Transport asymmetry in peritoneal dialysis: application of a serial heteroporous peritoneal membrane model

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Venturoli, Daniele, and Bengt Rippe. Transport asymmetry in peritoneal dialysis: application of a serial heteroporous peritoneal membrane model. Am J Physiol Renal Physiol 280: F599–F606, 2001.—The transport of macromolecules during peritoneal dialysis is highly selective when they move from blood to dialysate but nearly completely unselective in the opposite direction. Aiming at describing this asymmetry, we modeled the peritoneal barrier as a series arrangement of two heteroporous membranes. First a three-pore membrane was considered, crossed by small [radius of the small pore ($r_s$) = 45 Å], large [radius of the large pore ($r_L$) = 250 Å], and transcellular pores accounting for 90, 8, and 2% to the hydraulic conductance, respectively, and with a corresponding pore area over diffusion distance ($A_p/\Delta x$) set to 50,000 cm. We calculated the second membrane parameters by fitting simultaneously the bidirectional clearance of molecules ranging from sucrose [molecular weight = 360, permeating solute radius ($a_s$) = 5 Å] to $\alpha_2$-macroglobulin (molecular weight = 820,000, $a_s$ = 90 Å). The results describe a second two-pore membrane with very large pores ($r_L = 2,300$ Å) accounting for 95% of the hydraulic conductance, minor populations of small ($r_s = 67$ Å) and transcellular pores (3 and 2%, respectively), and an $A_p/\Delta x = 65,000$ cm. The estimated peritoneal lymph flow is $\approx 0.3$ ml/min. The two membranes can be identified as the capillary endothelium and an extracellular interstitium lumped with the peritoneal mesothelium.

extracellular interstitium; concentration hyperpolarization; composite membranes; pore theory; mathematical model

AFTER THE INTRODUCTION OF peritoneal dialysis (PD) as a tool to replace impaired renal function, much work has been devoted to the mathematical modeling of the exchanges of fluid and solutes through the peritoneum (for a review see, e.g., Ref. 18 or more recently Ref. 29). The proposed models usually describe the peritoneal exchanges as fluid flow and solute fluxes between two well-mixed compartments (namely, the patient’s blood and the peritoneal cavity content) through a “peritoneal membrane.” This equivalent peritoneal membrane is in fact “a complex and complicated system of membranes and pores, which may be described as a distributed, multilayer, heteroporous, and topographically nonuniform structure with intramembrane compartments and possible specific biological transport properties” (31). The concept of the peritoneal membrane has evolved from a black box simply described by some kinetic constants (18) to a heteroporous membrane with precise anatomical correlates to the structures allowing fluid and solute fluxes (23, 24). However, the only way to deal to some extent with the anisotropy and inhomogeneity of its composition has been so far to refer to a distributed model of peritoneum (8, 17, 25). At variance with the approach above, the distributed models of peritoneal exchanges consider the blood-peritoneal cavity barrier as a hydrogel matrix (representing the peritoneal tissue), with an embedded uniform distribution of blood vessels, lined on one side by a membrane (representing the peritoneal mesothelium). However, this distributed approach, although very powerful in its description of peritoneal exchanges, leads to a dramatic increase in the complexity of the governing equations and in the number of parameters needed to describe the system. Furthermore, the real values of some of these parameters are very difficult, if at all possible, to assess experimentally. Far simpler but as well powerful is the adaptation of the distributed model of Waniek et al. (30) to describe the bidirectional solute transport. However, this approach does not provide any insights about the structures responsible for the exchanges. Here we follow an intermediate way between the different approaches, considering the presently most advanced “planar” membrane model, the three-pore model (23, 24), and extending it to the description of a membrane composed of two heteroporous membrane in series.

