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### Research Article

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# Altered Permeability of the Peritoneal Membrane after Using Hypertonic Peritoneal Dialysis Fluid

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**ABSTRACT** Previous work has shown that use of hypertonic peritoneal dialysis fluid (7% glucose) results in ultrafiltration and enhanced urea transfer across the peritoneal membrane. Simultaneous creatinine studies showed a similar enhancement with hypertonic fluid which persisted in lesser degree during subsequent isotonic exchanges. The mechanism of solvent drag has been shown to contribute significantly to the increased urea removal with ultrafiltration. In the present study, the role of altered diffusive permeability of the peritoneal membrane as suggested by the creatinine data was evaluated as a possible additional mechanism. Hypertonic exchanges were bracketed by isotonic (1.5% glucose) exchanges during 11 studies in four patients. During six other studies in four patients, isotonic exchanges only were performed. A mathematical model for peritoneal solute transport by diffusion was developed and a method to distinguish alterations in peritoneal membrane permeability from changes in membrane area proposed. The method incorporates the determination and comparison of transport characteristics for two test solutes of widely different molecular weights. Alterations in inulin and urea transperitoneal transport characteristics in the above studies indicate a significant increase in membrane permeability after exposure to hypertonic solutions that persists during subsequent isotonic exchanges. Varying patterns of membrane area and permeability changes occurred during repeated exposure to only isotonic exchanges. The

findings are discussed in regard to recent concepts of passive transcapillary transport.

## INTRODUCTION

Previous work had demonstrated that ultrafiltration across the peritoneal membrane in response to dialysis solutions made hypertonic by the addition of 7.0% glucose results in the enhanced removal of urea (1). Solvent drag has been identified as one of the mechanisms responsible for this enhancement. A slight but consistent increase in the removal rate of creatinine with the use of isotonic solutions after exposure of the peritoneal membrane to hypertonic dialysis fluid suggested that an alteration in the passive transport characteristics of the membrane may have resulted from exposure to hypertonic solutions. Inulin and urea were used as test solutes, and their dialysances across the peritoneal membrane were calculated. Inulin dialysance increased more than urea, but both increased significantly after exposure to hypertonic solutions.

## METHODS

Inulin with a molecular weight of about 5200 and urea with a molecular weight of 60 were selected as test solutes because of their widely differing molecular size and neutral charge.

Previously described dialysis techniques and equipment were employed (1) to carry out 17 peritoneal clearance studies in six oliguric patients coming to dialysis for renal failure. Urine volume for all patients was less than 400 cc/24 hr, with endogenous creatinine clearances of less than 5 ml/min. The study was conducted during the first 10 exchanges of the dialysis. Inulin, 0.1 g/kg of body weight, was given i.v. before the dialysis was initiated. The inulin was permitted to equilibrate for at least 2 hr, after which a single washout exchange was conducted to insure the technical acceptability of the procedure and to empty any collection of peritoneal fluid which might be present. Blood was drawn at this point and the inulin space calculated. Urea space was assumed to be 60% of the total body weight, i.e., total

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body water. Fig. 1 is a plot of dialysance vs. body space for a variety of equilibration ratios. It is apparent that errors of 5-10 liters in body space do not alter dialysance at equilibration ratios below 0.60. After this exchange at least two and usually three control exchanges with 2 liters of dialysis fluid containing 1.5% glucose ("isotonic") were conducted using a 70 min exchange time (10 min inflow, 30 min dwell, 30 min drain). In protocol A (11 studies in four patients) two or three exchanges were then conducted with 7% glucose-containing dialysis fluid ("hypertonic"). Inulin and urea were added to the hypertonic dialysis fluid in amounts sufficient to approximate their plasma concentrations, and sieving coefficients were measured. The study concluded with a second set of isotonic exchanges. In protocol B (six studies in four patients) isotonic solutions were used throughout. Dialysis fluid was sampled after the drainage period was completed to obviate the problem of sampling error due to incomplete mixing of fluid within the peritoneal space. Blood was drawn every second or third exchange, and a concentration vs. time curve was constructed for urea and inulin from which blood values for the clearance periods were taken. Urea and osmolality were assayed by methods previously reported (1). The alkali stable fraction of inulin was determined by the method of Walser, Davidson, and Orloff (2). This method selects for assay a comparatively larger and more homogeneous molecular weight fraction of polymers within the total inulin population. The diffusive transport characteristics of the peritoneal membrane were compared before and after the use of 7% glucose-containing dialysis fluid (protocol A), and these values were compared with comparable exchanges when continuous 1.5% exchanges were run (protocol B).

A mathematical model of the system was set up (See Appendix), and peritoneal dialysance in milliliters per minute for each exchange was calculated for inulin ( $D_I$ ) and urea ( $D_U$ ) across the peritoneal membrane. The dialysance value for a given solute is physiologically a function of the peritoneal membrane properties of area and permeability as well as the extramembrane factors of dialysis fluid temperature, hydrostatic pressure in the belly, diffusion rate of the solute in water, and timing of the various phases of the exchange. Since care was taken to maintain the extramembrane factors constant from exchange to exchange, the peritoneal dialysance will reflect changes in membrane area and permeability. If the dialysance value for two solutes are compared in ratio fashion, e.g.

$$\frac{D_I}{D_U} = \frac{(\text{permeability to inulin}) (\text{membrane area for inulin})}{(\text{permeability to urea}) (\text{membrane area for urea})}$$

then alterations in this ratio ( $D_R$ ) will reflect changes in selective permeability of the peritoneal membrane provided the membrane area for diffusion of the two solutes considered is the same. Dialysance values for inulin and urea from both protocols were calculated for control and experimental exchanges. Sieving coefficients were calculated for the hypertonic exchanges of protocol A only if there was reasonably close agreement between the inulin and urea concentrations in the dialysis fluid before inflow and the plasma.

