LETTERS TO THE EDITOR

Comments on
"Transcapillary Water and Protein Flux in the Canine Intestine with Acute and Chronic Extrahepatic Portal Hypertension" which appeared in Circ. Res. 53: 622–629

Recently, Witte et al. (1983) reported data on transcapillary water and protein flux in intestine from dogs with acute and chronic extrahepatic portal hypertension. Measurements were made of lymph flow and total protein concentration in lymph and plasma. Additionally, plasma disappearance rate of radiiodinated albumin was determined in some animals. From these experiments, the authors concluded that about 80% of the transcapillary protein flux in control dogs was convective-filtrative, while a dissipative process (diffusion) was responsible for the rest. During both acute and chronic portal pressure elevation there was a shift from convective to diffusive protein transfer: diffusive fraction increased from 20% to 40% and convective fraction decreased from 80% to 60%. No relationship was found between transcapillary protein flux and portal pressure. In contrast to these experiments, we have estimated the transcapillary albumin flux from the plasma disappearance rate of radiiodinated albumin (Henriksen et al., 1981) in control pigs and during acute extrahepatic portal hypertension. As shown in Figure 1, the overall plasma clearance of albumin (plasma volume × fractional disappearance rate) was closely related to portal pressure. This indicates, to us, that convective-filtrative transcapillary albumin flux is dominant also during elevated portal pressure. In our experiments, the increase in albumin clearance was on the average three times that of Witte et al. (34 vs. 11 μl/min per kg), a finding which may, at least in part, be explained by the much larger digestive tract in pigs compared to dogs.

As admitted by Witte et al., their analysis of transport characteristics was complex, and the method applied may be inadequate. They determined the reflection coefficient (σ) and permeability surface area product (PS), and thereby the relative contribution of convective-filtrative vs. diffusive transport, by a cross-point method (Chang et al., 1975; Brace et al., 1978; Katz, 1980). During chronic portal hypertension, average plasma protein σ and PS rose in their study from 0.45 and 3.6 μl/min per kg to 0.86 and 8.3 μl/min per kg, respectively, and almost the same values were found in acute portal hypertension. If proven valid, an increased σ may, as stated by Witte et al., suggest that pores narrow with increasing pressure (e.g., flattening of endothelial cells with torque of interendothelial cell junctions or increased elliptical eccentricity of pores with decreased effective radius). However, a decrease in pore size cannot explain augmented PS. Therefore, a better suggestion would be an increased number of small pores due to a larger capillary surface area during venous congestion, as this will increase both σ and PS. However, this explanation is contradicted by other experimental results. Johnson et al. (1965), Mortillaro and Taylor (1976), and Granger and Taylor (1980) found a decreased filtration coefficient during acute portal congestion in dogs and cats, a finding that is inconsistent with increased numbers of small pores. Unfortunately, Witte et al. did not determine the filtration coefficient. A change in this value during portal pressure elevation might support or reject their conception of increased numbers of small pores in this condition.

The relationship between σ, pore-size, and effective molecular radius (Stokes-Einstein radius) can be calculated (Granger et al., 1979; Henriksen, 1983). These calculations are based on steric and frictional properties during passage of molecules through pores in a membrane. In controls, an average plasma protein σ = 0.45 corresponds to a pore-radius of approximately 100 Å, and σ = 0.86 corresponds to a pore-radius of approximately 60 Å (see Fig. 2). Further, it is seen that in the interval 60 to 100 Å, σ varies considerably among different plasma proteins: albumin (S-E radius 35 Å), immunoglobulin G (S-E radius 55 Å), and immunoglobulin M (S-E radius 95 Å). Accordingly, determination of σ and PS from measurements of individual plasma pro-
teins might give a much better picture of changes in pore-size during augmented portal pressure. In summary, the question of intestinal transcapillary protein transport needs more detailed investigations before final conclusions on transport mechanisms and permeability characteristics may be drawn.

