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EDITORIAL REVIEW

An hypothesis to explain the ultrafiltration characteristics of peritoneal dialysis

Net removal of fluid and sodium from the body during peritoneal dialysis is accomplished with dialysis solutions that contain high glucose concentrations and are hyperosmolar to body fluid [1]. Commercially available peritoneal dialysis solutions contain glucose concentrations ranging from 1.5 to 4.25 g/dl and have osmolalities ranging from 334 to 490 mOsm/kg H_2O. The solutions also contain concentrations of sodium, chloride, magnesium, and calcium that approach those of normal extracellular fluid. Acetate or lactate, rather than bicarbonate, is used as the nonchloride anion. Potassium may be added or, depending on the need for potassium removal, solutions may be potassium-free.

Characteristics of ultrafiltration. The rate of ultrafiltration into the peritoneal cavity is greatest at the beginning of an exchange and decreases exponentially as the osmotic difference between peritoneal dialysis solution and body fluids decreases [2, 3]. Without rapid replacement, the amount of fluid extractable from mesothelial cells, peritoneal interstitium, and lymphatics is limited. Therefore, the major source of ultrafiltrate is assumed to be from blood circulating in peritoneal capillaries [1]. Dialysis solution osmolality decreases with time, which is due to the dilutional effect of ultrafiltrate and the absorption of glucose. When 1.5% dextrose solutions are used, intraperitoneal volumes peak at about 2 hours; with 4.25% dextrose solutions, the peak is at about 3 hours [4]. Although ultrafiltration increases solute clearance (presumably due to the convective effects of bulk flow), the ultrafiltrate is hyponatric (that is, relatively low in sodium concentration compared with that in extracellular fluid) [3–8]. With repeated ultrafiltration, severe hypernatremia may develop in the extracellular fluid [5]. In the absence of a concentration gradient for net diffusion, even such neutral solutes as urea (60 daltons) and inulin (5200 daltons) do not accompany water movement in amounts proportional to their extracellular fluid concentrations [9].

That electrolytes and other neutral solutes do not move along with the ultrafiltrate in amounts proportional to extracellular fluid concentrations is a paradox. The peritoneal membrane allows albumin and other large proteins to enter the dialysis solution, [10–15] whereas the cellulosic membranes in man-made dialyzers essentially prevent the passage of large proteins. How can a "permeable" membrane that permits protein transit impede the movement of electrolytes with bulk flow? Various techniques for assessing the mean pore width yield conflicting results. Based on studies of solute diffusion across the peritoneal membrane in humans and morphologic and transport studies in the rat peritoneum, a likely assumption can be made that the endothelial intercellular gaps in peritoneal capillaries may function as pores with a width of 40 Å or greater that are available for transport [16–21]. On the other hand, clinical studies of osmotically induced ultrafiltration and examination of the reflection coefficients of multiple solutes reveal that a solute having a molecular radius of 15 Å has a peritoneal reflection coefficient of 0.5 [4].

Another interesting characteristic of peritoneal ultrafiltration is that ultrafiltration may be severely reduced without accompanying decreases in solute clearances. Even with hypertonic 4.25% to 7% dextrose exchanges, some patients lose ultrafiltration, even though solute clearances remain unchanged. Conversely, with peritonitis, protein loss and solute clearances increase, in conjunction with a net ultrafiltration decrease [22].

Thus, peritoneal ultrafiltration is a paradox in that the system "sieves" electrolytes and small neutral solutes during ultrafiltration while allowing protein loss. It is a system that displays characteristics of some very large-pore radii when assessed by diffusion studies, and some very small-pore radii when assessed by ultrafiltration and solute reflection coefficients.

The hypothesis of proximal capillary ultrafiltration with very low solute permeability and distal diffusion with high solute permeability during peritoneal dialysis

An hypothesis that accounts for proximal capillary ultrafiltration with low solute permeability and distal diffusion with high solute permeability during peritoneal dialysis is seen in Fig. 1, which shows blood flowing from left to right in a peritoneal capillary. In this hypothetical model, proximal hydraulic pressure is presumed to be 40 mm Hg and to decrease to 15 mm Hg at the venular (right) end of the capillary. The proximal oncotic pressure is 25 mm Hg. Distal oncotic pressure increases slightly as a result of the increase in protein concentration caused by capillary ultrafiltration. The endothelial junctions at the proximal portion of the capillary progressively increase in width as the distal portions of the capillary are approached. Evidence reviewed elsewhere suggests that it may be these intercellular gaps that are, at least in part, the functional pores during peritoneal dialysis [1, 23].

