodium out of the dialysis cell in the presence of serum protein or methyl cellulose an active phenomena. The source of energy for such an active transport is not apparent.

The lack of change of impedance of elution of  $^{22}\text{Na}$  by serum protein as influenced by temperature, pH, and potassium concentration, casts doubt upon the probability of the impedance of elution being due to chemical binding. The activation energy of 4.4 Kcal/mole is compatible with diffusion processes. The activation energy of chemical reaction is of a higher order of magnitude.

An alternate explanation of the identity of  $t_0$  and  $t_1$ , is to assume that they indeed are identical and that the dissociation of  $^{22}\text{Na}$  from serum protein is a slow process of diffusion and  $t_1$  and  $t_2$  may, therefore, be serial events. This phenomenon could assume binding by incorporation of  $^{22}\text{Na}$  in the sphere of immobilized water of protein hydration. Further assumption must make the protein solution a two-phase system as related to sodium ion; since serum protein is a mixture of many proteins, we must explain why phase two of the two-phase curve appears to be a single rate implying equal hydration of the various proteins. This explanation seems contrived and unlikely.

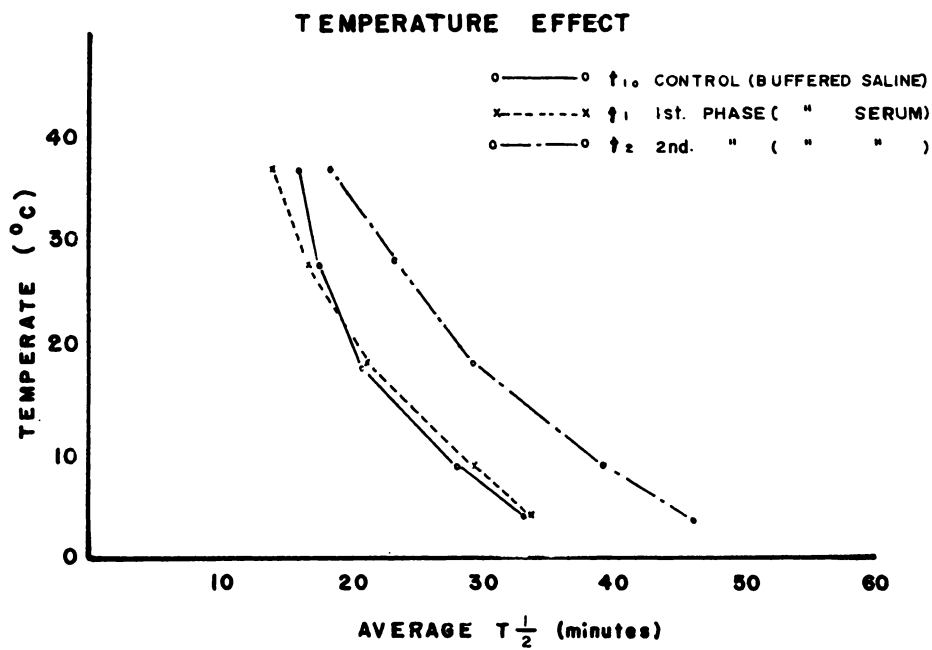
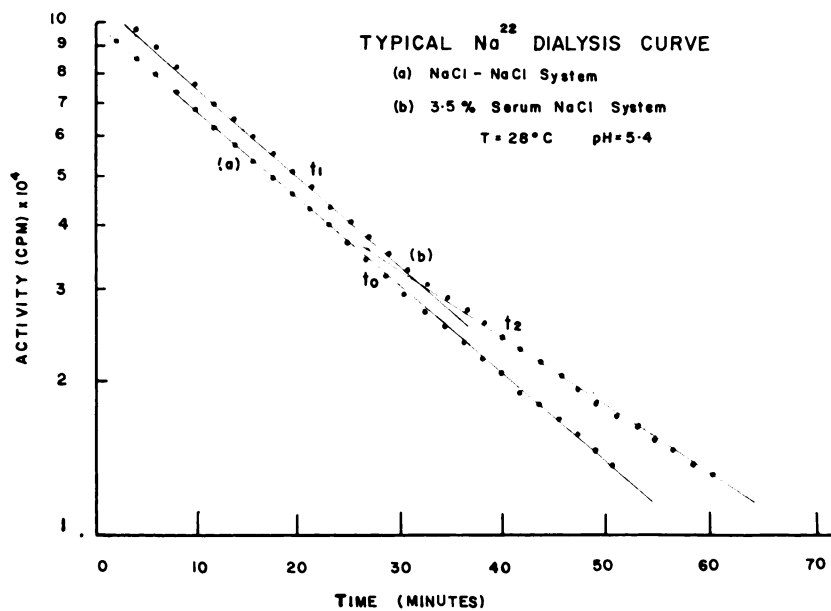
A more likely interpretation would deal with the compartment within the dialysis cell as being other than homogeneous. Since diffusion in all parts of the cylindrical compartment must be statistically equal, the escape of  $^{22}\text{Na}$  must take place at the boundary resulting in a gradient from this boundary to the center of the cell. In conditions of low viscosity, e.g. when a NaCl: NaCl system in water solution is observed at 37°C, a single phase is observed. It has been observed that at lower temperatures, slight second phase deviation may occur. In the presence of serum protein or methyl cellulose, the second slower phase is

