**Pro/Con Debate**

**Free water transport, small pore transport and the osmotic pressure gradient three-pore model of peritoneal transport**

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**Introduction**

In this issue of NDT, Flessner in a commentary [1] argues that the three-pore model (TPM) of peritoneal transport, although mathematically a powerful predictor of solute transport and ultrafiltration (UF) in peritoneal dialysis (PD), may be too simple as a tool for understanding the physiology of transperitoneal exchange. Flessner then disregards the fact that the TPM can be modified in a very simple fashion by taking both the capillary and the interstitial barriers into account in the modelling. This has in fact already been done by adding a second heteroporous barrier [2] or an interstitial gel–matrix barrier in series with the capillary membrane in the TPM; the latter model denoted the ‘three-pore membrane/fibre matrix model’ [3]. Flessner also brings up now the 30-year-old controversy whether the endothelial ‘fuzzy’ surface layer, the glycocalyx, has size-selective sieving properties or not.

In response to Flessner’s criticism of the TPM, I would like to cite Leonardo DaVinci: ‘Simplification is the ultimate form of sophistication’. The TPM is based on decades of basic capillary physiologic research, and the many simplifications made in the model have been done with due consideration of all the complexities of the peritoneal barrier. The usefulness of the model is illustrated by the fact that it can predict solute and fluid transport not only for glucose, but also for alternative osmotic agents, such as icodextrin and amino acid solutions [4,5], and also for solutions with altered electrolyte composition [6,7]. This is in contrast to the distributed model, which is in an early developmental phase. For example, it has great problems in predicting UF (glucose osmosis) from the peritoneal tissue to the peritoneal cavity. In contrast, the three-pore membrane/fibre matrix model can explain how osmotic fluid flow can occur from the peritoneal tissue to the peritoneal cavity against a glucose concentration gradient, and against a hydrostatic pressure gradient, at the same time as fluid and macromolecules move from the peritoneal cavity to the peritoneal tissue, by hydrostatic pressure driven flow.

Concerning the ‘glycocalyx (fibre matrix) hypothesis’, it may be regarded as a ‘soft’ hypothesis since it is hard to test experimentally. Actually, the pore theory and the fibre matrix theory are mathematically similar, and there is no way of actually distinguishing between the two models. In fact, the bimodal (‘small pore’/‘large pore’) solute selectivity of the TPM can be accurately described by the presence of a dense, but heterogeneous, fibre matrix filling out all spaces in between the endothelial cells of the capillary barrier. In this commentary I shall first review the key features of the TPM and how these have contributed to a deeper understanding of the physiology of peritoneal exchange. Especially I will discuss the puzzling discrepancy between the clearance of tracer macromolecules from the peritoneal cavity into the tissues \((K_D)\) and the net reabsorption of fluid from the peritoneal cavity to plasma. Second, arguments will be raised that the endothelial glycocalyx does not satisfy the criteria for being a highly size-selective barrier in the TPM.

**Key physiologic features of the TPM**

The capillary wall is the dominating peritoneal barrier, being heteroporous. Despite reflection coefficients \((\sigma)\) near zero, sieving coefficients \((\theta)\) for small solutes are 0.5–0.6 and not near unity \((1-\sigma)\).

The anatomic barrier separating the blood from the peritoneal fluid in PD contains a number of structures placed in series, mainly the peritoneal capillary walls, the interstitium and the mesothelium. According to the classical TPM, the capillary wall is by far the dominating transport barrier and it therefore, as a good approximation, neglects the other serial barriers under normal conditions. The second important principle of the TPM (not included in older models) is that the capillary barrier is heteroporous, with a bimodal size-selectivity for solute transport (‘small pores’/‘large pores’).
combined with a transcellular pathway exclusive for water (aquaporin-1: AQP-1). In fact, long before the cloning of AQP-1 [8], the TPM predicted that the phenomenon of ‘sodium sieving’ must be the result of passage of water devoid of solute through water-only transcellular pores. This paradigm was recently amply confirmed by PD experiments in mice lacking AQP-1 [9]. The consequence of the presence of water-only pores is that small solute sieving coefficients (filtrate-to-plasma concentration ratios; \( \theta \)) are usually 0.5–0.6 under conditions of crystalloid (e.g. glucose) osmosis, instead of near unity, as had been the case in the absence of aquaporins. At the same time, small solute reflection coefficients (\( \sigma \)), characterizing the osmotic efficiency of the solute, are very low (below 0.1), as in most continuous capillary walls [10,11]. This is in fact a key feature of the TPM and is the basis for the understanding of the difference in osmotic efficiency between colloid osmotic-type agents, such as icodextrin (\( \sigma > 0.4 \)) and crystalloid osmotic-type agents, such as glucose (\( \sigma < 0.1 \)). In older models [12] or newer [13] where \( \sigma \) for small solutes are set \( >0.4 \) [12], it is impossible to correctly model UF for colloid osmotic-type agents [14].

