Permselectivity of the glomerular capillary wall. Studies of experimental glomerulonephritis in the rat using neutral dextran.

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Permselectivity of the Glomerular Capillary Wall

STUDIES OF EXPERIMENTAL GLOMERULONEPHRITIS IN THE RAT USING NEUTRAL DEXTRAN

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ABSTRACT Polydisperse [3H]dextran was infused into eight Munich-Wistar rats in the early autologous phase of nephrotic serum nephritis (NSN), thereby permitting direct measurements of pressures and flows in surface glomeruli and fractional clearances for dextrans [(U/P)dextran/(U/P)inulin] ranging in radius from 18 to 42 Å. Despite glomerular injury, evidenced morphologically and by a marked reduction in the glomerular capillary ultrafiltration coefficient, the glomerular filtration rate remained normal because of a compensating increase in the mean net ultrafiltration pressure. In NSN rats, as in normal controls, inulin was found to permeate the glomerular capillary wall without measurable restriction, and dextrans were shown to be neither secreted nor reabsorbed. For dextran radii of 18, 22, 26, 30, 34, 38, and 42 Å, (U/P)dextran/(U/P)inulin in NSN and control rats, respectively, averaged 0.90 vs. 0.99, 0.81 vs. 0.97, 0.63 vs. 0.83, 0.38 vs 0.55, 0.20 vs. 0.30, 0.08 vs. 0.11, and 0.02 vs. 0.03. Using a theory based on macromolecular transport through pores, the results indicate that in NSN rats, effective pore radius is the same as in controls, ~50 Å. In NSN, however, the ratio of total pore surface area to pore length, a measure of the number of pores, is reduced to ~1/2 that of control, probably due to a reduction in capillary surface area. These results suggest that proteinuria in glomerular disease is not due simply to increases in effective pore radius or number of pores, as previously believed. Using a second theoretical approach, based on the Kedem-Katchalsky flux equations, dextran permeability across glomerular capillaries was found to be slightly lower, and reflection coefficient slightly higher in NSN than in control rats.

INTRODUCTION

The composition of the fluid passing through the glomerular capillary wall normally conforms to that of a nearly ideal ultrafiltrate of plasma, closely resembling plasma water with respect to low molecular weight solute concentrations (1). For solutes with mol wt greater than approximately 5,000, however, transport becomes restricted; the extent of restriction being almost complete for molecules the size of serum albumin or above. Alterations in this permselectivity to macromolecules, manifested as proteinuria, are a hallmark of disorders affecting the glomerular capillary bed. To a large extent, our present understanding of the mechanisms governing the altered permselectivity

Ms. Rasmussen died on 25 June 1975.

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Received for publication 22 September 1975 and in revised form 18 December 1975.
derives from differential solute clearance studies, in which the urinary excretion of some test macromolecule (such as polyvinylpyrrolidone, dextran, or protein) is compared to that of a reference solute assumed to appear in Bowman’s space in the same concentration as in plasma water (albumin or creatinine) (2–7).

The fractional clearance profiles obtained for these macromolecules in both normal and pathological states are generally taken to reflect the permeselective properties of the glomerular capillary wall alone. It has been clearly shown by us and others (8–11), however, that these fractional clearance profiles are influenced not only by the properties of the capillary wall, but also by the other determinants of glomerular ultrafiltration, namely, the transcapillary hydraulic and oncotic pressure differences and the glomerular capillary plasma flow rate. Since the pertinent driving forces and flows were not evaluated in previous studies of glomerular injury, conclusions regarding mechanisms of altered macromolecular transport across glomerular capillaries from fractional clearance profiles alone become difficult to interpret.

The present study was therefore undertaken to examine the transport of neutral dextrans of well-defined molecular size across accessible glomerular capillaries in rats with altered permeselectivity brought about by induction of nephrotoxic serum nephritis (NSN).1 From the results of these experiments, together with a theory which combines mass balances for solutes and water with flux equations derived either from restricted transport through small pores or the Kedem-Katchalsky formulation, it has been possible to examine the relative contributions of diffusion and bulk flow to the overall glomerular transport of dextrans. This approach also permits characterization of the glomerular capillary wall with regard to effective pore radius and number of pores (using pore theory) or in terms of phenomenological coefficients which include the hydraulic conductivity, the reflection coefficient, and dextran permeability coefficient (using the Kedem-Katchalsky equations).