## RESULTS

Table I is a representative set of data for study L. M. using protocol A. The first and seventh exchanges were conducted with no dwell time and were for the purpose

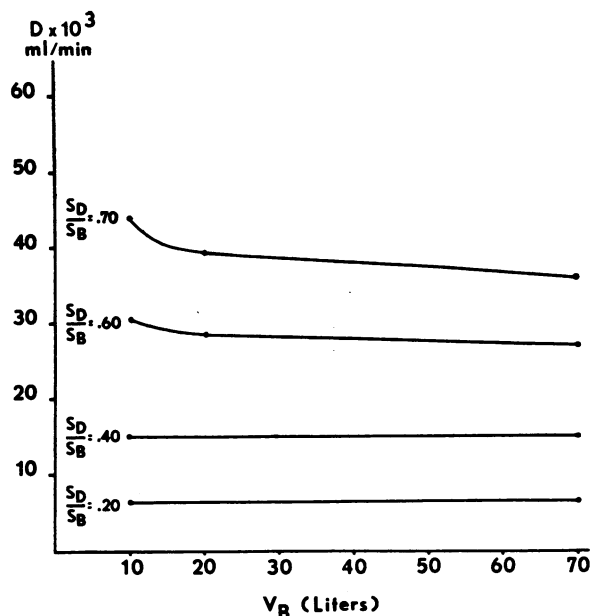


FIGURE 1 Dialysance ( $D$ ) is plotted against body space of distribution ( $V_B$ ) for a variety of equilibration ratios ( $S_D/S_B$ ). The dialysance values used to plot these curves were generated from the equation for dialysance formulated in the Appendix for a given equilibration ratio by varying  $V_B$ . At a given equilibration ratio the body space was varied and a theoretical dialysance calculated.

of "washing out" the peritoneal space. In the first instance this was conducted to insure that there was no ascites present and in the second to reduce the likelihood of any contamination of the experimental exchanges by the preceding hypertonic solution. The volume returned in the drainage from both experimental and control isotonic exchanges exceeds that infused (2050 cc) by a maximum of 200 cc. This results from the slight osmotic gradient from dialysis fluid to plasma present when "isotonic" 1.5% glucose-containing dialysis fluid is used. Dialysis fluid-to-plasma osmotic ratios ( $S_D$  osm/ $S_B$  osm) for the isotonic exchanges (2-4, 8-10) were 1.04-1.06, indicating the equilibration at the close of an exchange is virtually complete. This small degree of ultrafiltration when present was about equivalent in both control and experimental exchanges. Fig. 2 shows the inulin dialysance ( $D_I$ ) values for the Table I study in bar graph form as well as all other studies conducted using protocol A. The statistical significance of the differences of the means for each study appears along the abscissa. It is apparent that  $D_I$  rose in every instance after exposure of the membrane to 7% glucose-containing solution. Fig. 3 is a comparable bar graph plot of urea dialysance ( $D_U$ ) for all of the values obtained. Once again, it is apparent that in every instance the  $D_U$  values rose. Finally, Fig. 4 gives the ratio of inulin-

TABLE I  
Representative Study on *L. M.* using Protocol A

Exchange	Return volume	V	$S_{D\text{osm}}/S_{B\text{osm}}$	Inulin			Urea			$D_R$
				$S_B$	$S_D/S_B$	$D_I \times 10^3$	$S_B$	$S_D/S_B$	$D_U \times 10^3$	
	ml	ml/min		mg/ml		ml/min	mg/ml		ml/min	
1	1820	45.5	1.07	0.2565	—	—	1.010	—	—	—
2	2200	31.4	1.05	0.2033	0.129	4.0	0.975	0.499	20.3	0.197
3	2056	29.3	1.06	0.1980	0.150	4.7	0.950	0.453	17.6	0.267
4	2248	32.1	1.06	0.1938	0.130	4.0	0.926	0.486	19.3	0.207
5 (7%)	2740	39.1	1.45	0.1990	0.580	—	0.933	0.824	—	—
6 (7%)	2930	41.9	1.39	0.2052	0.503	—	0.942	0.786	—	—
7	1945	46.3	1.07	0.2030	—	—	0.928	—	—	—
8	2185	31.2	1.04	0.2033	0.189	6.2	0.910	0.540	22.8	0.271
9	2090	29.9	1.04	0.2020	0.241	8.1	0.908	0.549	23.4	0.346
10	2108	30.1	1.04	0.2014	0.185	6.0	0.906	0.541	22.8	0.263

V, volume;  $S_{D\text{osm}}/S_{B\text{osm}}$ , dialysis fluid-to-plasma osmotic ratio;  $S_B$ , concentration of a solute S in the body compartment of its distribution;  $S_D$ , concentration of the same solute in dialysis fluid;  $D_I$ , inulin dialysance;  $D_U$ , urea dialysance;  $D_R$ , ratio of inulin-to-urea dialysance.

to-urea dialysance ( $D_R$ ) in graphic form. There is an increase in the mean values in all but two instances, and there is considerable overlap in the ranges for each study. By treating the mean dialysance values for pre- and postexposure to 7% solutions as paired variables and analyzing the difference for all 11 studies, we de-

rived a  $P$  value for the change in  $D_I$  of less than 0.01, for  $D_U$  of less than 0.001, and for their ratio ( $D_R$ ) of less than 0.05 (3). Sieving coefficients for inulin and urea are given in Table II. There were seven inulin and three urea exchanges in which the concentrations of solute in dialysis fluid and plasma were sufficiently