**Transendothelial macromolecule transport occurs by convection through large pores and not by ‘transcytosis’**

Yet another unique feature of the TPM is that it handles the transport of macromolecules separately from that of small solutes. The size-selectivity of the TPM for macromolecules larger than albumin is compatible with the presence of very infrequent large pores (radius \( \sim 250 \text{ Å} \); 0.01% of the total number of pores) across which plasma proteins can reach the interstitium and the peritoneal cavity by pressure-driven flow, unaffected by the oncotic or colloid osmotic pressures acting across small and transcellular pores. Thus, large pore transport is dictated only by changes in the transcapillary hydrostatic pressure gradient and/or the number of large pores available for transport, both of which can increase dramatically in states of inflammation. While the TPM has consistently predicted that the transvascular transport of macromolecules must occur through large pores, many morphologists and cell biologists have considered this process to be due to transendothelial shuffling of proteins by plasmalemmal vesicles (caveolae), so-called transcytosis. However, it was recently shown that caveolin-1 deficient mice completely lacking endothelial caveolae (vesicles), and therefore being incapable of transcytosis, actually show an increased, not a reduced, transport of macromolecules across their microvessels [15]. It thus seems clear that transcytosis does not significantly contribute to the transport of proteins between the plasma and the peritoneal cavity.

The reabsorption of isotonic fluid from the peritoneal cavity to plasma occurs via the small capillary pores due to the Starling mechanism, because of the high plasma to peritoneal colloid osmotic pressure gradient (\( \Delta \pi \)) during PD

Another key feature of the TPM is that it predicts the reabsorption of isotonic fluid devoid of colloid (e.g. isotonic NaCl) as occurring through small pores, with only a minor contribution of lymphatic absorption (0.2–0.3 mL/min). This transport behaviour of the peritoneum has recently been shown for 1.36% glucose solutions using a modified ‘LaMilia technique’ (see below) [16], but it is more difficult to show for hypertonic glucose in short (4 h) dwell times, when net reabsorption is low or absent, as in the study by Parikova et al. in this issue of NDT [17]. Using the ‘LaMilia technique’ [18], the UF occurring through small pores (SPUF) is based on the assessment of the transperitoneal clearance of Na\(^+\) because Na\(^+\) almost exclusively traverses the small pores by convection during the first 0–1 h of the dwell. Subtracting SPUF from total (net) UF, the ultrasmall pore-mediated UF (USPUF) can be calculated. However, the technique becomes increasingly inaccurate (even after corrections for Na\(^+\) diffusion) for dwell times longer than 1–2 h [19]. This problem, combined with the absence of net reabsorption (fluid loss) in the study by Parikova et al. [17], may be responsible for the problems of showing back-filtration through the small pores in their study. Another source of ambiguity seems to be related to the estimation of intraperitoneal (i.p.) volume as a function of dwell time using a macromolecular volume marker, the clearance of which out of the peritoneal cavity, usually denoted \( K_E \), will be discussed next.

The clearance of a macromolecular marker from the peritoneum to peritoneal tissues (\( K_E \)) is a complex parameter determined by several different processes: convection into the tissue, ‘volume recirculation’ between tissue and cavity, lymphatic reabsorption, and capillary small pore fluid, but not macromolecule, reabsorption

Because the TPM is based on direct volumetric measurements of drained peritoneal volume versus time it avoids the complexity associated with the use of a macromolecular volume marker, continuously disappearing at a high rate from the peritoneal cavity. The clearance of a macromolecular marker into the peritoneal tissues, \( K_E \), can increase due to increases in peritoneal hydrostatic pressure, also causing some oedema in the tissue, as discussed at some length by Flessner [1]. In a steady state, however, \( K_E \) is mainly dependent on four processes, namely (1) the convective fluid transport into the tissue, drained by (2) lymphatic absorption (~0.2 mL/min) and (3) back-filtration of fluid, but not of marker, through the small pores in the capillary walls (~0.9 mL/min), and also, as suggested here, by (4) ‘volume recirculation’ between the peritoneal cavity and the peritoneal tissue (~0.7–1.0 mL/min). The latter process is not associated with net fluid movement, but with net macromolecule permeation, into the tissue. Binding of a marker to the peritoneal tissue and marker diffusion also contribute to \( K_E \), which is thus larger than the sum of lymphatic reabsorption and capillary small pore back-filtration.