TABLE VIII  
ELUTION OF  $^{22}\text{Na}$  FROM DIALYSIS CELL #3

Contact area 5.38 cm <sup>2</sup>		Fluid thickness 0.74 mm	
Cell volume 0.4 ml		Core diameter 5.0 mm	
<i>Dialysis Cell Content</i>		<i>Dialysate</i>	<i>Half Time</i>
<i>Non-permeable</i>		<i>Permeable</i>	<i>1st 2nd</i>
1. ———		NaCl 0.85%	5.4 min —
2. Serum	67%	NaCl 0.85%	5.7 —
3. Serum	75%	NaCl 0.85%	5.6 —
4. Serum	100%	———	5.9 —
5. Methyl Cellulose	0.07%	NaCl 0.85%	5.2 —
6. Methyl Cellulose	0.35%	NaCl 0.85%	5.6 —
7. Methyl Cellulose	0.7%	NaCl 0.85%	5.6 —
8. Methyl Cellulose	1.4%	NaCl 0.85%	5.7 —
9. {	Serum 75%	NaCl 0.85%	5.6 —
	Methyl Cellulose 0.07% (1 : 1)		



always observed when the radius of the dialysis cell is 3.17 mm. When the thickness of the fluid layer through which the sodium ion diffuses is decreased by addition of a teflon core, the rate of diffusion is not altered by the presence of



substances of high viscosity. The kinetics of compartmental exchange from a system of concentric cylinders has been derived and are presented by the authors in the two papers to follow (20, 21).

The relation between viscosity due to non-electrolytes and diffusion of small electrolytes has been discussed by Stokes and Mills (22). Viscosity may change markedly with very small proportional changes in diffusion rates. The observation in the system reported that diffusion of  $^{22}\text{Na}$  across small distances is not influenced in an observable way and is not at variance with the Nernst modification of the Fick formulation.

$$D = RT/fN$$

where  $D$  is the diffusion constant,  $f$  is the frictional force,  $N$  is the number of molecules/mole; nor the Stokes law defining  $f$  for spherical particles:

$$f = 6\pi\eta r_0$$

where  $\eta$  is the viscosity of the medium and  $r_0$  is the molecular radius; nor the Sutherland-Einstein formula:

$$D = RT/6\pi\eta r_0 N$$

It must be assumed in conformity with the discussion by Stokes and Mills on lack of proportionality between diffusion of small electrolytes and viscosity, that under the specific condition of observation referred to, the length of pathway observed is a factor in addition to the frictional force and the number of molecules present. A significant impedance of diffusion related to distance produces the second phase when a fluid thickness of 3.17 mm is the net distance of diffusion. This impedance of diffusion is not apparent when the distance is less than 1.15 mm, the forces of diffusion being of such magnitude that the frictional forces as observed are inconsequential. The definition of "diffusion" as expressed by the

TABLE IX

ELUTION OF  $^{22}\text{Na}$  FROM DIALYSIS CELL #1

Contact area 5.38 cm <sup>2</sup> Cell volume 1 ml		Fluid radius 3.17 mm Core diameter 0		
<i>Dialysis Cell Content</i>		<i>Dialysate</i>	<i>Half Time</i>	
<i>Non-permeable</i>	<i>Permeable</i>		<i>1st</i>	<i>2nd</i>
—————	NaCl 0.85%	NaCl 0.85%	13.0 min	——
Serum 75%	NaCl 0.85%	NaCl 0.85%	14.4	18.8
{ Serum 75%				
Methyl Cellulose 0.07%	NaCl 0.85%	NaCl 0.85%	13.7	18.5
Methyl Cellulose 0.014%	NaCl 0.85%	NaCl 0.85%	13.0	19.5
Methyl Cellulose 0.07%	NaCl 0.85%	NaCl 0.85%	12.5	16.8
Methyl Cellulose 0.35%	NaCl 0.85%	NaCl 0.85%	14.0	20.0
Methyl Cellulose 0.7%	NaCl 0.85%	NaCl 0.85%	16.0 <sup>1</sup>	22.0
Methyl Cellulose 1.4%	NaCl 0.85%	NaCl 0.85%	——	22.4