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INDEX TERMS: Capillary pore-size • Portal hypertension • Protein transport mechanisms

Reply to the Preceding Letter

Henriksen and Lassen propose that the "leak rate" of albumin from plasma, as determined by the disappearance curve of radiotagged albumin, is an accurate gauge of transcapillary albumin flux in normal and pathological states. However, this process is extremely complex in part because of differences in capillary beds (e.g., the porous liver sinusoid with discontinuous endothelium compared with less permeable intestinal capillaries), and, in the special case of liver disease, structural alterations in the cirrhotic liver, which displays intense fibrosis, particularly throughout Disse's space (periportal and portal lymphatics) and along sinusoids ("capillarization"). To minimize the possibility of bloodstream recirculation of tracer albumin via lymph, Lassen et al. (1974) limit serial determinations to the first 40-60 minutes after tracer injection, and further assert that albumin leak rate is comparable to net capillary filtration or lymph flow (Lassen et al., 1974; Henriksen, 1984). Based on rough calculations in the normal state where escape of both plasma water and protein is comparatively small and of similar magnitude, Lassen et al. (1974) also conclude that plasma proteins escape solely by convection-filtration or solvent drag in accordance with microvascular pressure. Despite these assertions, these workers have as yet to corroborate that the value obtained by radiotagged plasma albumin leak is indeed comparable to that measured by native albumin transport in thoracic duct lymph (>80% of net capillary filtration returns via this route), and, more importantly, that this relationship, if valid under normal circumstances, continues to hold in pathological states such as portal hypertension. Indeed, when we compared these two methods (Kintner et al., 1979), there was a marked disparity. In our studies in patients with hepatic cirrhosis (Witte et al., 1981) and "chronic" portal hypertension in dogs (Witte et al., 1983), we were unable to substantiate a relationship between extrahepatic splanchic protein \( J_s \) and water \( J_v \) flux. Despite a sharp increase in \( J_v \) with elevated microvascular pressure, \( J_s \) was unchanged. Although, theoretically, solvent drag may still be operative, it is clear from these data that equating \( J_v \) with \( J_s \) is inappropriate, especially in abnormal states. Even if, as we suggest, a slight shift in \( J_v \) occurs from convection to diffusion with rising microvascular portal pressure, this change is quantitatively very small, as \( J_s \) overall is not significantly altered. Furthermore, even if there is a rise in \( J_v \), as Henriksen and Lassen claim, this finding does not necessarily signify the primacy of...
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convection. As extrahepatic microvascular pressure increases, there is a pronounced "washdown" of interstitial protein such that the product of permeability-surface product (PS) and the transcapillary protein concentration gradient (ΔC) (the diffusive component of the Kedem-Katchalsky equation) rises accordingly. Moreover, with an increase in PS as demonstrated in our study (Witte et al., 1983), the fraction of diffusive transport also rises.

As Henriksen and Lassen indicate, their control albumin "leak rate" based on tracer disappearance is three times that calculated from native protein clearance into central lymph. Although they suggest this discrepancy may be due to volume distribution differences in the pig, we have found the same discrepancy in the dog (Kintner et al., 1979). Moreover, contrary to their assertion, calculations of normal lymph flow based on the albumin leak rate are consistently far too high. Thus, normal thoracic duct lymph flow (10–15 µl/kg per min) is only one-third of the value estimated by albumin leak rate in both dogs (Witte et al., 1983) and patients (Witte et al., 1981). Finally, in patients with hepatic cirrhosis and ascites, we found albumin leak rates to be quite variable and, occasionally, even normal (personal observations), whereas lymph flow is consistently elevated. Taken together, these findings indicate that not only is albumin "leak" an unreliable indicator of both Jw and Js, but the excessive values could be used as evidence for backdiffusion of albumin, as suggested by Szabo (1976). Alternatively, in normal and particularly in pathological conditions, there may be uneven mixing and distribution of the tracer.

We also suggested (Witte et al., 1983, p. 628, lines 11-12) that a rise in the reflection coefficient (σ) and PS is compatible with an increase in number of small pores as well as pore narrowing. Although measurement of hydraulic conductivity surface area product (LpS) along with PS, would be useful (but impossible to determine in our experiments), this information is unlikely to resolve this issue. For concordant findings to occur between hydraulic conductivity and PS, both Jw and Js would have to occur at the same microvascular axial site, a highly remote possibility. A decrease in LpS with rising microvascular pressure may reflect either a decrease in number of pores (LpS) or diminution in the size of the pores (LP) or, alternatively, some combination of the two. It is even possible, in a heteroporous system with a preponderance of small pores (σ = 1) and only an occasional large pore (σ = 0), that LpS might decrease by closing off some capillaries, and that PS might increase by adding a few large pores to the ones remaining open. Any of these possibilities is compatible with the results we reported.

Finally, we agree that a multisolute analysis provides a more detailed profile of membrane transport properties. Although some of the protein values might well need modification, it is nonetheless reasonable to conclude that, during persistent extrahepatic portal hypertension, Jw increases, Js is fairly constant, σ, and PS and ΔC increase; based on these divergent effects, both diffusive and fractional diffusive transport increase.

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*Circ Res.* 1984;54:773-775
doi: 10.1161/01.RES.54.6.773
*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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