‘Volume recirculation’ is a concept taken from capillary physiology and is a phenomenon that occurs in heterogeneous (e.g. large pore/small pore) membranes. It has been described in detail in a number of previous publications [20–22]. In isolated perfused muscle capillary beds, volume recirculation was demonstrated under conditions of zero net
fluid movement from plasma to the interstitium. Such conditions can be created by lowering the capillary hydrostatic pressure slightly (by 0.5–1.5 mmHg) from the normal level, so that net filtration (lymph flow) ceases. Under such conditions the normal filtration of albumin and other proteins occurring through the large pores, unopposed by any oncotic gradients, is exactly counterbalanced by reabsorption of tissue fluid (devoid of proteins) via the small pores due to the altered Starling balance (following upon the reduction in capillary hydrostatic pressure) (Figure 1a). Small pore back-filtration is due to the fact that the effective colloid osmotic pressure across the small pores is now larger than the effective transcapillary hydrostatic pressure gradient. Under such ‘isovolumetric’ conditions, filtration through the large pores, containing fluid and plasma proteins, is in exact equilibrium with the reabsorption of tissue fluid, devoid of proteins, through the small pores. Thus, there is net movement of proteins (albumin) out of the capillaries in the absence of net fluid transport.

All the elements needed to set up volume recirculation are present at the interphase between the peritoneal cavity and the peritoneal tissue. As discussed by Flessner [1] the interstitial tissue is extremely permeable, yet offering at least some resistance to solute and water transport, except in areas with free fluid channels. Volume recirculation between the peritoneal cavity and tissue can occur due to the higher hydrostatic pressure in the peritoneal cavity than in the tissue, and also due to the usually much higher crystalloid osmotic pressure in the peritoneal cavity than in the tissue. Even in the absence of these conditions, a ‘volume recirculation term’ has to be added to the equations that describe transport through a heteroporous barrier [21]. It is thus likely that the peritoneal tissue is heterogeneous, with a matrix of fibres, which is penetrated by very large parallel channels of fluid (regions of extremely low size-selectivity). Along these channels, fluid and macromolecules can move into the tissue by hydrostatic pressure-driven flow. At the same time (at least during the early phase of the dwell) fluid and small solutes are ‘dragged’ in the opposite direction out from the peritoneal tissue to the cavity by crystalloid (glucose) osmosis through the interstitial fibre matrix (Figure 1b). A heterogeneous interstitial fibre matrix can thus explain how vectorial osmotic water flow can occur through the normal peritoneum against the glucose concentration gradient (and along the glucose osmotic gradient), and also against the hydrostatic pressure gradient, at the same time as fluid and macromolecules move into the tissue through regions devoid of fibres driven by hydrostatic pressure and unopposed by crystalloid osmotic pressure.

In summary, the classical TPM can predict the measured drained volume as a function of time and does not need to...
predict the virtual volume that appears from the volume of distribution of an i.p. macromolecular marker in the peritoneal cavity and tissue. \( K_F \) is a very complex parameter, which is only partly dependent on net fluid reabsorption from the peritoneal cavity to lymphatics and blood capillaries. According to the TPM, it is not correct to add \( K_F \) to the net UF during the dwell to establish a transcapillary UF (TCUF) curve since only a part of \( K_F \) is related to (net) fluid transport across the peritoneum. According to the TPM, TCUF is just the net UF + the lymphatic re-absorption term (0.2–0.3 mL/min). The net fluid loss from the peritoneal cavity (1.2 mL/min) is the sum of the small pore back-filtration (0.9 mL/min) and the lymphatic re-absorption term. Since TCUF has a different meaning in the study of Parikova et al. [26], leading to higher values of both TCUF and small pore UF than predicted by the TPM, this may have contributed to the deviation of the experimentally assessed small pore UF from the TPM predicted small pore UF at 2–4 h. Had net reabsorption prevailed, as for 1.36% glucose, it is likely that small pore ‘back-filtration’ would have been demonstrated [16].