<sup>1</sup>Very short first phase

idealized formulae of Nernst, Stokes, Sutherland and Einstein do not express the observed rate of dialysis in the system being studied. The added factors of distance, regular heterogeneity and mixing are pragmatic complications of transport which must be considered by the biologist. Fick's second law should be used when dealing with transport phenomena in this situation. A derivation has been made in which the observed dialysis rate is influenced by these added factors and is presented in the following paper (20).

In addition to the complication added by distance, heterogeneity and mixing to the diffusion of small electrolytes and molecules, the frictional impedence to this diffusion by the cellulose membrane is a significant factor. When the diffusion through the membrane occurs at a slower rate than through a water or protein solution boundary, the diffusion from either solution is rate limited by the membrane. Any thickness of water solution or viscous solution presenting a lesser friction to the particles than the membrane would result in identical rates of diffusion from the dialysis cell as determined by the membrane friction. The factor of distance assumes significance when the summation of frictional components in water solutions exceeds the friction of the membrane resulting in a second and slower phase of dialysis. This summation is significant at 3.17 mm for  $^{22}\text{Na}$  and  $^{131}\text{I}$  in protein and methyl cellulose solution, while not significant at 1.15 mm or less.

The conventional explanation for the two-phase curve observed as representing two independent, simultaneous, first order reactions, may be described as an infinite number of independent consecutive first order reactions of decreas-

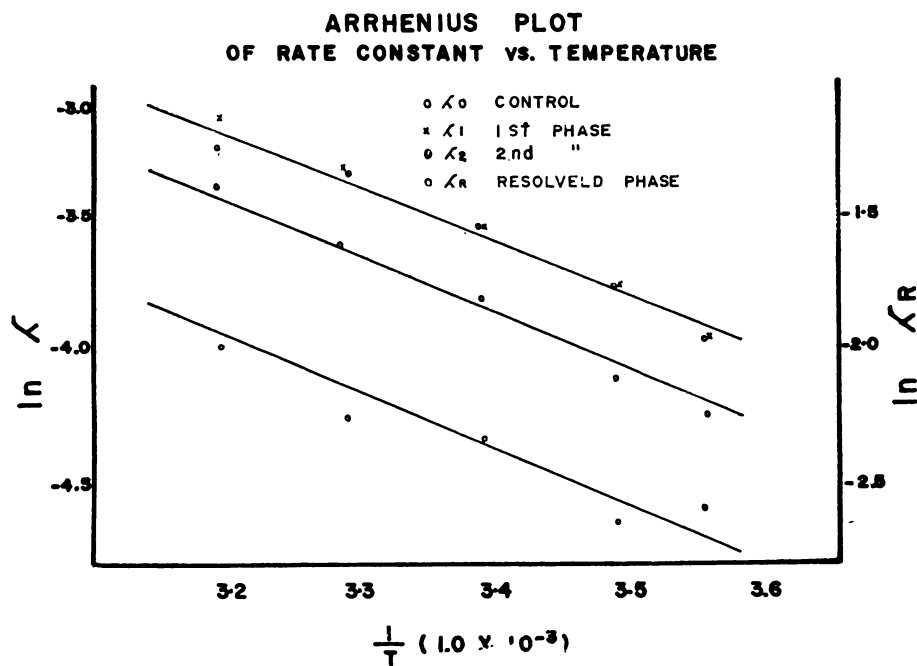


Fig. 3

ing rate modified by the membrane friction factor and the cylindrical configuration of the dialysis cell to appear as a two-phase curve.

If it is assumed that the characteristics discussed above are a generalized relationship between small particles and membranes, the biologic implication should be significant. Biologic membranes would then become rate limiting for passive transfer despite the frictional properties of the adjacent solution, if the total friction is of lesser magnitude than that of the membrane.