THEORY

Pore Theory of Peritoneal Exchanges

In the pore model of peritoneal exchanges (23, 24) the equivalent peritoneal membrane is considered to be crossed by straight cylindrical channels, then applying the pore theory heretofore used in the description of the movement of fluid and solute through the capillary walls (6, 27). In this framework, the parameters defining a membrane are the number of pores of different radii and their relative weight and unrestricted (and “restricted”) surface area available for exchange over the diffusion path length ($A_p/\Delta x$). The corre-

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sponding fluid and solute permeability parameters are summarized in Table 1. The equivalent peritoneal membrane has been characterized (23) as a three-pore membrane crossed by small pores, large pores, and transcellular pores. The small pores, radius \( r \sim 45 \, \text{Å} \), approximately account for 90% of the hydraulic conductance and represent the main route of passage for small solutes, whereas 8% of the hydraulic conductance is accounted for by large pores \((r \sim 250 \, \text{Å})\), allowing the passage of macromolecules. Transcellular pores representing a water-only conductive pathway account for the remaining 2% of the hydraulic conductance. This was introduced to explain the paradox of an apparently “open” peritoneal membrane effectively sieving small solutes. These pores have been recently identified as the plasmalemmal “aquaporins” (5). The three-pore model has been successfully applied in the interpretation of a large set of experimental data obtained in studies of fluid and solute exchanges in PD (21). However, some problems arise when the three-pore model is applied to the observation that the peritoneal transport of molecules across the peritoneum is not symmetric. In fact, if a solute is moving from the blood to the peritoneal cavity, it has to permeate the capillary endothelium, the interstitium, and the mesothelial layer, whereas in the opposite direction, an additional pathway exists provided by the lymphatic drainage. Also, the addition of a peritoneal lymphatic drainage to one side of the “peritoneal” membrane described by the three-pore model does not account completely for the possibly different permeability properties of the different layers. Therefore, we try to address the problem of estimating the relative weight of the two different fluxes from the peritoneal cavity by considering an equivalent peritoneal membrane structured as two three-pore membranes arranged in series.

### Table 1. Basic permeability coefficients according to the pore theory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflection coefficient, ( \sigma )</td>
<td>( 1 - \frac{(1 - \nu)^2 \cdot [2 - (1 - \nu)^{-2}] \cdot (1 - \frac{3}{\nu})}{3} )</td>
</tr>
<tr>
<td>Total reflection coefficient</td>
<td>( \alpha_s + \alpha_p \alpha_r + \alpha_s \alpha_t )</td>
</tr>
<tr>
<td>Free diffusion coefficient, ( D_s )</td>
<td>( \frac{RT}{6\pi \eta N_A \alpha_s} )</td>
</tr>
<tr>
<td>Hydrodynamic function, ( A_{A_0} )</td>
<td>( \frac{1 - 0.3956 \cdot \gamma + 1.0616 \cdot \gamma^2}{(1 - \gamma)^{yz}} )</td>
</tr>
<tr>
<td>Large pores fractional area, ( A_L )</td>
<td>( \frac{\alpha_L \cdot (r_s)^2}{1 - \alpha_s \cdot (r_s)} )</td>
</tr>
<tr>
<td>Permeability surface area, ( PS )</td>
<td>( \frac{A_0 - A_0}{A_0 + D_s} )</td>
</tr>
<tr>
<td>Total permeability surface area</td>
<td>( \left[ (1 - A_s) \cdot \left( A_{b_0} + A_0 \cdot \left( A_{b_0} \right) \right) \right] \cdot \frac{A_0}{\Delta x} \cdot D_s )</td>
</tr>
</tbody>
</table>

The ratio between the permeating solute radius \( \alpha_s \) and the pore radius \( r \) is denoted by \( \gamma \). The total reflection coefficient is indicated for a three-pore membrane with transcellular, small, and large pores with relative weights \( \alpha_s, \alpha_r, \) and \( \alpha_t \), respectively. For the free diffusion coefficient definition \( T \) is the gas constant, \( T \) is the absolute temperature, \( \nu \) is the viscosity, and \( N_A \) is Avogadro’s number. For the permeability surface area definition, \( A_0 / \Delta x \) is the surface area available for exchange over the diffusion path length. \( r_s \) and \( r_L \) are the radius of the small and large pores, respectively.