**How does an endothelial glyocalyx affect the TPM?**

The answer to this question is ‘little’, or even ‘not at all’! The glyocalyx (fibre matrix) model is in fact much older than the TPM. Already in 1940, Chambers and Zweifach [23] suggested that an ‘intercellular cement’ would represent a molecular size-selective sieving material in the slits (clefts) that separate endothelial cells from each other in the capillary wall. With the advent of the pore theory of Pappenheimer et al. [24], it was suggested that the equivalent small pores might lie within the ‘intercellular cement’ or be determined by other structures within the interendothelial clefts. These structures were later found to be ‘junctional strands’ formed by integral membrane adhesion proteins (occludin and claudin-5), which form incomplete lines of cell-to-cell adhesion of endothelial cells at the luminal aspect of the interendothelial cleft [25].

In 1980 Curry and Michel proposed ‘the fibre matrix theory’ [26], implying that the selectivity of the interendothelial clefts would be dictated by the presence of a matrix of fibrous molecules filling out all pores and having a high density (5–6% of total water volume) and a radius of 0.5–0.6 nm. The rationale for suggesting a fibre matrix filling out the capillary pores is the striking similarity of the high size-selectivity (high \( \sigma \) to albumin) among different capillaries, or among various capillary beds, despite their great variability with respect to both hydraulic conductance (‘water permeability’, ‘LpS’) and small solute permeability–surface area products (PS; also denoted mass transfer area coefficients; MTAC). PS and LpS also seem to co-vary to a great extent. An alternative explanation to the rather uniform selectivity of capillaries, despite highly variable exchange (pore) areas is that the dimensions of the size-selective structures (slits/small pores) may be invariant from capillary to capillary, while the number of pores is highly variable.

The structural counterpart to the fibre matrix has been assumed to be the endothelial surface coat, or its innermost layer, the ‘glyocalyx’. The glyocalyx was discovered by Luft [27] using a cationic dye, ruthenium-red, that was found to stain the endothelial surface both at the luminal and the abluminal side of the endothelium, and also within the interendothelial clefts. Until recently, the glyocalyx was considered to be a 0.1-µm-thick endothelial layer consisting of endothelial cell-derived proteoglycans, glycoproteins and glycosaminoglycans, and also containing plasma proteins (albumin and orosomucoid). The glyocalyx confers a negative charge to the endothelial surface and seems to be a major contributor to the negative charge of the glomerular filtration barrier [28], while being of little functional importance as a charge barrier in the peritoneum [29,30]. It is also crucial for the proper interactions of leukocytes with the endothelium, especially in inflammation, for the mechanosensing of shear rate, and for the regulation of the coagulation cascade [31]. However, at present, there is no clear-cut evidence that the endothelial glyocalyx would really contribute to the size-selectivity of the capillary wall.

The glyocalyx hypothesis has been debated among capillary physiologists for over three decades, and remains very controversial, since it cannot be unambiguously tested. This is due to the fact that the fibre matrix model can be made to more or less exactly fit the behaviour of the two-pore model by adjusting its critical determinants, (1) the fibre density (or the matrix ‘void volume’), (2) the fibre radius and (3) the surface area (over unit diffusion path length, \( A_0/\Delta X \)) of the matrix available for exchange. For example, a matrix having fibres of radius 0.5 nm and 5.5% matrix density (fractional void volume = 94.5%), offers a size-selectivity corresponding to that of the small pores of the TPM (radius ∼4.5 nm). A very ‘loose’ matrix (∼99.6% void volume) occupying a minimal ‘surface area’ would correspond to the very few large pores of the TPM. Mathematically, there is thus no fundamental difference between the two different ways of the modelling transcapillary solute transport. Actually, the TPM is based on an equivalent pore concept, which describes the physiological behaviour of the porous pathways, and not the anatomic. Therefore, transperitoneal transport can be modelled using either equivalent pore models, slit models or the fibre matrix model. If the fibre matrix theory is to be applied, then the fibre matrix should be made partly heterogeneous in order to describe transport as occurring through small pores (slits) or large pores (large slits), while the third pathway is offered by the AQP-1.