GLOSSARY OF SYMBOLS

\begin{align*}
\Delta P & \quad \text{Mean arterial pressure.} \\
C_B(r), C_P(r) & \quad \text{Solute and plasma protein concentration at any point, } r, \text{ along an idealized glomerular capillary, respectively.} \\
C_{BA}, C_{PA} & \quad \text{Initial glomerular capillary (or afferent arteriolar) solute and plasma protein concentration, respectively.} \\
C_{PB} & \quad \text{Efferent arteriolar plasma protein concentration.} \\
C_{SB} & \quad \text{Solute concentration in Bowman’s space.} \\
C_{SB'} & \quad \text{Mean transmembrane solute concentration at any point, } r, \text{ along an idealized glomerular capillary, } C_{SB} \equiv C_{SB'} = -\ln \left(\frac{C_{SB}}{C_{PB}}\right). \\
D_w & \quad \text{Solute diffusivity in free solution.} \\
J_s & \quad \text{Transcapillary solute flux at any point, } r, \text{ along an idealized glomerular capillary.} \\
J_v & \quad \text{Transcapillary volume flux at any point, } r, \text{ along an idealized glomerular capillary.} \\
k & \quad \text{Effective hydraulic permeability coefficient.} \\
k' & \quad \text{Hydraulic permeability coefficient using Poiseuille’s equation.} \\
K_f & \quad \text{Ultrafiltration coefficient, } (K_f = S'\pi \delta/8 \mu \text{ and } K_f = k' S' = k \cdot S). \\
\alpha & \quad \text{Pore length.} \\
\Delta \alpha & \quad \text{Length-averaged value of the glomerular transcapillary hydraulic pressure difference, } P_{00} - P_T. \\
\bar{\Delta P} & \quad \text{Length-averaged value of the glomerular capillary hydraulic pressure.} \\
P_T & \quad \text{Hydraulic pressure in the proximal tubule.} \\
P_C & \quad \text{Hydraulic pressure in third-order branch peritubular capillaries.} \\
Q & \quad \text{Glomerular capillary plasma flow rate.} \\
Q_A & \quad \text{Initial (afferent) glomerular plasma flow rate.} \\
\rho & \quad \text{Pore radius.} \\
R & \quad \text{Universal gas constant.} \\
S & \quad \text{Total glomerular capillary surface area available for transcapillary exchange of water and solute.} \\
S' & \quad \text{Total effective pore area.} \\
\text{SNF} & \quad \text{Single nephron filtration fraction.} \\
\text{SNFF} & \quad \text{Single nephron glomerular filtration rate.} \\
T & \quad \text{Absolute temperature.} \\
(TF/PI)_N & \quad \text{Tubule fluid-to-plasma inulin concentration ratio.} \\
V_T & \quad \text{Tubule fluid flow rate.} \\

\begin{align*}
\gamma & \quad \text{Modified pore Péclet number, } \gamma = \frac{x_s J_f}{\xi_0 D_w}. \\
\xi & \quad \text{Dimensionless axial position along an idealized glomerular capillary, } 0 \leq \xi \leq 1. \\
\mu & \quad \text{Solvent viscosity.} \\
\xi_0 & \quad \text{Ratio of pore-to-bulk solute diffusivity.} \\
\tau & \quad \text{Initial glomerular capillary and efferent arteriolar colloid osmotic pressure, respectively.} \\
\Delta \tau & \quad \text{The difference between colloid osmotic pressure at any point, } \tau, \text{ along an idealized glomerular capillary, and colloid osmotic pressure in Bowman’s space.} \\
\sigma & \quad \text{Reflection coefficient.} \\
\tau & \quad \text{Transit time.} \\
\omega & \quad \text{Solute permeability.}
\end{align*}

\[1\text{Abbreviations used in this paper: (A/G), albumin to globulin ratio; (BS/P), Bowman’s space to plasma ratio; NSN, nephrotoxic serum nephritis; (U/P), urine to plasma ratio.}\]