### Table 2. Basic permeability coefficients (single membrane and series arrangement)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single</th>
<th>Series Array</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydraulic conductivity</td>
<td>( L_p )</td>
<td>( f \left( \frac{L_{p,a} \cdot L_{p,b}}{L_{p,a} + L_{p,b}} \cdot C_{w} \cdot J_{v} \right) )</td>
</tr>
<tr>
<td>Diffusional permeability</td>
<td>( P )</td>
<td>( \frac{P_b \cdot P_s}{P_s + P_b} )</td>
</tr>
<tr>
<td>Reflection coefficient</td>
<td>( \sigma )</td>
<td>( \frac{\alpha_p}{P_s + P_p} \cdot \sigma_b \cdot \frac{P_p}{P_s + P_p} )</td>
</tr>
</tbody>
</table>

See text for the definition of \( f \left( \frac{L_{p,a} \cdot L_{p,b}}{L_{p,a} + L_{p,b}} \cdot C_{w} \cdot J_{v} \right) \)

### Theory of Composite Membranes

A system model for a series array of membranes can be considered as composed by two membranes that we name \( a \) and \( b \). In Table 2 are the definitions of hydraulic conductivity, diffusional permeability, and reflection coefficient for two membranes arranged in series as obtained by Kedem and Katchalsky (15). It is readily apparent that the usual Kirchoff’s law, which states that the reciprocal of the resulting resistance of a series arrangement of two membranes and \( \lambda = (\alpha_r - \alpha_p)(PS_a + PS_b) \), where \( PS_a \) and \( PS_b \) are the permeability surface area products for each membrane. The last term in Eq. 1 takes into account the appearance of an intermediate layer at the interface between the two layers. The fluid flow for a series arrangement is then defined by the implicit equation (15)

\[
J_v = \left[ \frac{1}{L_{p,a}} + \frac{1}{L_{p,b}} + \frac{RT}{J_v} \cdot C_{w} \cdot (1 - e^{-\lambda V}) \cdot (\sigma_a - \sigma_b) \right]^{-1} \times (\Delta P - \sigma \cdot \Delta V)
\]

where \( \sigma \) is the total reflection coefficient for a membrane series as reported in Table 2 and \( \Delta P \) and \( \Delta V \) are the hydraulic and colloid-osmotic pressure gradients across the series arrangement. A similar implicit equation has been obtained by Pathak et al. (20) by considering a system in which two membranes in series are delimiting an inner compartment with finite volume. With the same assumptions, it is possible also to obtain the general solute flux (\( J_s \)) equation for a membrane series arrangement (20) as

\[
J_s = J_v (1 - \sigma_a)(1 - \sigma_b) - \frac{C_{ds} - C_{dw}(e^{-\lambda V} \cdot \Phi_{w})}{(1 - \sigma_a) \cdot e^{-\lambda V} + (1 - \sigma_b)(1 - e^{-\lambda V})}
\]
Intermediate layer concentration, \( C_{il} \)

\[
J_v \cdot \frac{1 - \sigma}{PS} \quad Pe_a + Pe_b
\]

Sieving coefficient, \( S \)

\[
\frac{1 - \sigma}{1 - \sigma \cdot e^{-Pe}} \quad \left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma_b \right)
\]

Unidirectional clearance, \( C_l \)

\[
J_v \cdot \frac{1 - \sigma}{1 - e^{-Pe}} \quad \left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma_b \right)
\]

Intermediate layer concentration, \( C_{il} \)

\[
J_v \cdot \left( 1 - \sigma \right) \cdot \left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma_b \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_a} \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_b} \right)
\]

\[
\left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_a} \right) \cdot \left( 1 - \sigma_b \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_b} \right)
\]

\[
\left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_a} \right) \cdot C_{us} + \left( 1 - \sigma \cdot e^{-Pe_b} \right) \cdot \left( 1 - \sigma_b \right) \cdot e^{-Pe_b} \cdot C_{ds}
\]

\[
\left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_a} \right) \cdot \left( 1 - \sigma_b \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_b} \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_b} \right)
\]

\[
\left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_a} \right) \cdot \left( 1 - \sigma_b \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_b} \right)
\]

\[
\left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_a} \right) \cdot \left( 1 - \sigma_b \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_b} \right)
\]

where \( C_{ds} \) is the downstream concentration and \( Pe_a \) and \( Pe_b \) are the Peclet number \( J_v / \left( 1 - \sigma / PS \right) \) for each membrane (2).