**Why is pore theory preferred to glyocalyx theory in the TPM?**

1. The glyocalyx is a poorly defined ‘fuzzy’ layer of endothelial cell-anchored proteoglycans and glycosaminoglycans. Depending on staining and fixation techniques its thickness varies from 0.1 µm to several µm. The glyocalyx is usually regarded as very ‘loose’ and fragile. However, to offer a size-selectivity similar to that of small pores, its density should be >5% (fractional void volume <95%) for a fibre radius of 0.5–0.6 nm. The morphological appearance of the glyocalyx, however, indicates
that it is too loose and fragile to offer a substantial sieving barrier for uncharged solutes.

2. The permeability of the endothelial surface layer demonstrated so far is drastically different from that of normal capillary walls! Vink and Duling [32] thus demonstrated that the endothelial surface layer was largely impermeable to dextran 70 (and red cells), but highly permeable to dextran 40, albumin and fibrinogen. This does not comply with the numerous transcapillary (lymph) sieving studies performed using dextran of different sizes. They, in contrast, show that the permeability of monodisperse dextran 40 is usually only 20% higher than that of dextran 70 [33,34]. Furthermore, the transcapillary clearance of fibrinogen is low [21,35]. Indeed, Krediet et al. have demonstrated that the transperitoneal fractional clearance of dextran 70 and 40 only differed moderately [29], as recently confirmed by our laboratory [30]. Furthermore, the peritoneal clearance of albumin (negatively charged) and dextran 40 (neutral, and only slightly larger than albumin) were nearly identical [29,30]. Across the glomerular filtration barrier, however, dextran 40 shows at least a hundredfold higher permeability than albumin [36]. Thus, the permeability characteristics of the endothelial capillary surface layer, such as described by Vink and Duling, is markedly different from the sieving properties of most capillary walls.

3. In inflammation focal endothelial cell retractions cause an increased number of dynamic intercellular gaps (large pores) by active contraction of the endothelial cell actin cytoskeleton [37–40]. This is a highly dynamic, rapid and reversible process, occurring within seconds and reversible within minutes. Conceivably, the glyocalyx may be rapidly disrupted in inflammation, but could the glyocalyx really be resynthesized and reorganized within seconds (or minutes), similar to the dynamic behaviour of the (contractile) endothelial cell actin cytoskeleton?

4. There is no physiological technique available at present that can accurately assess the glyocalyx (volume). The techniques used by Vink and Duling and associates, based on comparing red cell (or dextran 70) intravascular distribution volume(s) with the distribution volume of dextran 40 are largely defective. This is due to the very inhomogeneous distribution of red cells among various vascular beds. A fundamental principle applied in tracer dilution measurements of volume is that the tracer must be evenly distributed in the volume to be under study. However, the well-known Fähræus–Lindquist effect (for review see e.g. [41]) makes red cells flow much faster through small arteries and arterioles, in e.g. heart and skeletal muscle, causing the haematocrit in these tissues to be very low. Also, ‘plasma-skimming’ effects in certain tissues, such as in the renal medulla, cause regionally very low haematocrit values. Conversely, in parenchymatous organs, such as in the liver and the lung, haematocrit is high. Red cells are thus unevenly distributed in the various vascular beds of the circulation and are therefore disqualified as intravascular volume markers! Another problem in the studies of Vink and associates is the extremely high clearance of dextran 40 from the circulation, thought to be due to its permeation through the endothelial glyocalyx [42], but in reality being dependent on its marked excretion to the urine by glomerular filtration [36]. The Vink and Duling techniques are also based on labelling polydisperse dextran fractions. The permeabilities of these fractions are not only dependent on the average size of the fraction used, but also critically dependent on the (non-characterized) grade of polydispersity.

5. We have so far found no evidence that the (negatively charged) glyocalyx is specifically altered in, for example, ischaemia-reperfusion (I/R) injury, or in other pathophysiological situations. After 60 min of total renal artery occlusion and I/R injury, the functionally most important change of the glomerular filtration barrier was a reduced size-selectivity with only a very minor component of reduced charge selectivity [43], indicating that the negatively charged glyocalyx was only partly involved in these changes. In early microalbuminuric experimental diabetes mellitus in rats, we recently observed, using Ficoll as sieving marker, that the glomerular filter displayed a reduced size-selectivity with only secondary changes in charge selectivity, confirming a previous Ficoll sieving study by Andersen et al. [44]. Thus, the glomerular glyocalyx is not likely to be involved in these changes [45].