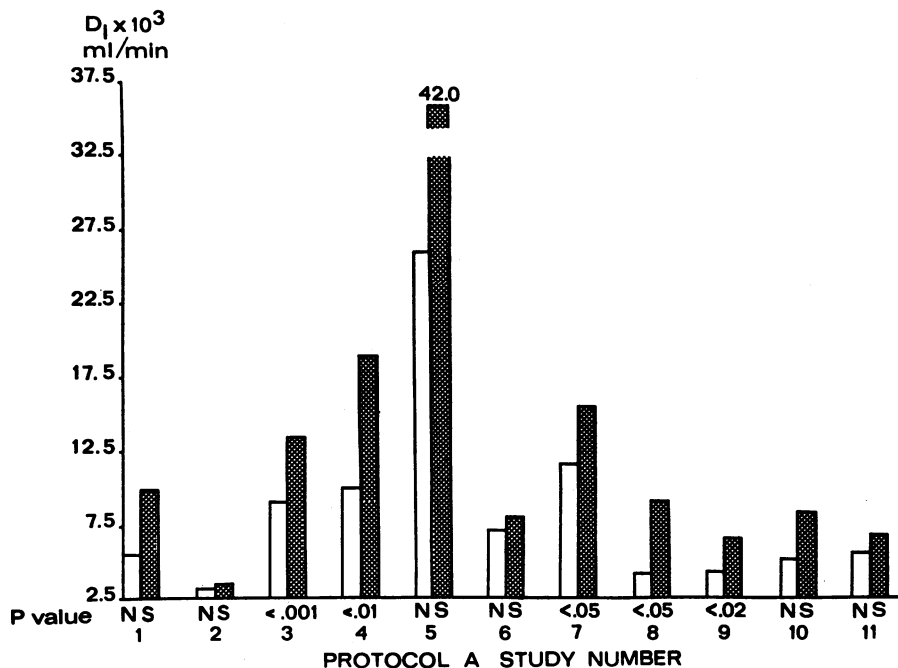


FIGURE 2 Dialysance values for inulin in control (open bars) and experimental (hatched bars) exchanges for the studies in protocol A. Paired analysis of all 11 studies gives a  $P$  value of less than 0.01 for the difference in control and experimental observations.  $P$  values for the significance of the difference of the means for each study is given along the abscissa.

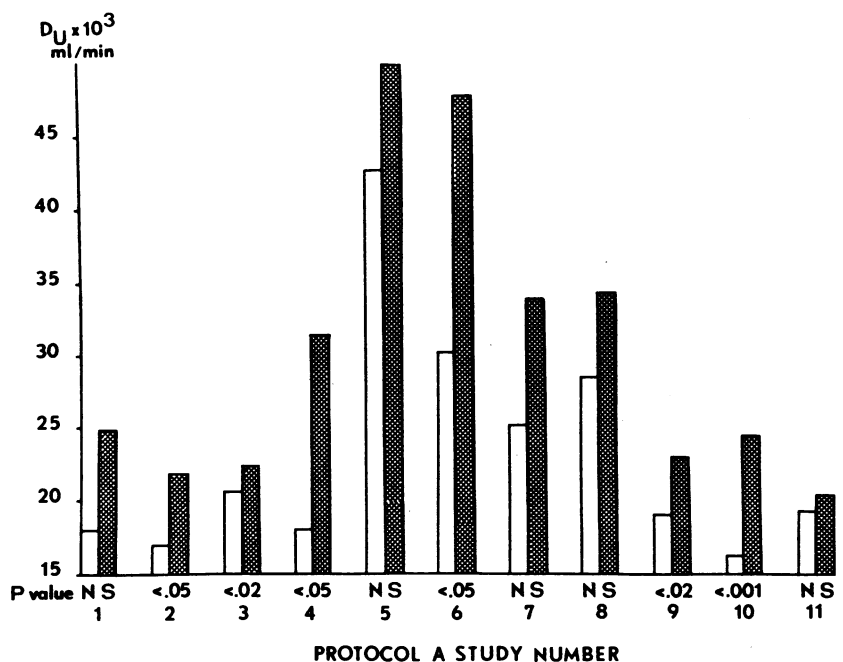


FIGURE 3 Dialysance values for urea in control (open bars) and experimental (hatched bars) exchanges for the studies in protocol A. The  $P$  value for paired analysis of all 11 studies was less than 0.001. See caption to Fig. 2 for further explanation.

close to minimize contributions of solute transfer by diffusion. The mean values of 0.83 and 0.81 for inulin and urea are very similar.

Table III is a representative set of data for study

G. K. using protocol B. During exchanges 5 and 6, 1.5% glucose solutions were used, and hence no "wash-out" exchange was required as in protocol A.  $D_I$  and  $D_U$  values were calculated for all exchanges, but only 2, 3,

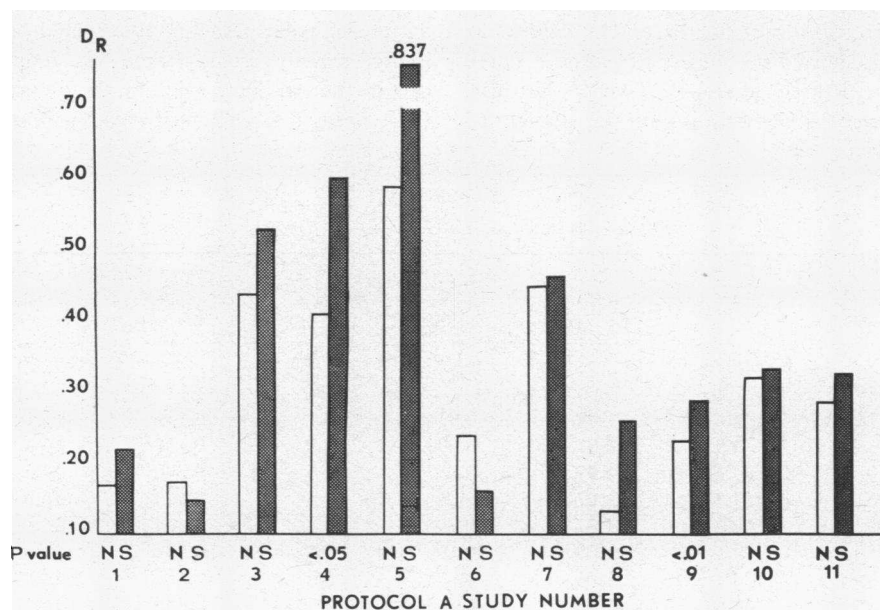


FIGURE 4 Inulin:urea dialysance ratios in control (open bars) and experimental (hatched bars) exchanges for the studies in protocol A. The  $P$  value for paired analysis of all 11 studies was less than 0.05. See caption to Fig. 2 for further explanation.