From the relationships in Table 2 and Eq. 3 we obtained the Peclet number, the sieving coefficient, the unidirectional clearance, and the intermediate layer concentration of the filtrate crossing a membrane series array. In Table 3, the definitions of each parameter are compared for a single membrane and a series of two membranes.

Peclet number. We obtained the Peclet number for a series arrangement of membranes by substituting the expressions for total \( P \) and \( \sigma \) in Table 1 in the Peclet number definition. The resulting overall Peclet number is the sum of the Peclet number of each membrane.

Sieving coefficient. The sieving coefficient is defined as the ratio between the downstream and the upstream concentrations of the filtrate crossing a membrane. We obtained the sieving coefficient for the series arrangement by considering that the equilibrium concentration in ultrafiltration conditions (no changes in filtrate concentration with time) is given by \( C_{ds} = J_v / \sigma \cdot \sigma_a \cdot \sigma_b \). The equation reported in Table 3 follows by substituting Eq. 3 for \( J_v \) and rearranging the resulting expression. Interestingly, the equation is identical to that obtained by integrating the flow equations on a path crossing the two membranes (4).

Clearance. The unidirectional clearance of a solute through a membrane is defined as the ratio between the solute flux and the upstream solute concentration, considering the downstream concentration equal to zero. The extension of the unidirectional clearance to a series of two membranes reported in Table 3 is straightforward, applying the definition to Eq. 3.

Intermediate layer concentration. For the sake of simplicity, we assumed in our model that fluid flow and solute fluxes are completely developed after crossing the membrane. This allowed us to describe the basic permeability coefficients of each membrane according to the three-pore theory but considering only one overall fluid flow or solute flux across the membrane. This assumption lead us to consider that an intermediate region (or layer) has to be present delimited by the two membranes. On the other hand, the concept of “intermediate layer” follows by the consideration that two membranes in series should always include an intermediate region at the interface between the contacting sides. This region may be infinitesimally thin, as in the theoretical approach in Ref. 15, or may have a definite volume (20). However, it is interesting to observe that both approaches lead to similar equations, as stated above, e.g., for the sieving coefficient. We address the search for the equation defining the intermediate layer concentration by considering that the Patlak form of the solute flux equation for a single membrane should apply simultaneously to both membranes, so that

\[
J_v \cdot \left( 1 - \sigma \right) \cdot \left( 1 - \sigma_a \right) \cdot \left( 1 - \sigma_b \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_a} \right) \cdot \left( 1 - \sigma \cdot e^{-Pe_b} \right)
\]

This equation follows immediately considering that for two membranes arranged in series the solute flux crossing the overall system is equal to the solute flux crossing each membrane. Equation 4 can be solved for \( C_{il} \) by obtaining the corresponding equation in Table 3.

Characterization of the Double-Layered Equivalent Peritoneal Membrane

We extend the pore theory of peritoneal exchanges by considering the equivalent peritoneal membrane as composed by two heteroporous membranes arranged in series. Therefore, to characterize the equivalent membrane, we have to determine the number of pores of different radii and their relative weight and the unrestricted (and restricted) surface area available for exchange over the diffusion path length \( (A_v / \Delta x) \) for each membrane. As experimental reference points, we took the unidirectional clearances measured simultaneously for both flow directions, namely from blood to dialysate and from dialysate to blood (see below). Furthermore, if we simulate the lymphatic drainage of biological tissues by adding a nonsieving purely convective flow as a possible egress route from the peritoneum, the clearance to blood simply becomes

\[
Cl_{TOT} = Cl_m + J_L
\]

where \( Cl_m \) represents the clearance through the membrane system and \( J_L \) is the lymph flow contribution to the total clearance \( Cl_{TOT} \). In equilibrium, steady-state \( Cl_{TOT} \) equals \( J_L \).