The fundamental assumptions of the hypothesis are: *(1)* heteroporosity (a population of pathways through the endothelium that have various dimensions) and *(2)* a predominance of large "pores" in the venular capillaries. Evidence based on physiologic studies of the microcirculation in animals and thermodynamic analyses of peritoneal dialysis kinetics in humans lends credence to these assumptions.

Physiologic evidence for heteroporosity and high venular permeability. Although many endothelial pathways, including

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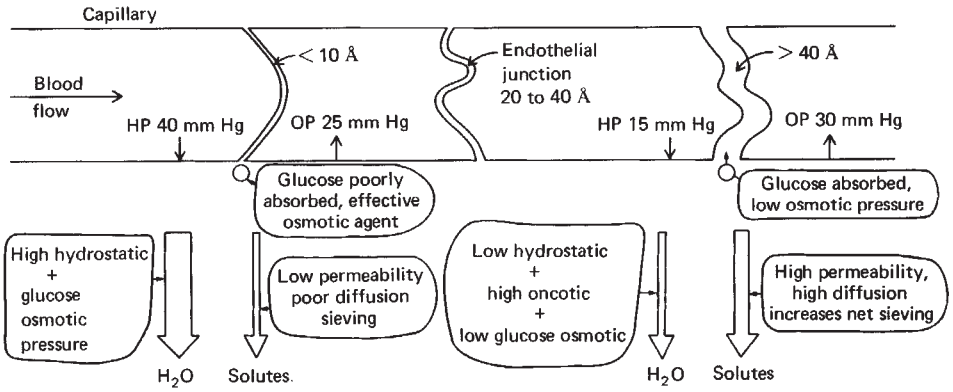

Fig. 1. *Diagrammatic summary of a hypothesis to explain the features of peritoneal ultrafiltration at low permeability and distal diffusion at high permeability during peritoneal dialysis.* HP denotes hydrostatic pressure; OP, oncotic pressure.

various fenestrations, vesicles, and gaps at cell junctions, are potentially available for solute transport [24], the relative contribution of each pathway to total solute (large or small) movement has not been established. Our hypothesis conceptualizes these pathways as "pores" having various controlling parameters that function as restrictors of solute movement.

The seemingly simple structure of the capillary (an endothelial cell lining and a basal lamina) has many variations in the peritoneal cavity that may be characterized by endothelium type, that is, continuous endothelium (as in mesenteric vessels), fenestrated endothelium (as in mouse intestinal villi), and discontinuous endothelium (found in the liver sinusoids and in the spleen).

Capillaries of the visceral and parietal peritoneum generally contain the continuous endothelium with many micropinocytotic vesicles. Measurements in the mouse diaphragm show that the average thickness of these capillaries is 0.25 ± 0.01 to 0.17 ± 0.07 μm (arteriolar capillary to venular capillary), and that there is an increased number of vesicles at the venular end of the capillary per cubic micrometer of endothelium [25].

The microvasculature of the mouse intestinal villus is characterized by the presence of numerous fenestrae accounting for approximately 10% of the total luminal capillary surface area [26]. Compared with arteriolar capillaries, venular capillaries have far more fenestrae (approximately 12 times). For solute transfer in both arteriolar and venular capillaries, the gaps between endothelial junctions may be less important and the fenestrae more important because the ratio of fenestrae area to gap area is 16 : 1 in the arteriolar capillary and 240 : 1 in the venular capillary. Although fenestrated capillaries may not participate in human peritoneal dialysis, the mouse intestinal villus vessels present additional evidence of the tendency toward greater venular permeability in many types of capillary beds.

In the mesenteric microcirculation of the cat, the postcapillary and collecting venules appear to be most important in protein transfer; fenestrae and vesicles, as well as junctional gaps, could provide "pores" for protein transfer [27]. The venule endothelium contains not only small micropinocytotic (400 to 800 Å) vesicles such as those found in the arterial endothelium, but many large vesicles (2000 to 3000 Å) as well. These large vesicles may fuse to form a vesicular channel, or "pore," that provides a direct pathway for protein transport from intravascular to extravascular space [25, 28].