TABLE II  
Sieving Coefficients for Inulin and Urea

Study No.	Ultrafiltrate volume (cc)	Sieving coefficients	
		Inulin	Urea
5-4	640	1.00	—
5-5	680	0.87	0.88
6-4	624	—	0.78
6-5	800	0.93	0.78
7-4	670	0.82	—
7-5	620	0.80	—
8-4	800	0.82	—
8-5	730	0.60	—
Mean	695	0.83	0.81

and 4 were used for the control dialysance ratios ( $D_R$ ) and 8, 9, and 10 for the experimental dialysance ratios presented in Fig. 7. In this study  $D_I$  increased in the experimental exchanges. Fig. 5 shows inulin dialysance in this and the remaining studies utilizing protocol B in bar graph form. The significance of the changes is noted along the abscissa. In contrast to the uniform rise of  $D_I$  noted in protocol A, these studies showed no particular pattern. Only in study 4 did  $D_I$  rise, and in study 5 it fell.

Values for  $D_U$  and  $D_R$  in study G. K. are given in Table III. These values for all six studies are plotted in Figs. 6 and 7. Urea dialysance values were the most consistent, showing either an increase or no change. Only study 6 showed a significant increase.  $D_R$  values, as would be expected, showed no consistent pattern. Three studies increased and three decreased. Two of the three studies that decreased showed a significant change (5

and 6). Only one of the increasing studies was significant. By treating the difference in pre- and postmean values as nonindependent, paired variables and analyzing the difference in all six studies as we have done for the protocol A data, we have found no significant difference from zero in the change of  $D_I$ ,  $D_U$ , and  $D_R$ .

## DISCUSSION

The peritoneum covers all structures in the peritoneal space and is the membrane through which solute must move in order to enter the dialysis fluid. Urea and inulin occupy different body spaces. Urea with an intracellular distribution has the potential for a larger membrane for diffusion into the peritoneal space than does inulin. Muscle and visceral cells that abut on the peritoneal mesothelium provide potential membrane available to urea for this diffusion. However, Karnovsky (4) has shown that for "small" solutes (molecular weight of 40,000 or less) such as urea and inulin, the major path of egress from capillaries is via intercellular channels with no major transcellular transfer occurring. Thus, even though urea can traverse the limiting plasma membrane of cells, it would be expected to do so at a considerably slower rate than via intercellular channels. In addition, the urea content of the mesothelial cells is small and would be exhausted promptly except for cells in immediate juxtaposition to a capillary. The contribution of urea by other than capillary membranes to the total urea in the dialysis fluid after the first or second exchange would be expected to be negligible. Should these theoretical considerations be correct, the major diffusion path for urea would be the same as for inulin, namely from plasma via intercellular channels across the capillary wall to the interstitium and from there across the peritoneal mesothelium. This would im-

TABLE III  
Representative Study on G. K. using Protocol B

Exchange	Return volume	V	$S_{D_{osm}}/S_{B_{osm}}$	Inulin		Urea		$D_R$
				$S_D/S_B$	$D_I \times 10^3$	$S_D/S_B$	$D_U \times 10^3$	
	ml	ml/min			ml/min		ml/min	
1	1820	27.2	1.06	—	—	—	—	—
2	2178	31.1	1.08	0.096	3.1	0.449	17.4	0.178
3	2133	30.5	1.07	0.093	2.8	0.431	16.4	0.170
4	2105	30.1	1.07	0.087	2.6	0.390	14.3	0.181
5	2084	29.8	1.07	0.093	2.8	0.424	16.0	0.175
6	2092	29.9	1.07	0.095	2.8	0.404	15.1	0.185
7	2060	29.4	1.05	0.106	3.1	0.432	16.4	0.189
8	1990	28.4	1.04	0.099	3.0	0.422	16.0	0.187
9	2188	31.3	1.03	0.114	3.3	0.435	16.6	0.198
10	2116	30.2	1.03	0.132	4.1	0.441	16.9	0.242

See Table I for explanation of abbreviations.