We described the dependence of the permeability coefficients on membrane structure parameters and solute size by applying the pore theory. We calculated the unidirectional clearance by applying the composite membranes theory (see the equation reported in Table 3) for the different solute sizes and flow direction. We searched for the membrane structure parameters and the peritoneal lymph flow using a best-fit procedure, iteratively minimizing the function \( \chi^2 \) defined as

\[
\chi^2 = \sum \left( \frac{Cl_{TOT, th} - Cl_{exp}}{Cl_{exp}} \right)^2
\]
where $C_{\text{TOT,th}}$ is the total theoretical clearance from the peritoneal cavity and $C_{\text{exp}}$ is the corresponding experimental clearance for a given solute. The sum is extended over all of the considered solutes.

We fixed the parameters of the blood-facing membrane to the values determined in Refs. 22 and 23 and calculated the parameters for the dialysate-facing membrane and the peritoneal lymph flow. We set the fluid flow from plasma to the peritoneal cavity at 1.5 ml/min and the reverse fluid flow to 1 ml/min.

The best-fitting procedure was performed using a Mathcad program (Mathsoft, Cambridge, MA) on a personal computer (Compaq Deskpro; Compaq Computer, Houston, TX).

The bidirectional clearance data. The clearance data used as experimental points to direct the best-fitting procedure are represented in Fig. 1. We considered molecules with a molecular weight ranging from 360 (sucrose) to 820,000 (α₅-macroglobulin), corresponding to molecular sizes between 5 and 90 Å. We obtained the values for the small solutes (sucrose and vitamin B₁₂) from Babb et al. (2) and the inulin value from Struijk et al. (26). We used macromolecule data using the clearances measured in Ref. 16 that compared dextran and protein bidirectional transport. For the intermediate layer concentration between the molecules. Figure 2, represents one minus the osmotic reflection coefficient, $(1 - \sigma)$, which corresponds to the sieving coefficient when $J_V \rightarrow \infty$. Figure 2, middle, shows the PS, and Fig. 2, bottom, shows the Peclet number $[J_V/(1-\sigma)/PS]$ as calculated for a fluid flow of 1 ml/min. The curves for the two single membranes and their series arrangements are compared in the same graph.

In Fig. 3, we determined the flow dependence of the sieving coefficient $(A)$ and unidirectional albumin clearance $(B)$ for this membrane series arrangement. Positive values on the abscissa correspond to a flow directed from the blood to the peritoneal cavity, whereas negative values represent flow in the opposite direction.

Figure 4 is another way to represent the asymmetry in the intermediate layer concentration between the

Table 4. Characterization of the double-layered peritoneal equivalent membrane

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Blood-Facing Side</th>
<th>Dialysate-Facing Side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fixed</td>
<td></td>
</tr>
<tr>
<td>Small-pore radius, $r_s$ (Å)</td>
<td>43</td>
<td>67 ± 3 (−)</td>
</tr>
<tr>
<td>%</td>
<td>90</td>
<td>10–43–200</td>
</tr>
<tr>
<td>Large-pore radius, $r_L$ (Å)</td>
<td>250</td>
<td>2,336 ± 777 (1,428)</td>
</tr>
<tr>
<td>%</td>
<td>8</td>
<td>50–250–1,000</td>
</tr>
<tr>
<td>Transcellular pores, %</td>
<td>2</td>
<td>95 ± 2 (92.6)</td>
</tr>
<tr>
<td>$A_p/\Delta x \times 10^4$ cm</td>
<td>5</td>
<td>2 ± 2 (7.4)</td>
</tr>
<tr>
<td>Lymph flow, $J_{L, f}$, ml/min</td>
<td>0.27 ± 0.01 (0.26)</td>
<td>0–2–0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although the fixed-parameter values describing the blood-facing side were obtained from (22, 23), the calculated dialysate-facing side parameter values (means ± SD) were obtained by the best-fit procedure outlined in the text. The procedure has been repeated for each of the 216 allowable combinations of the values reported in the last column. Means and SD refer only to the best-fit results having $\chi^2 < 0.5$ (n = 85). The values in parentheses correspond to a best fit with an equivalent peritoneal membrane composite of two identical membranes as starting point.