## SUMMARY

A continuously monitored perfusion-dialysis system has been previously described by the authors (1) permitting the determination of the rate of diffusion of labeled sodium from a dialysis cell. This system has been employed to study the interaction between sodium ion and serum protein. In a cylindrical dialysis cell of 3.17 mm radius, the elution rate ( $t_o$ ) of sodium ion is constant. With addition of serum proteins to the solution in the cell, an initial elution rate ( $t_1$ ) is observed equal to  $t_o$ , followed by a slower rate ( $t_2$ ). The ratio of  $t_2/t_1$  is 1.35; this ratio is unchanged by altering temperature, pH or added potassium. Changing protein concentration results in equivocal change in ratio. Reduction of the fluid thickness to 1.15 mm or less results in the elimination of  $t_2$  in the presence of serum protein and  $t_1$  is equal to  $t_o$ . This phenomenon is interpreted as a disproportion of the frictional impedance to diffusion by the diffusional forces acting over short distances and more significantly to the rate limiting characteristics of the membrane due to increased membrane friction to diffusion when compared to the lesser frictional properties of water solutions of various viscosity.

TABLE X

ELUTION OF  $^{131}\text{I}$  FROM DIALYSIS CELL #1

Contact area 5.38 cm <sup>2</sup> Cell volume 1 ml		Fluid radius 3.17 mm Core diameter 0		
<i>Dialysis Cell Content</i>		<i>Dialysate</i>	<i>Half Time</i>	
<i>Non-permeable</i>	<i>Permeable</i>		<i>1st</i>	<i>2nd</i>
—	NaI 2.2%	NaI 2.2%	6.7 min	10.2 min
—	NaI 2.2%	H <sub>2</sub> O	8.9	13.8
Serum	NaI 1.0%	NaI 2.2%	7.2	13.7
Serum	NaI 1.0%	H <sub>2</sub> O	8.6	14.8

No retained  $^{131}\text{I}$ ELUTION OF  $^{131}\text{I}$  FROM DIALYSIS CELL #2

Contact are 5.38 cm <sup>2</sup> Cell volume 0.6 ml		Fluid thickness 1.15 mm Core Diameter 4.0 mm		
—	NaI 2.2%	NaI 2.2%	6.1 min	
—	NaI 2.2%	H <sub>2</sub> O	6.1	—
Serum	NaI 1.0%	NaI 2.2%	6.0	—
Serum	NaI 1.0%	H <sub>2</sub> O	6.0	—

No retained  $^{131}\text{I}$

TABLE XI

DISTRIBUTION OF  $^{22}\text{Na}$  BETWEEN SERUM AND VARIOUS CONCENTRATIONS OF SALINE SOLUTION AT EQUILIBRIUM

Conditions: 1 ml of serum in dialysis cell allowed to equilibrate with 100 ml of NaCl solution with  $^{22}\text{Na}$  label.

<i>Equilibrium Concentration</i>		<i>b/a</i>	<i>Na Bound by Serum</i>	
<i>(a) Na in Saline</i>	<i>(b) Na in Serum</i>		<i>mg/100 ml</i>	<i>m.e./l of Serum*</i>
0.0520%	0.0712%	1.37	19.2	8.35
0.0422%	0.0620%	1.47	19.8	8.61
0.0359%	0.0594%	1.67	23.3	10.22
0.0223%	0.0444%	1.99	22.1	9.61
0.0145%	0.0363%	2.50	21.8	9.47

*1 ml of Serum Equilibrated Against NaI Solution*

<i>(a) Na in NaI</i>	<i>(b) Na in Serum</i>			
0.0826%	0.1045%	1.26	22.0	9.58
<i>(a) I in NaI</i>	<i>(b) I in Serum</i>			
0.4402%	0.3764%	0.81	(-) 6.4	(-) 0.52

\*7.0 g% serum protein

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#### INTERNATIONAL SYMPOSIUM ON RADIATION THERAPY

A three-day international symposium on radiation therapy will be held in New York City on March 13, 14, 15, 1968, under the auspices of Memorial Sloan-Kettering Cancer Center.

Among the speakers will be world-renowned radiologists from Canada, Denmark, England and Sweden, as well as from six institutions in the United States.

The subjects will include the radiation therapy center as a teaching institution; clinical trials, follow-up, and evaluation in the radiation therapy center; treatment planning, and radiocurable cancers in children and adults. The program will also include a tour of the new Russell A. Firestone Radiation Therapy Center, followed by a reception.

Invitations may be obtained by writing to Dr. Ralph Phillips, Memorial Sloan-Kettering Cancer Center, 444 East 68th Street, New York, New York 10021. There is no fee connected with the symposium, however, registration will be limited and admission will be by invitation only.