METHODS

Animal studies

\textit{Induction of experimental glomerulonephritis.} NSN was induced in eight adult Munich-Wistar rats of both sexes in
the manner described recently (12). After 24-h urine collections for protein determination, rats were preimmunized by footpad injection with 0.5–1.0 mg of partially aggregated rabbit gamma globulin in complete Freund’s adjuvant. 48 h later a small dose of rabbit antirat glomerular basement membrane antisemur (containing 41 μg of kidney-fixing antibody in 0.25 ml) was injected into the tail vein. 24-h urine collections for protein determination were begun immediately after injection of the antisemur and at various times thereafter until the day of micropuncture. The determinants of glomerular ultrafiltration were measured by appropriate micropuncture techniques (9, 12, 13) 5–15 days after injection of nephrotoxic serum.

After micropuncture measurements, the kidney was prepared for histological examination utilizing light, electron, and immunofluorescence techniques as described previously (12). Studies were undertaken initially to determine whether fractional dextran clearances obtained for the kidney as a whole (estimated from comparison of the urinary clearance of various sized dextrans to that of inulin) can be equated with clearances of these substances across single accessible surface glomeruli. Such equality has been demonstrated by us previously for this strain of rats under normal hypodrienc conditions and after plasma volume expansion (9). As in this previous study (9), it was necessary to determine in NSN rats that inulin serves as an ideal marker for water movement across the glomerular capillary wall. This was accomplished by comparing inulin concentrations in accessible Bowman’s spaces with simultaneously measured concentrations in plasma water.3 Experiments examining the validity of equating fractional dextran clearances for a single glomerulus with those for the kidney as a whole were then performed as follows. Tritiated dextrans of narrow molecular size distribution, prepared in the manner described previously (9), and characterized with respect to average Stokes-Einstein radius, were used as test solutes in four rats. A 0.4-mI priming infusion, containing nonisotopic inulin (6 g/100 ml) and tritiated dextran (<200 mg/100 ml, activity = 0.25 mCi/ml), was injected into the left jugular vein 30 min before micropuncture, followed immediately by continuous infusion of the same solution at the rate of 1.2 ml/h. This infusion was continued throughout the duration of each experiment. During this hydrodynamic period, 15-min urine samples were collected from a catheter in the left ureter for measurement of urine flow rate and inulin and dextran concentrations. During each urine collection period, two or three samples of fluid from Bowman’s space (30–50 nl each) were also collected for determination of inulin and dextran concentrations. At the midpoint of each urine collection period, 100 μl of blood was withdrawn from the femoral artery for determination of dextran, inulin, and protein concentrations and measurements of arterial hematocrit.

Studies with dextrans of wide molecular size distribution. Having established in the above studies that inulin appears in Bowman’s space in the same concentration as in plasma water in NSN rats and that fractional urinary dextran clearances are the same as fractional dextran clearances measured for single accessible glomeruli in the same kidney (i.e., dextrans are neither secreted nor reabsorbed), justification is provided for relying on urinary clearances to assess the permselectivity characteristics for all glomeruli in a single kidney, now using an homologous series of dextrans of widely varying molecular size. These experiments were performed in eight hydroptic NSN rats (ranging in body weight from 174 to 243 g) in which 0.4 ml of a solution of nonisotopic inulin in isotonic saline (10 g/100 ml) was infused intravenously 45 min before micropuncture, followed immediately by a constant infusion of the same solution at the rate of 1.2 ml/h. 0.4 ml of an isotonic solution containing tritiated dextran of wide molecular size distribution (dextran concentration <200 mg/100 ml, activity = 0.25 mCi/ml, see [reference 9] for details of preparation), was infused intravenously, followed immediately by a constant infusion of the same solution at the rate of 1.2 ml/h. Approximately 2–3 min after completion of the priming injection, a continuous collection of blood from the femoral artery was begun at a constant rate (1.2 ml/h), using a continuous withdrawal pump (model 941, Harvard Apparatus Co., Inc., Willis, Mass.). To determine the transit time (τ) for tubule fluid to travel from Bowman’s space to the tip of the ureteral catheter, a bolus of Lissamine green dye was injected intravenously (13). Urine collection was initiated τ min (approximately 2–3 min) after initiation of the continuous femoral arterial blood collection and terminated τ min after the end of the blood collection period. 40–100 μl of the femoral arterial blood plasma and 15–100 μl of the urine collected were each mixed with 1 ml of distilled water and 2 mg of blue dextran and chromatographed on Sephadex G-100. Additional aliquots of urine and blood were used for subsequent determinations of inulin concentration and, in the case of femoral arterial blood, total protein concentration as well.