RESULTS

The parameter values resulting from the best-fitting program are reported in Table 4 while the corresponding curves are plotted in Fig. 1. The resulting parameters show that the measured clearance data are compatible with a second membrane containing mostly very large pores with radius ~2,300 Å and a small number of transcellular pores (~2%). The small pores account in average for 4% of the overall hydraulic conductance and have an average radius of ~70 Å. The calculated lymph flow is ~0.3 ml/min.

In Fig. 2, the relationships between the basic permeability parameters are a function of molecular size of the molecules. Figure 2, top, represents one minus the osmotic reflection coefficient, $(1 - \sigma)$, which corresponds to the sieving coefficient when $J_V \rightarrow \infty$. Figure 2, middle, shows the PS, and Fig. 2, bottom, shows the Peclet number $[J_V/(1-\sigma)/PS]$ as calculated for a fluid flow of 1 ml/min. The curves for the two single membranes and their series arrangements are compared in the same graph.

In Fig. 3, we determined the flow dependence of the sieving coefficient $(A)$ and unidirectional albumin clearance $(B)$ for this membrane series arrangement. Positive values on the abscissa correspond to a flow directed from the blood to the peritoneal cavity, whereas negative values represent flow in the opposite direction.

Figure 4 is another way to represent the asymmetry in the intermediate layer concentration between the
different flow directions as a function of molecular size. The three curves represent the ratio between the two directional intermediate layer concentrations for a fluid flow of 0.5 ml/min in each direction and a ratio between the downstream and the upstream concentrations equal to 0.1, 1, or 10. The vertical lines correspond to the molecular radii of sodium (2.3 Å), urea (2.6 Å), glucose (3.7 Å), and albumin (35.5 Å).

By considering the simultaneous membrane transport of the four solutes of interest with the concentrations reported in Table 5, we calculated the overall hydraulic conductance, compared with a constant resulting from the Kirchoff’s summation rule, in Fig. 5.

It is readily apparent from Fig. 4 that the molecules most affected by the introduction of this membrane series arrangement are the macromolecules. To apply our model to a real case, we selected one measurement of the albumin kinetics during PD, as reported in Ref. 14, and applied our model to predict the albumin concentration in the intermediate layer during the dwell. In Fig. 6A, a representative volume vs. dwell time curve for a 1.36% PD is shown together with the calculated net flow in and out of the peritoneal cavity. Figure 6B represents the blood and dialysate concentrations of an intravenously or intraperitoneally injected tracer albumin expressed relative to the blood concentration at time 0. Also represented is the intermediate layer concentration calculated by the measured upstream and downstream concentrations and the fluid flow reported in Fig. 6A.

DISCUSSION

According to the theoretical model fit of the experimental data, two different membranes compose the peritoneal membrane. A three-pore membrane as proposed by Rippe and coworkers (22–24) represents the endothelial (capillary) barrier, whereas a second membrane traversed by a great amount of very large pores (~94% of the total pore area) and few small and transcellular pores lines the peritoneal cavity. A unidirectional lymphatic channel directly connects the peritoneal cavity by the blood. We can identify the second membrane with the extracellular interstitium lumped with the mesothelial cell layer lining the peritoneal cavity. The predominant presence of very large pores is consistent with some of the morphological changes of the peritoneal barrier occurring.
in conjunction with PD, such as widening of the mesothelial intercellular junctions (7). This will impart to the solutes a nearly free access to the underlying interstitium. As in a number of other organs, the interstitium in the rat mesentery has been shown to be organized as a heterogeneous matrix of collagen fibers crossed by wide channels (3). Furthermore, the presence of “interstitial” pores as large as 1,000 Å was also found by Granger et al. (11) in their study of the liver blood-lymph barrier. During a PD session with two liters of fluid with a hydraulic pressure in the peritoneal cavity averaging ~9 mmHg (28), we can assume that the same conditions apply for transport from the peritoneal cavity to blood. A similar explanation has been proposed by Flessner et al. (9) to explain data on exchange of macromolecules between the peritoneal cavity and plasma. Furthermore, the presence of few transcellular pores is not at all unexpected since aquaporins are common to a wide variety of cells (1) and have been found in the mesothelium using immune histochemical and immunogold labeling techniques (5).