6. If the recently proposed ‘glyocalyx-junction-break model’ of capillary permeability described by Weinbaum and Curry (reviewed in [46] and [47]), discussed by Flessner [1], were correct, then the size-selectivity of the small pore pathway would be accounted for by two separate barriers in series: first the glyocalyx at the luminal entrance of the interendothelial slit, and second, more downhill, the interendothelial junctional strands, which are its leaky ‘breaks’. This means that there would be a ‘protected region’ underneath the glyocalyx and above the plane of the junctional strands. This in turn implies that the Starling equilibrium would be nearly unaffected by the interstitial colloid osmotic pressure acting from the tissue side of the junctional strands because of limited permeation of albumin into the ‘protected’ region. If that were really true, then the action of i.p. colloidal osmotic agents, such as icodextrin or albumin, would be negligible. However, both albumin and icodextrin can produce considerable i.p. osmotic pressure and enhance fluid movement from plasma to the peritoneal cavity, which can be simulated by the TPM [4,10,48]. These facts seem to invalidate the glyocalyx-junction-break model of capillary permeability.

Conclusions

A moderately extended TPM, including the capillary wall and a serial barrier consisting of heterogeneously and loosely arranged fibres in the interstitium, can correct some of the apparent shortcomings of the two-dimensional (planar) TPM. Such a model has the potential of explaining how (tracer) macromolecules move from the peritoneal cavity into the tissues driven by hydrostatic pressure in the partial absence of net tissue (volume) changes, according to the so-called volume recirculation principle. Also, the
pathophysiological changes occurring in long-term PD associated with submesothelial fibrosis and neoangiogenesis can be amply described by an extended TPM [3].

The fibre matrix theory, introduced nearly 30 years ago by Curry and Michel, remains an alternative to the pore theory for explaining the selectivity of small and large pores in the capillary wall of the TPM, while the ultra-small pores of the TPM undoubtedly must be represented by AQP-1. If applying the fibre matrix model, the bimodal selectivity of the capillary wall requires the presence of a non-uniform fibre matrix, essentially showing a functional ‘two-pore’ behaviour. The endothelial glycocalyx seems, however, to be too delicate to offer the size-selectivity of a dense fibre matrix. In inflammation, there is ample evidence of large pore (gap) formation by focal endothelial cell retractions, as a consequence of rapid reorganization of the endothelial actin cytoskeleton. Over the last 30 years, these processes have been amply documented [46], whereas the potential permeability changes occurring due to alterations of the fragile endothelial glycocalyx have not been unambiguously demonstrated. The sieving properties of the glycocalyx demonstrated so far are confusing and not at all compatible with the well-documented sieving behaviour of microvascular walls to macromolecules [21,47,49]! However, in the renal microcirculation, the glycocalyx is likely to form a negatively charged gel-like structure with implications for the charge selectivity of the glomerular filtration barrier [28]. Functionally, a fibre matrix is not likely to be as dynamic as the endothelial cells in producing permeability changes in response to e.g. inflammation or I/R. Furthermore, there is good evidence that changes in colloid osmotic pressure in the peritoneal cavity by adding albumin or icodextrin [4,10,48] will markedly affect the capillary Starling equilibrium to produce an enhanced fluid movement from plasma to the peritoneum. Therefore, the hypothesis that the endothelial glycocalyx would be a size-selective primary barrier placed in front of the semi-leaky junctional strands in the clefts of the capillary endothelium must be put into serious doubt.

The glycocalyx is a poorly defined ‘fuzzy’ layer of cell-anchored proteoglycans and glycoproteins surrounding most cells of the body, including the peritoneal endothelial and mesothelial [50] cells. It is difficult to assess by conventional staining and fixation techniques, and its presence defies physiological testing. With its delicate ‘architecture’ it is not likely to represent a highly size-selective sieving barrier to uncharged macromolecules. Furthermore, why should the endothelial glycocalyx be of such importance and not the mesothelial glycocalyx? The incorporation of an endothelial glycocalyx as a separate capillary barrier in the TPM will neither enhance the ability of the TPM to predict peritoneal transport, nor will it deepen our understanding of the physiology and pathophysiology of peritoneal exchange.

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