In cat and rat studies, Fox, Galey, and Wayland demonstrated a concentration-dependent, histamine-induced protein leakage across mesenteric vessel walls [29]. Protein leakage was correlated with electron microscopic identification of endothelial gaps (up to 1 μm in diameter) that developed after histamine application. These gaps appeared in the area of the endothelium junctions of the nonmuscular venules. The data support the report by Nakamura and Wayland, whose studies demonstrated that small molecules (mol wt, < 3400 daltons) pass across membranes of all microvascular components (arterioles, capillaries, and venules) in the rat mesentery, whereas larger molecules (> 19,000 daltons) primarily diffuse either across venules or the venular end of capillaries, with virtually no passage across arterioles [27].

Thus, most transport pathways ("pores"), whether functional gaps, fenestrae, or vesicles, have been shown to be in the thinner-walled venular end of capillaries and in the smallest venules. These same areas seem to be sites for transcapillary movement of very large solutes, as suggested above and in other reports [30–34].

Hydrodynamic evidence for heteroporosity. The concept of peritoneal heteroporosity is supported by the clinical and theoretical results of studies by Pyle, Moncrief, and Popovich on peritoneal dialysis in humans [4, 35]. They applied their in vivo data from 19 studies to a mathematical model of the peritoneal dialysis system, which was based on a membrane transport theory derived from basic mass transport theory [36, 37]. These theories allow them to calculate the simultaneous diffusion and convection of solutes and fluid transport through the membrane. The peritoneum is characterized for each solute by two macroscopic membrane parameters: the mass transfer area coefficient for diffusion, and the reflection coefficient for convection. By measuring fluid transfer through isotope dilution techniques and fitting the mathematical model to clinical concentration-time data, they determined the average membrane parameters for seven solutes, ranging in size from 50 to 340,000 daltons [4, 35].

Their results for the human peritoneal reflection coefficients as a function of solute radius, reproduced in Fig. 2, indicate that small solutes are only slightly hindered by the membrane. For urea, the reflection coefficient (mean ± SD) was 0.27 ± 0.24. Larger solutes encounter more restrictions, as shown by an average protein reflection coefficient of 0.92 ± 0.008.

When these data are analyzed in a manner consistent with hydrodynamic theory, it is possible to determine the effective pore size encountered by each solute [35, 38]. Figure 3 shows the relationship between effective pore radius and solute radius, as determined by Pyle [35]. This relationship clearly shows that

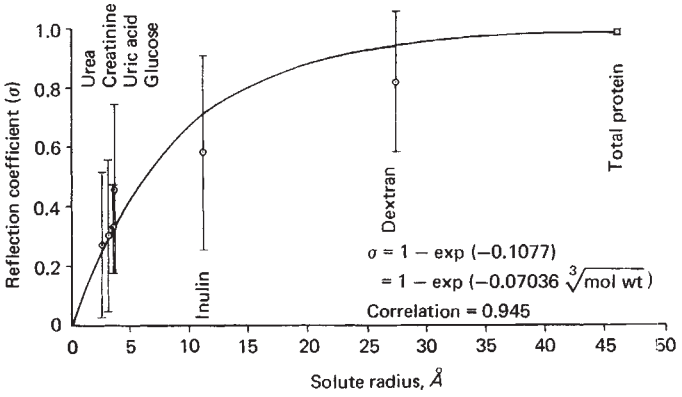

Fig. 2. *Reflection coefficients related to molecular radius during peritoneal ultrafiltration in humans.*

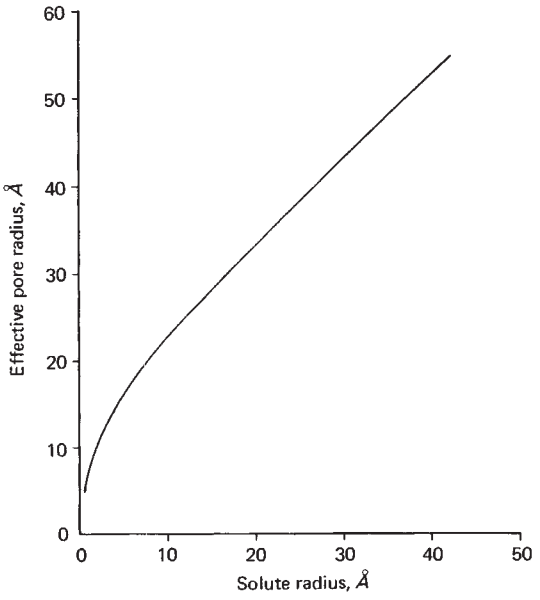

Fig. 3. *Effective pore radius related to molecular radius as determined from solute convective transport during peritoneal ultrafiltration in humans.*