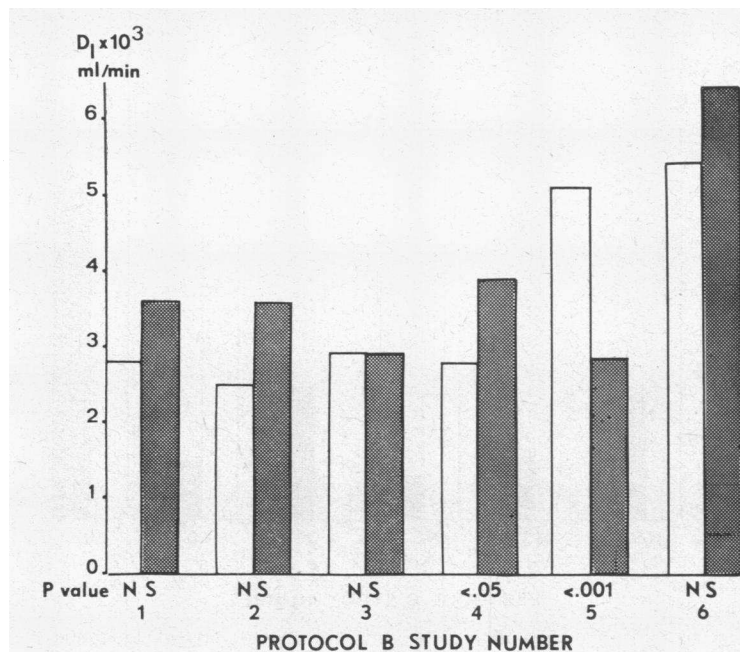


FIGURE 5 Dialysance values for inulin in control (open bars) and experimental (hatched bars) exchanges for the studies in protocol B. Paired analysis of all six studies indicates no significant difference from zero for the changes in inulin dialysance. *P* values for the significance of the difference of the means is given along the abscissa.

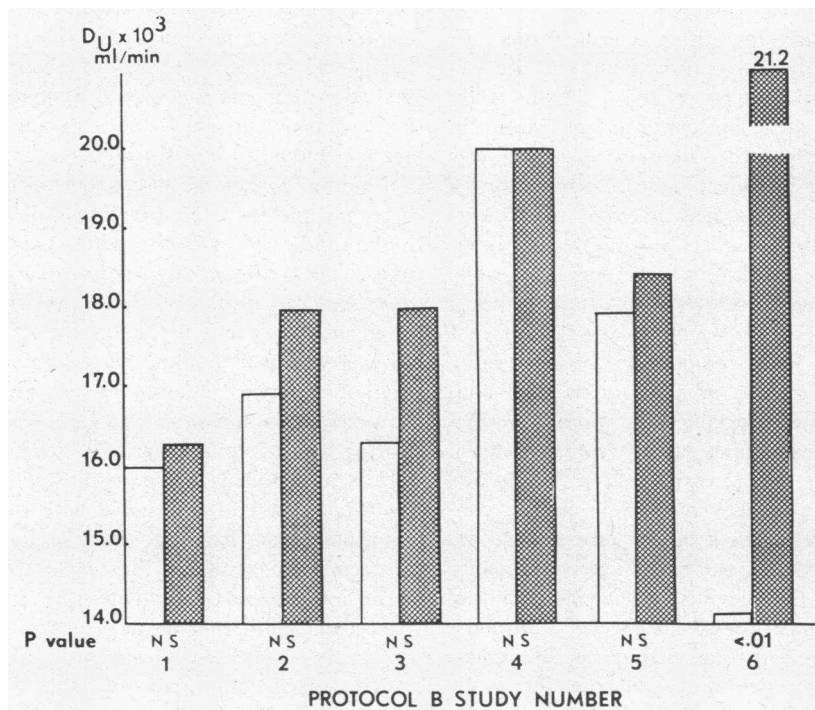


FIGURE 6 Dialysance values for urea in control (open bars) and experimental (hatched bars) exchanges for the studies in protocol B. Paired analysis for all six studies indicates no difference from zero for the change in urea dialysance. See caption to Fig. 5 for further explanation.

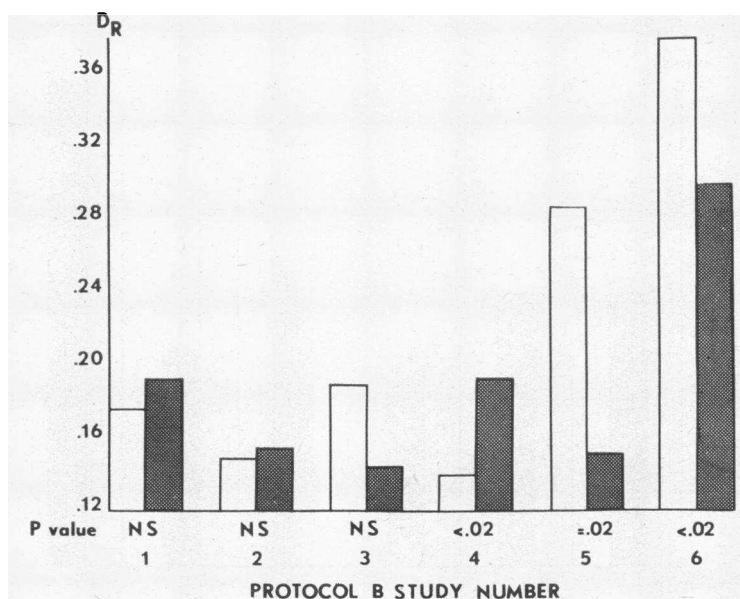


FIGURE 7 Inulin:urea dialysance ratios in control (open bars) and experimental (hatched bars) exchanges for the studies in protocol B. Paired analysis for all six studies indicates no difference from zero for the change in the dialysance ratio. See caption to Fig. 5 for further explanation.

ply that the membrane area for the passive transport of urea and inulin is virtually<sup>1</sup> identical.

Experimental support for these considerations is found in the high dialysance ratios found in the experimental exchanges of protocol A (mean  $D_R$  for study 5 = 0.84). Since the diffusion constant for inulin in water is less than that for urea,  $D_R$  must always be less than one. A value near one must indicate circumstances in which no significant difference in either total membrane area or permeability exists for the two solutes, and only the diffusion coefficient difference keeps the ratio from reaching one. In studies 7 and 10 of protocol A no detectable change in  $D_R$  occurs in the face of substantial increases in both components of the ratio. This indicates an increase in area for passage of both inulin and urea with no detectable alteration in permeability. Such a response points away from an initial disparity in membrane area available for inulin and urea transport. A larger urea membrane in the control situation would result in a larger proportional increase in the experimental inulin membrane with an increased  $D_R$ . Finally, the sieving coefficients for inulin and urea across the peritoneal membrane in response to hypertonic solutions are frequently quite comparable (Table II). The high sieving coefficients for inulin

point away from a significant contribution of intracellular water to the ultrafiltrate. The sieving coefficients for urea given in Table II agree with previously published figures (1). All of these experimental observations support the second assumption of the mathematical model in which the urea and inulin membranes are considered to be the same.

