

# Transport of Macromolecules Across The Glomerular Capillary Wall

by

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## **Abstracts**

Chapter 1: The hydrodynamic model of restricted transport through pores is developed and applied to the study of macromolecular transport across renal glomerular capillaries. This model, which traces the glomerular capillary wall as a membrane containing uniform cylindrical pores and solutes as hard spheres, has been found successful in describing the solute size-selectivity of this microcirculatory system. Effective pore radii and the number of pores have been determined for glomerular capillaries based on measurements of the transport of macromolecules across these capillary walls. In addition, this model predicts that the transglomerular transport of macromolecules will be influenced by variations in the glomerular filtration rate of water. The influence of variations in the individual determinants of glomerular filtration on solute transport are examined with this model. It is predicted that the permeability properties of the glomerular capillary wall as well as the glomerular capillary plasma flow rate and the transcapillary hydraulic and oncotic pressure differences will influence the transport of macromolecular solutes.

Chapter 2: The ability of rennin and angiotensin II (AII) to produce increased urinary protein excretion, proteinuria, had long been known. To investigate the mechanism(s) involved, polydisperse <sup>3</sup>H-dextran (D) (radius = 18-42 Å) was infused into seven Munich-Wistar rats prior to and during intravenous infusion of AII (0.35 µg/kg/min). During AII infusion, urinary total protein excretion rose from 660 to 1300 µg/hr, and fractional clearances of D  $[(U/P)_D / (U/P)_{IN}]$  increased significantly for dextrans with radii > 22 Å. Single nephron filtration fraction increased due to a marked rise in the glomerular transcapillary hydraulic pressure difference from 34 to 43 mm Hg. Near-constancy of single nephron glomerular filtration rate resulted however from the offsetting effect of a decrease in glomerular plasma flow rate from 83 to 60 nl/min. These measured hemodynamic changes were found, by the use of pore theory, to account to a large extent for the measured increases in  $(U/P)_D / (U/P)_{IN}$ . In seven other rats, fractional clearances of polyanionic dextran sulfate (a more reliable marker of albumin filtration than D) were also found to increase significantly with AII, suggesting that the proteinuria induced by AII can be explained, in large part, by hemodynamic factors.

Chapter 3: To investigate the mechanism(s) of increased filtration of serum proteins following glomerular injury, polydisperse samples of uncharged  $^3\text{H}$ -dextran (D) or anionic  $^3\text{H}$ -dextran sulfate (DS) were infused into 14 control and 16 puromycin aminonucleoside (PAN) treated Munich-Wistar rats. Fractional clearances of D or DS ranging in effective molecular radius from 18 to 42 Å were determined in these rats, together with direct measurements of the forces governing the glomerular filtration rate of water. Whole kidney and single nephron glomerular filtration rates were ~40% lower in PAN-treated rats, relative to controls, due mainly to a marked reduction in the glomerular capillary ultrafiltration coefficient and, to a lesser extent, to a small reduction in glomerular plasma flow rate. In PAN-treated rats, as in normal controls, inulin was found to permeate the glomerular capillary wall without measurable restriction, and both D and DS were shown to be neither secreted nor reabsorbed. Fractional clearances of uncharged D were reduced following PAN administration, falling significantly for effective D radii from 22 to 38 Å. Utilizing a theory based on macromolecular transport through pores, these results indicate that in PAN-treated rats, effective pore radius is the same as in controls, ~44 Å. In PAN nephrosis, however, the ratio of total pore surface area/pore length, a measure of pore density, is reduced to approximately one-third that of control, due very likely to a reduction in filtration surface area. In contrast to the results with uncharged D, fractional clearances of DS were found to increase following PAN administration for all DS radii studied. These results with D and DS suggest that proteinuria in PAN nephrosis is due, not to an increase in effective pore radius or number of pores, but rather to a diminution of the electrostatic barrier function of the glomerular capillary wall, thereby allowing increased passage of polyanions such as DS and albumin.

Chapter 4: To examine the electrostatic effects of fixed negative charges on the glomerular capillary wall, polydisperse  $^3\text{H}$ -diethylaminoethyl dextran (DEAE), a polycationic form of dextran, was infused into 10 Munich-Wistar rats. Fractional clearances of DEAE ranging in effective molecular radius from 18 to 44 Å were determined in these rats, together with direct measurements of the forces and flows governing the glomerular filtration rate of water. These results were compared with data previously obtained in Munich-Wistar rats receiving  $^3\text{H}$ -neutral dextran (D) and polyanionic dextran sulfate (DS). Measured values for the determinants of the glomerular filtration rate of water in rats given DEAE were found to be essentially identical to those in rats given either D or DS. In addition, DEAE was shown to be neither secreted nor reabsorbed. Fractional clearances of polycationic DEAE were increased relative to both D and DS, the increase relative to D being significant for effective molecular radii ranging from 24 to 44 Å.

Fractional DEAE clearances were also measured in a separate group of 6 Munich-Wistar rats in the early autologous phase of nephrotoxic serum nephritis (NSN). Fractional DEAE clearances in NSN rats were reduced significantly, relative to values measured in normal rats, for effective DEAE radii ranging from 18 to 42 Å. Moreover, in NSN rats, fixed negative charges on the glomerular capillary wall were reduced relative to non-NSN rats, as evidenced by a reduction in intensity of colloidal ion staining. Thus in NSN rats, DEAE clearances were essentially indistinguishable from values obtained with both neutral D and polyanionic DS.

Chapter 5: The influence of molecular configuration on the filtration of macromolecules across glomerular capillary walls was examined by comparing fractional clearances of two uncharged polysaccharides of distinctly different molecular configuration in the Munich-Wistar rat. The macromolecules employed were dextran, a slightly branched polymer of glucopyranose, and ficoll, a highly cross-linked copolymer of sucrose and epichlorohydrin. Differences in effective shape between these two polymers were determined from measurements of the intrinsic viscosities, sedimentation coefficients, partial specific volumes, and densities of aqueous solutions containing either dextran or ficoll. Assuming a prolate ellipsoid model, axial ratios of 3-5, 8-11 and 16-20 were found to represent best dextran molecules with Stokes-Einstein radii of 22, 32, and 40 Å respectively. On the other hand, ficoll is more closely approximated as spherical since the axial ratio was found to be between 1 and 2 for all molecular sizes.

Fractional clearances of dextran and ficoll ranging in effective radius from 18 to 44 Å were determined in each of 7 Munich-Wistar rats. Fractional clearances of dextran were found to be greater than those of ficoll, the differences being significant for molecular radii ranging from 24 to 44 Å. In addition as shown previously for dextran, ficoll was found to be neither secreted nor reabsorbed by the renal tubules. These results, therefore, suggest that in addition to molecular size and charge, molecular configuration is also a determinant of the filtration of macromolecules across the glomerular capillary wall.

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