the peritoneum is heteroporous because a homoporous system would be characterized by a horizontal line (that is, each solute would "see" the same effective pore radius). This analysis also suggests two other important results: *(1)* the largest pores must have a radius greater than 54 Å because this is the effective radius encountered by the proteins (average radius, 45 Å), and *(2)* there must be a great many peritoneal pores smaller than 3 Å, because the effective pore size drops so rapidly as solute size decreases below this size. These results could explain the apparent ease of water movement across the membrane (radius of water molecule = 1.5 Å).

Effects of heteroporosity on ultrafiltrate kinetics. We suggest that ultrafiltration during peritoneal dialysis takes place primarily through proximal portions of capillaries where hydrostatic pressure is greatest. We also propose that compared with glucose absorption in the distal capillary, glucose in the proximal capillary would be poorly absorbed and thus would exert greatest osmotic pressure at the proximal site. Therefore, the high ultrafiltration rates in the proximal portion of the capillary would reflect combined hydraulic and glucose osmotic pressure.

Sieving of solutes during ultrafiltration might occur because of the small mean pore width in the proximal portion of the capillary. Cell surface charges in close proximity to one another along the endothelial junctions or polarized proteins on endothelial surfaces could also interfere with electrolyte movement. Furthermore, it is possible that the combination of high transmembrane hydraulic and osmotic pressures contributes to transcellular water movement [6]. Solutes dissolved in extracellular fluid may be unable to proportionally accompany any transcellular water movement. Also, if some glucose absorption does take place proximally, in vitro evidence suggests that glucose diffusion countercurrent to ultrafiltration may impede the convective movement of solutes cocurrent with net hydraulic flow [39–40]. These findings may be due to some type of molecular interaction within the membrane, manifested as a net increase in sieving.

The situation at the distal end of the capillary is different. There, the hydraulic pressure is low and oncotic pressure increases in proportion to the amount of ultrafiltration. At this site, compared with the less permeable proximal capillary, glucose is readily absorbed and generates less water movement at any transcapillary glucose concentration gradient. This would thus be a site of relatively lower ultrafiltration rate and, under nearly physiologic conditions, a site of fluid reabsorption. During the first hour of a peritoneal dialysis exchange, however, it is unlikely that distal net water flux is into the capillaries. If we assume a glucose concentration of 500 mg/dl in the interstitium, the interstitial osmotic pressure will be about 540 mm Hg. By applying standard expressions for fluid flux under osmotic and/or pressure gradients, one may determine that the glucose reflection coefficient necessary to exactly counter the effect of 25 mm Hg of oncotic pressure is about 0.05 [41]. Pyle, Moncrief, and Popovich have reported that the overall peritoneal reflection coefficient for glucose is about 0.37 [4, 35]. The distal capillary reflection coefficient is probably well below 0.37 if most of the large peritoneal pores are found in this region. But fluid flux into the capillary under the above conditions would require a reflection coefficient of less than 0.05. So long as the distal reflection coefficient for glucose exceeds 0.05, there likely is some small amount of fluid flux out of the distal capillaries at interstitial glucose levels of 500 mg/dl or more. Further studies are required before the exact distal glucose reflection coefficient can be determined.

Much of the total pore area available for diffusion could be restricted to the distal portion of the capillary, which could be the exit site of large solutes, as well as the site of most solute clearances by diffusion. During long-dwell exchanges, solute diffusion across distal portions of the capillary would partly obliterate the "sieving effects" that result from ultrafiltration across the more proximal, less permeable membrane. The net sieving effect would be most striking during hypertonic exchanges in short cycles that allow less time for distal diffusion to diminish the concentration gradients created by proximal ultrafiltration of "solute-poor" water [3].