Examination of the data from protocol A shows that in every instance the individual dialysance values for inulin and urea increase after exposure of the peritoneal membrane to hypertonic dialysis fluid. This as discussed can result from either an increase in the area of membrane participating in the diffusion process, or an increase in membrane permeability, or any combination of the two. On looking at the dialysance ratios, however, it is apparent that  $D_I$  rises more than  $D_U$  resulting in a significant ( $P < 0.05$ ) increase in  $D_R$ . Three mechanisms could result in a selective increase in transfer of inulin as noted with the rising  $D_R$  values in protocol A. First, a selective increase in the area of membrane available for inulin transfer could result in an increase in  $D_R$ , provided that urea membrane area exceeded inulin membrane area initially. Such an increase in shared membrane area could be pictured as an increased total area available for shared transfer routes or an increased number of pores per unit area of membrane available for diffusion of both solutes with no change in pore size or shape. The result would be a greater proportional increase in total inulin transport

<sup>1</sup>The area of peritoneal membrane served by a given capillary would be larger for urea than for inulin in proportion to the ratio of the diffusion constants for the two solutes.



pathways than in urea transport pathways. As discussed there are several reasons to reject this explanation.

A second mechanism to explain a greater increase in inulin dialysance would be an increasing inulin space. If the volume of distribution of a solute increases, the true dialysance (clearance at time  $\rightarrow 0$ ) does not change, but the solute concentration gradient will fall less rapidly, and a greater clearance rate will persist during the exchange. At time  $t$  there will be a greater  $S_D/S_R$  ratio (see Appendix) and, if the former smaller volume of solute distribution is used to *calculate* dialysance, this *calculated* dialysance will be falsely increased. Several factors minimize this mechanism. Finkenstaedt, O'Meara, and Merrill (5) have shown that inulin space is quite stable in anuric patients during the period of our study (8 hr). We have confirmed that observation in three of our patients. It must also be expected that with some ultrafiltration and perhaps some shift of water into cells during dialysis, inulin space would be more likely to decrease causing calculated inulin dialysance to fall. Most important, however, as shown in Fig. 1, is the fact that errors in the space of distribution of 5–10 liters account for very little error in calculated dialysance in the volume ranges at which we are working.

Thirdly, an alteration in pore configuration could also explain the data. An increase in mean pore radius would result in a greater reduction in steric hindrance for inulin than for urea. Should the over-all pore area increase as a result of this change in configuration, then the individual dialysance values for these solutes would be expected to rise in conjunction with their ratio. Should no change in over-all pore area occur with a change in pore configuration, we would speculate that  $D_I$  and  $D_R$  would increase with no change in  $D_U$ . Protocol A showed no such results. In study 4 of protocol B, however, such a pattern is observed. Of the three explanations available alterations in pore configuration, and thereby selective membrane permeability, seems to best explain the observation of an increase in  $D_R$  noted with protocol A. In view of the slight osmotic gradient from dialysis fluid to plasma present with isotonic solutions solvent drag was examined as a possible explanation for the observed changes in equilibration ratio for inulin and urea. Calculations assuming bulk flow of plasma water with inulin or urea for the discharge of the small osmotic gradient observed point up this explanation as unsatisfactory on quantitative grounds. The amount of solute delivered would be a factor of 20 too low.

The six studies in protocol B provide an interesting contrast to those in protocol A. There is no constant pattern of change in  $D_I$  or  $D_R$ , which may increase or decrease in any given study.  $D_U$  generally shows only slight increase. In study 4,  $D_I$  and  $D_R$  increase signifi-

cantly, while  $D_U$  does not change. This change in selective permeability of the membrane only is best explained as a change in pore configuration such that steric hindrance to the passage of inulin is reduced, but no alteration occurs in the over-all area available for the diffusion of urea. Of particular interest is study 6 in which  $D_R$  falls significantly in spite of a rising  $D_I$  and  $D_U$ . This could be interpreted anatomically as an increase in the pore area available for diffusion and, in addition, as an alteration in the pore configuration such that the permeability for inulin is somewhat less. It is apparent that under more physiologic conditions in which only isotonic solutions are used, changes in membrane area and permeability show no constant relationship and behave as independent variables in their contribution to solute transport.

Several reasonable speculations as to why these changes occur should be considered. Clearly any factor influencing blood flow to the peritoneum will influence solute transfer across the membrane. Increased blood flow might influence solute transfer by the delivery of more solute to the blood side of the membrane, thereby maintaining the blood-to-dialysis fluid concentration gradient at a maximum. In addition, this might reduce the capillary endothelial stagnant fluid film. Also, an increase in blood flow might clearly be expected to expand the capillary bed and provide greater membrane area by opening previously unperfused capillaries and distending capillaries already perfused. The work of Hare, Valtin, and Gosselin (6) suggests the importance of vasoactive compounds acting on the splanchnic bed. With the reasonable supposition that neither of these compounds is blood flow limited, all of the mechanisms cited would result in a proportional increase in both  $D_I$  and  $D_U$ . Should distention of a capillary also open pores of larger diameter then the ratio will rise. Protocol A in which solutions with over twice normal osmolality are used could well be expected to produce peritoneal irritation with a postexposure reactive dilatation of the capillary bed. Protocol A always produced an increase in dialysance of both solutes, but the dialysance ratio did not always rise. If vasodilatation is the basis for the increase, there would have to be two components involved to explain the data, namely an increase in the number of capillaries perfused (area) and second, an increase in capillary membrane pore size (permeability).