It is interesting to note that, although there are great differences in structure of the two membranes, the resulting basic permeability coefficients are not much different from those of the least permeable mem-

![Graph](http://ajprenal.physiology.org/)

**Fig. 4.** Concentration hyperpolarization phenomenon. Intermediate layer concentration, expressed as relative to the upstream concentration, as function of molecular size for different combinations of upstream and downstream concentrations. The curves refer to equal upstream and downstream concentrations (solid line) or to a downstream concentration equal to 10 times or [1/10] of the upstream concentration (dashed and dotted curves, respectively). The vertical lines indicate, from left to right, the size of sodium (2.3 Å), urea (2.6 Å), glucose (3.7 Å), and albumin (35.5 Å). The accumulation of solute molecules in the intermediate layer is particularly evident for the larger solutes. C, concentration; Cus, upstream concentration.

![Graph](http://ajprenal.physiology.org/)

**Fig. 5.** Hydraulic conductance for the concentrations reported in Table 5. Horizontal dotted line represents the hydraulic conductance obtained by the usual Kirchoff’s summation rule. As in Fig. 3, positive fluid flows represent transport between blood and peritoneal cavity, whereas negative fluid flows correspond to the reverse transport direction. The flow direction-dependent asymmetry is a consequence of the concentration hyperpolarization phenomenon. L, hydraulic conductance.

Table 5. Blood and peritoneal concentrations of the solutes of interest used in the simulations

<table>
<thead>
<tr>
<th>Solute</th>
<th>Molecular Weight</th>
<th>Molecular Weight</th>
<th>Concentration, mmol/l</th>
<th>Concentration, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>23</td>
<td>2.3</td>
<td>Blood</td>
<td>Dialysate</td>
</tr>
<tr>
<td>Urea</td>
<td>60</td>
<td>2.6</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>Glucose</td>
<td>180</td>
<td>3.7</td>
<td>6.5</td>
<td>67</td>
</tr>
<tr>
<td>Albumin</td>
<td>69,000</td>
<td>35.5</td>
<td>1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

brane (Fig. 2). However, the difference between the structures of the two membranes accounts for the striking feature of this system, which is the transport asymmetry between the two flow directions, and the importance of this phenomenon increases with increasing solute molecular size. The asymmetry is not important for small solutes (up to ~10 Å) but is an important component of the sieving and clearance curves for albumin (r = 35 Å) presented in Fig 3. The sieving coefficient for albumin from blood to the peritoneal cavity is ~0.11 for all of the (hydraulic) fluid flows, but in the reverse direction it increases to 0.92 at ~1 ml/min flow and remains actually constant for higher flows. The peak of the sieving curve for zero flow is due to the fact that at very low fluxes, solute diffusion tends to equalize solute concentrations at the two sides of the membrane. One of the most important consequences of the asymmetry in the sieving coefficient is its effect on the concentration of solutes in the intermediate layer. In Fig 4, this effect is expressed as a ratio between the intermediate layer concentrations developing for an equal fluid flow but in the opposite direction.