Observations compatible with the hypothesis

The following observations or hypotheses are compatible with our hypothesis that peritoneal ultrafiltration primarily occurs through proximal capillaries with low permeability: *(1)* Starling's hypothesis of proximal capillary ultrafiltration [18,

42], *(2)* anatomical and functional studies previously cited that suggest heteroporosity and greater permeability in distal portions of the capillary, *(3)* the model's explanation for the paradox of a membrane that can "sieve" small solutes during ultrafiltration and at the same time permit a substantial protein leakage, and *(4)* clinical observations of ultrafiltration loss without solute clearance changes, decreased ultrafiltration with decreased solute clearance, and increased ultrafiltration with decreased solute clearance. Many of the clinical observations are anecdotal and require better documentation. But, mechanisms to explain these possible permutations of changes in ultrafiltration and solute clearances are discussed in terms of our hypothesis.

Explanations for ultrafiltration loss without solute clearance changes. First, according to the hypothesis, if there were decreases in proximal capillary hydrostatic pressure, ultrafiltration in response to a given type of peritoneal dialysis solution could be reduced without simultaneous decreases in solute clearance or protein loss. Because of the relatively greater glucose osmotic pressure, however, this would seem to be of minor importance. Second, due to proximal capillary endothelial alterations, isolated changes in permeability or total pore area in the proximal portions of the capillary might exist without distal capillary involvement. If proximal permeability decreases slightly, with no distal changes, the glucose reflection coefficient would increase and the osmotic effectiveness of glucose could increase, with little or no change in water permeability. Thus, ultrafiltration should increase across the proximal capillary. Ultrafiltration should be decreased only by large decreases in proximal permeability that affect water permeability. Alternatively, if permeability to glucose increases in the proximal capillary, glucose should transfer more rapidly, the reflection coefficient for glucose should decrease, and ultrafiltration should be less. Third, ultrafiltration also might be decreased in association with stable or increased clearances as a result of increased permeability of the distal portion of the capillary. Here, rapid glucose absorption could, in essence, provide a "run-off" to minimize the osmotic gradient across the distal capillary wall and decrease the osmotic gradient across the proximal capillary wall. The ultrafiltration loss and increases in protein loss seen with peritonitis suggest increased distal permeability.

Decreased ultrafiltration with decreased solute clearance. A decrease in ultrafiltration may occur simultaneously with decreases in solute clearance and protein loss if the number of capillaries perfused decreased. This could occur with vasoconstriction because there would be a large decrease in capillary membrane area available for solute movement. Also, widespread capillary wall changes that decrease permeability in both proximal and distal capillaries could simultaneously impair both proximal and distal transport.

Increased ultrafiltration with decreased solute clearance. If our hypothesis is correct, other predictable phenomena exist. For example, if permeability decreases only in distal portions of the capillaries, protein loss might be reduced, diffusive clearances of creatinine and urea be decreased, and ultrafiltration be increased. Increased ultrafiltration would reflect decreased glucose absorption and the maintenance of a higher transmembrane osmotic gradient across distal and proximal capillary walls. We have followed a diabetic patient who has just such a low clearance and high ultrafiltration pattern [2, 43].

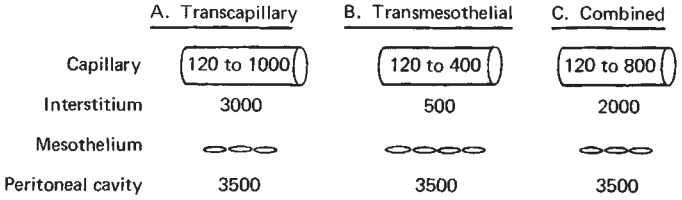

Fig. 4. *Three hypothetical distributions of glucose in the peritoneal cavity and peritoneum.* Numbers represent hypothetical glucose concentrations (in milligrams per deciliter) early in an exchange with 4.25% dextrose solution.

Teleologic considerations

One of the functions of the microcirculation is to deliver peptide hormones, antibodies, and other large molecular substances to tissues. Thus, capillary membranes at some site must be permeable to such molecules. On the other hand, if the most permeable portions of a capillary were in areas of high transmembrane hydrostatic pressure, massive protein leakage by convective effects of bulk flow might occur. Proximal ultrafiltration through a less permeable portion of the capillary wall would allow some convective transport of small solutes. Under physiologic conditions, ultrafiltration and reabsorption allow rapid turnover of fluid and the small solute composition of the interstitium, and thus, the media in which cells reside. The delivery of large molecules such as proteins would occur distally without massive transcapillary protein movement.