In protocol B as contrasted with A no consistent pattern developed. The lack of consistent relationship between changes in  $D_I$  and  $D_R$  point away from a common factor causing these changes. Variations in the membrane probably result more from physiologic variables rather than from the dialysis procedure. A reasonable speculation as to why these changes occur would

be that membrane area and pore configuration are independently mediated by nervous and (or) hormonal stimuli.

## APPENDIX

Solute movement across the peritoneal membrane when 1.5% glucose-containing dialysis fluid is used can be treated as a problem of simple diffusion in a two compartment system. Peritoneal membrane is here defined to mean any membrane, visceral or parietal, and its stagnant fluid films, separating blood from dialysis fluid. Changes in the passive transport characteristics of the peritoneal membrane for solutes of differing size may result in either proportional or disproportional changes in the transfer of the various solutes. Any proportional changes in solute transfer are considered to represent an alteration in membrane area, while any disproportional changes are considered to represent alteration in the selective permeability of the membrane. It is recognized that discrete anatomical pores are not unequivocally implicated in the mechanisms for solute and water transfer across biological membranes. In most instances, however, the functional behavior of such membranes can be most satisfactorily described and understood using the anatomical concept of pores and classical pore theory (7-9).

Four simplifying assumptions have been made. Firstly, diffusion is considered to proceed smoothly throughout the exchange starting at the time of inflow and stopping at the termination of the exchange 70 min later. It is recognized that variations in the volume of dialysis fluid present in the peritoneal space occur during inflow and outflow. As a result, solute does not cross the peritoneal membrane smoothly but rather at a rate which would be primarily a reflection of the area of membrane exposed. As each exchange was conducted with the same inflow and outflow times, the error introduced into the model is a constant factor that would drop away when isotonic control exchanges are compared with postultrafiltration, isotonic experimental exchanges. It is recognized that by making this assumption, the absolute rate of solute transfer is in error.

Secondly, the total membrane surface area available for urea diffusion is the same as that for inulin (see Discussion).

Thirdly, it is assumed that there is no ultrafiltration, either osmotic or hydrostatic, from blood to dialysis fluid during 1.5% glucose exchanges. Contributions of solute by bulk flow or solvent drag mechanisms would thereby be eliminated, and all solute movement could then be ascribed to simple diffusion. At times slightly more (100 cc) dialysis fluid returns on drainage than was introduced. The error introduced by this assumption is not considered significant.

Finally, it is also assumed that the volume of distribution in the body for each solute is homogeneous and does not change significantly during the study.

Inulin space was measured during each study after the 2 hr equilibration period. The work of Finkenstaedt, O'Meara, and Merrill (5) on the stability of the inulin space in oliguric man over 24 hr was confirmed by three studies of our own. Urea space was estimated as 60% of body weight. All patients were essentially anuric, and any fall in blood concentration of the study solutes or body weight was considered to result from dialysis. In some studies, a 1-2 liter total ultrafiltration loss of volume occurred. Changes of such magnitude (1-2 liters) have no significant effect on the calculated dialysance (Fig. 1).

With these assumptions solute movement across the peritoneal membrane can be expressed with a standard equation (10) for the dissipation of a concentration gradient by diffusion.

$$\frac{d(S_B - S_D)}{dt} = -K(S_B - S_D) \quad (1)$$

where

$S_B$  = the concentration of a solute S in the body compartment of its distribution at any t

$S_D$  = the concentration of the same solute in dialysis fluid at any t

t = the time in minutes from the beginning of the exchange

K = a first-order rate constant with units of reciprocal minutes. K incorporates the factors of temperature gradient (patient to dialysis fluid), cycle patterns of the exchange, total membrane surface area, the volumes of solute distribution in the body and peritoneal cavity, and permeability. All factors but the total area and permeability of the membrane can be held constant.

Equation 1 can be expressed in exponential form:

$$S_B - S_D = Ce^{-Kt} \text{ where}$$

C = a constant

t = 0

$S_D = 0$

$S_B = C$ , thus, since  $S_B$  does not change significantly

during one exchange

$$S_B - S_D = S_B e^{-Kt} \quad (2)$$

Now since

$$\frac{dS_D}{dt} \cdot V_D = -\frac{dS_B}{dt} \cdot V_B \left( \text{or } \frac{dS_D}{dt} = -\frac{dS_B}{dt} \cdot \frac{V_B}{V_D} \right)$$

where

$V_B$  = the volume of distribution for a solute within the body and outside the peritoneal space

$V_D$  = the 2 liter volume of dialysis fluid returned at the end of an exchange

and

$$\frac{d(S_B - S_D)}{dt} = \frac{dS_B}{dt} - \frac{dS_D}{dt}$$

then

$$\frac{d(S_B - S_D)}{dt} = \frac{dS_B}{dt} + \left( \frac{dS_D}{dt} \cdot \frac{V_B}{V_D} \right)$$

or

$$= \frac{dS_B}{dt} \left( 1 + \frac{V_B}{V_D} \right)$$

and

$$\frac{dS_B}{dt} = \left( \frac{d(S_B - S_D)}{dt} \cdot \frac{V_D}{V_D + V_B} \right)$$

or substituting from equation 1

$$\frac{dS_B}{dt} = -K(S_B - S_D) \frac{V_D}{V_D + V_B}$$

then substituting from equation 2 we have

$$\frac{dS_B}{dt} = -K(S_B e^{-Kt}) \frac{V_D}{V_D + V_B} \quad (3)$$

The actual clearance rate of solute at any time  $t$  is expressed as

$$\text{Actual clearance rate} = \frac{dS_B}{dt} \cdot \frac{V_B}{S_B}$$

or by substituting from equation 3

$$= \frac{-K e^{-Kt} V_B V_D}{V_D + V_B} \quad (4)$$

The total volume of extracellular fluid cleared of solute after time  $t$  is the integral of equation 4 or

$$\begin{aligned} &= \int_0^t -K e^{-Kt} \frac{V_B V_D}{V_D + V_B} dt \\ &= \left[ \frac{V_B V_D}{V_D + V_B} e^{-Kt} \right]_0^t \\ &= \frac{V_B V_D}{V_D + V_B} (e^{-Kt} - 1) \end{aligned} \quad (5)$$