Let us now consider the intermediate curve, obtained for equal downstream and upstream concentrations. The intermediate layer concentration in this case is equal for flow in both directions (ratio = 1) for a molecular size ≤15 Å. As the molecular size increases, a steep increase in concentration occurs to about r = 42 Å, and the curve continues to increase, but with a lesser slope. This effect is due to the fact that, when the solute first crosses the most permeable membrane, the barrier represented by the second membrane is not at all important for small solutes but becomes more and more difficult for macromolecules to cross. In turn, this leads to an accumulation of molecules in the intermediate layer and a “concentration hyperpolarization” phenomenon. The lower curve represents an upstream
peritoneal (can quite easily leave the intermediate compartment. The asymmetry of the sieving properties of the series layer because of their difficulty to move both against the opposing concentration gradient. It is then conceivable that a great quantity of molecules remains in the intermediate layer concentration ratio in this case slowly decreases up to a molecular size of 23 Å, but then the same phenomenon begins to appear and the ratio increases to 15 for a molecular size of 45 Å. The last portion of the curve is almost parallel to the other curve. Finally, considering the upper curve, we can see that a huge hyperpolarization phenomenon is present for small solutes. However, we should consider that this curve represents an extreme situation in which the solutes are flowing against a concentration gradient in which the upstream concentration is 10 times greater than the downstream one. It is then conceivable that a great quantity of molecules remains in the intermediate layer because of their difficulty to move both against the asymmetry of the sieving properties of the series arrangement and the opposing concentration gradient.

Once the flow is stopped, the smaller solutes will move mainly by diffusion (like the three smaller solutes represented by the left vertical lines in Fig. 4) and can quite easily leave the intermediate compartment. At variance, macromolecules, like albumin (Fig. 4, line on right), should remain trapped in this compartment if some clearing mechanism such as the lymphatic system is not sufficiently active. One consequence of this concentration hyperpolarization phenomenon is the asymmetry that is generated in hydraulic conductance. In fact, if we refer to Fig. 5, we can observe that the hydraulic conductance increases or decreases after the direction of flow. These consequences of the series membrane arrangement and hyperpolarization in PD are in reality somewhat hypothetical, however, since fluid flows from the peritoneum to the plasma in PD and is not driven by hydrostatic pressure gradients. Instead, the convective transport of fluid from peritoneum to plasma under these conditions is driven by the difference in oncotic pressures between the plasma and the interstitium, created by the continual removal of bulk proteins from the peritoneal cavity occurring during chronic PD. In PD, the hydraulic conductance will actually be unchanged regardless of the direction of flow, because a “macroscopic” concentration hyperpolarization of plasma proteins does not occur. However, the present model can be used to understand the behavior of tracer macromolecular clearances between plasma and the peritoneal cavity or vice versa when the macroscopic (nontracer) albumin concentrations do not show a hyperpolarization concentration. We can, for example, consider the typical data for tracer albumin kinetics during a 1.36% glucose dialysis dwell reported by Joffe and Henriksen (14), and we can calculate from these data a tentative intermediate layer tracer albumin concentration. By considering a representative volume vs. time curve (reported in Fig. 6A), we calculated the net fluid flow by the differences between subsequent points divided by the corresponding time difference (also represented in Fig. 6A). By considering the intermediate layer albumin concentration (expressed as relative to the initial serum concentration in Fig. 6B), we see that the concentration remains in the low and high concentrations when the flow is directed from blood to the peritoneal cavity. However, when the flow is reversed, the hyperpolarization phenomenon occurs and at the end of the dwell the intermediate layer tracer albumin concentration would be as high as about eight times the initial blood concentration. Also, if the lymphatic drainage is actively clearing this albumin, a long-lasting hyperpolarization is predicted due to the volume exclusion effect that impedes albumin free motion. This accumulation has been observed experimentally by several different techniques in mice (19) and in rats (10). Furthermore, the slow release of this sequestered albumin to blood could explain the observation that several days after an intraperitoneal injection of radioactive albumin the blood tracer activity continues to increase (12, 14).

The model presented here can be considered as complementary to the “distributed model” of Flessner et al. (8) and the simplified version of this model recently presented by Waniewski et al. (30) in describing the bidirectional peritoneal solute transport. Although the model may be too simplistic to deal with membrane transport phenomena, it should be useful for understanding the role of membrane transport in chronic peritoneal dialysis.
permeability in terms of straight cylindrical channels (" pores"), our modeling technique is still sufficiently powerful to allow a prediction of the bidirectional clearance through a relatively simple two-membrane system. Furthermore, the application of modern pore theory allows us to consider the effects of molecular weight (or size) on transport of the different solutes, since the proposed insights concerning the structure of an "equivalent peritoneal membrane" are dependent upon a lesser number of parameters compared with the distributed model approach.

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