Transmesothelial ultrafiltration

The mechanism for the net movement of ultrafiltrate from the peritoneal interstitium into the peritoneal cavity is not known. Accumulation of the capillary ultrafiltrate in the interstitum could increase interstitial pressure. Transmesothelial hydraulic pressure could account, at least in part, for fluid movement into the peritoneal cavity.

Transmesothelial osmotic pressure due to glucose concentration differences between intraperitoneal and interstitial fluid could also explain net fluid movement across the mesothelium. Some studies of transmesothelial diffusion suggest, however, that the mesothelium is very permeable [16, 17]. Solute movement through the mesothelium appears to be mainly through intercellular gaps up to 500 Å wide [16–20]. Glucose concentrations in the interstitium may rapidly approach those in peritoneal dialysate, and glucose concentration gradients may be more transcapillary than transmesothelial. Figure 4 shows three hypothetical distributions of peritoneal glucose concentrations early in an exchange using 4.25% dextrose dialysis solution. These are *(A)* mainly transcapillary, *(B)* mainly transmesothelial, and *(C)* a combination of transcapillary and transmesothelial gradients. The most likely distributions would seem to be A or C, because mesothelial permeability probably is greater than capillary permeability [16–20]. But, if surface charges on mesothelial cells influence net electrolyte movements, then it is possible that the mesothelium could contribute to sieving.

In addition to capillary and mesothelial membranes, the interstitium is a third factor that could influence glucose distribution and sieving effects during peritoneal dialysis. There is some experimental and anatomical evidence to suggest that the interstitium is a network of water channels through collagenous and mucopolysaccharide gels [31]. Surface charges on such gels

might also influence electrolyte movements. Effective water channel diameters could be decreased by hypertonic ultrafiltration during peritoneal dialysis, resulting in net sieving effects either directly or by molecular interaction in channels [31, 40].

Other hypotheses

Other hypotheses could be generated that would partly explain the characteristics of peritoneal ultrafiltration. Active transport of electrolytes across cell membranes could influence electrolyte sieving patterns but would not explain neutral solute sieving. Heteroporosity randomly distributed along the capillary might explain sieving with protein leakage; isolated loss of ultrafiltration could occur with closure of smaller "pores." Physiologic studies suggest, however, that larger "pores" are more prevalent in the distal capillary [24–29].

Interstitial physico-chemical interactions of solutes with collagen and mucopolysaccharides might have unique effects on solute movements independent of molecular weight. Polarized substances lining interstitial and basement membrane pathways, for instance, could to some extent influence the net movement of charged solutes, but in order to explain the many different observations, the influence would necessarily be very complex.

A preferential loss of small pores in any membrane might lead to a greater decrease in hydraulic permeability, compared with diffusive permeability, to solutes larger than water. Alternatively, increases in the number of capillaries perfused could increase pore area and blunt any decreases in diffusive clearances. Various combinations of changes in numbers of capillaries perfused and mean pore radius in a homogeneous pore system could explain many findings. Such changes also could occur in a heterogenous pore system in combination with the hypothesis we propose.

Summary

We present an hypothesis that could account for many characteristics of ultrafiltration and solute movement during peritoneal dialysis. The hypothesis describes transcapillary ultrafiltration and can account for (*1*) the osmotic effectiveness of rapidly absorbed glucose, (*2*) small solute sieving in a system permitting protein loss, (*3*) functional estimates of effective pore sizes as low as 11 Å for urea and as high as 62 Å for proteins from hydrodynamic analyses, (*4*) isolated loss of ultrafiltration without loss of clearance, (*5*) decreased ultrafiltration with decreased clearances, and (*6*) increased ultrafiltration with decreased clearances.

Mechanisms for fluid movement from the peritoneal interstitium into the peritoneal cavity may involve both hydrostatic and osmotic pressure. Interstitial water pathway dimensions, interstitial gel surface charges, mesothelial cell surface charges, and transmesothelial-cell water movement might also account for sieving effects during peritoneal ultrafiltration.

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