The total cleared can also be expressed as

$$= -\frac{S_D V_D}{S_B}$$

thus

$$\begin{aligned} -\frac{S_D V_D}{S_B} &= \frac{V_B V_D}{V_D + V_B} (e^{-Kt} - 1) \\ e^{-Kt} &= \left[ -\frac{S_D V_D}{S_B} \cdot \frac{V_D + V_B}{V_B \cdot V_D} \right] + 1 \end{aligned}$$

Taking the natural log of each side and rearranging terms we have

$$-K = \frac{\ln \left[ 1 - \frac{S_D (V_D + V_B)}{S_B V_B} \right]}{t} \quad (6)$$

Note that  $V_B$  appears in both numerator and denominator, and that  $V_B$  changes produce very little change in  $K$  (see Discussion).

It can be seen in equation 4 that the clearance rate at the start of an exchange ( $t \rightarrow 0$ ) in a diffusion system in which the starting sink solute concentration is zero is equivalent to dialysance. Using the simple form of the dialysance equation (dialysance =  $Q \frac{A - V}{A - B}$ , where  $Q$  equals machine blood flow in milliliters per minute and  $A$ ,  $V$ , and  $B$  are the given solute concentrations in artery, vein, and bath, respectively) it can be seen that at  $t = 0$ , then  $B = 0$ , and dialysance equals clearance.  $-K(V_B \cdot V_D)/(V_B + V_D)$  is thus referred to as dialysance ( $D$ ). ( $D_I$  = inulin dialysance,  $D_U$  = urea dialysance.)

Dividing dialysance by total membrane area would yield a value with the characteristic units of a permeability constant and would represent the initial clearance rate per exchange per unit area of total membrane.

$$-K \frac{V_B \cdot V_D}{V_B + V_D} = \text{dialysance} = \text{permeability} \cdot \text{area}$$

If the total surface area available for diffusion of inulin and urea are assumed to be the same, and if volumes of distribution are assumed to change insignificantly in relation to one another, then changes in the ratio  $D_I/D_U$  measured during identical exchanges must reflect functional membrane alterations affecting one solute proportionately more than the other, i.e., a permeability change.

$$\frac{D_I}{D_{Urea}} = \text{dialysance ratio } (D_R) = \frac{\text{inulin permeability}}{\text{urea permeability}}$$

"Permeability" would be determined by the diffusion rate of the solute through the membrane and (or) through solvent-filled pores therein and would be influenced by such factors as molecular weight, charge, and hydrated radius of the solute particle. The effective "pore" radius, length of diffusion path, and fixed membrane charge, as well as the influence of stagnant fluid films at the membrane surface would also be important. Since the solutes examined in the present study are uncharged, variations in the individual dialysance values from control to experiment would reflect variation in pore configuration or changes in total membrane area with or without associated changes in pore configuration. Variation in pore size or shape while altering the true area for diffusion and hence the individual dialysance values would also be expected to alter the passage of inulin more strikingly than urea. Such an alteration in mean pore radius can be identified by a change in  $D_R$ , i.e., a disproportional change in solute transfer. Changes in dialysance values due to area change alone would change  $D_I$  and  $D_U$  but would not alter  $D_R$ .

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## REFERENCES

1. Henderson, L. W. 1966. Peritoneal ultrafiltration dialysis: Enhanced urea transfer using hypertonic peritoneal dialysis fluid. *J. Clin. Invest.* **45**: 950.
2. Walser, M., D. G. Davidson, and J. Orloff. 1955. The renal clearance of alkali-stable inulin. *J. Clin. Invest.* **34**: 1520.
3. Croxton, F. E. 1959. Elementary Statistics with Applications in Medicine and the Biological Sciences. Dover Publications, Inc., New York. 376.
4. Karnovsky, M. J. 1967. The ultrastructural basis of capillary permeability studied with peroxidase as a tracer. *J. Cell Biol.* **35**: 213.
5. Finkenstaedt, J. T., M. P. O'Meara, and J. P. Merrill. 1953. Observations on the volume of distribution of inulin in anuric subjects. *J. Clin. Invest.* **32**: 209.
6. Hare, H. G., H. Valtin, and R. E. Gosselin. 1964. Effect of drugs on peritoneal dialysis in the dog. *J. Pharmacol. Exp. Ther.* **145**: 122.
7. Dick, D. A. T. 1967. An approach to the molecular structure of the living cell by water flux studies. In *Physical Bases of Circulatory Transport: Regulation and Exchange*. E. B. Reeve and A. C. Guyton, editors. W. B. Saunders Company, Philadelphia. 217.
8. Pappenheimer, J. R., E. M. Renkin, and L. M. Borrero. 1951. Filtration, diffusion, and molecular sieving through peripheral capillary membranes. A contribution to the pore theory of capillary permeability. *Amer. J. Physiol.* **167**: 13.
9. Mayerson, H. S., C. G. Wolfram, H. H. Shirley, Jr., and K. Wasserman. 1960. Regional differences in capillary permeability. *Amer. J. Physiol.* **198**: 155.
10. Daniels, F. 1959. Mathematical Preparation for Physical Chemistry. McGraw-Hill Book Company, New York. 132.