During this hydrodynamic period, two to three exactly timed (1–2-min) samples of fluid were collected from surface proximal convoluted tubules for determination of flow rate and inulin concentration, and calculation of single nephron glomerular filtration rate, SNGFR. In addition, samples of blood (50–150 nl each) were collected from two to three surface efferent arterioles for determination of total protein concentration. Total protein concentrations measured in femoral arterial plasma are taken as representative of concentrations in afferent arteriolar plasma. These estimates of afferent (CPA) and efferent (CPB) arteriolar protein concentration permit calculation of single nephron filtration fraction, SNFF, and initial glomerular capillary plasma flow rate, QA (see equations below). Mean arterial pressure, AP, was monitored using an electronic transducer (model P23Db, Stratham Instruments Div., Gould Inc., Oxnard, Calif.) connected to a direct-writing recorder (model 7702B, Hewlett-Packard Co., Palo Alto, Calif.). Hydraulic pressure measurements were obtained in surface glomerular capillaries, PGC, proximal tubules, PT, and third-order branch peritubular capillaries, PC, using a continuous-recording, servonull micropipette transducer (15–17).

After measurements in hydropyenia, five of these eight NSN rats received an intravenous infusion of homologous rat plasma given at the rate of 0.1 ml/min until a total volume equal to 5% body weight had been given. After volume expansion, priming and sustaining infusions of inulin and tritiated dextrans were again administered, as in hydropyenia, after which fractional dextran clearance and micropuncture measurements were repeated. This maneuver was performed to permit determination of parameters characterizing the glomerular capillary wall (see below) as well as an assessment of the relative contributions of diffusion and bulk flow to total dextran transport (9).

The colloidal osmotic pressure of plasma entering (τA) and leaving (τB) glomerular capillaries in normal rats can be
calculated from measured values of $C_F$ (18) using the equation:

$$\pi = 1.63C_P + 0.294C_F^2,$$

(1)

where $4 \leq C_F \leq 10$ g/100 ml (19). Eq. 1 assumes an albumin/globulin (A/G) ratio of 1.0, the ratio found in normal hyperonic rats in the laboratory. We have previously determined that the A/G ratio is usually less than 1.0 in NSN rats (12), averaging 0.76±0.06 SE. For this A/G ratio, however, values of $\pi$ for protein concentrations over the range of 4–10 g/100 ml do not differ significantly from values calculated using Eq. 1 (12). As reported previously (12), for NSN rats with an A/G ratio of 0.4, values of $\pi$ for protein concentration over the range of 4–10 g/100 ml are described by the equation:

$$\pi = 2.24C_P + 0.180C_F^2.$$

(2)

Accordingly, for rats in the present study with A/G ratios between 0.4 and 0.8, the coefficients were determined by linear interpolation of the coefficients in Eqs. 1 and 2.

**Analytical determinations**

The volumes of fluid obtained from proximal tubules and Bowman’s species were estimated from the length of the fluid column in a constant-bore capillary tube of known internal diameter. The concentration of nonisotopic inulin in tubule fluid was measured, usually in duplicate, by the microfluorescence method of Varek and Pegram (20). Nonisotopic inulin concentrations in plasma and urine were determined by the macroanion method of Führ et al. (21). Protein concentrations in efferent arteriolar and femoral arterial blood plasmas were determined, usually in duplicate, with an ultramicrocolorimeter (American Instrument Co., Travenol Laboratories Inc., Silver Spring, Md.) using a microadaptation (18) of the technique of Lowry et al. (22). Unlabeled dextran concentrations were measured by the Molisch reaction (9). The specific activities of tritiated dextran were determined using a liquid scintillation spectrometer (model 2425 Tri-Carb, Packard Instrument Co., Inc., Downers Grove, Ill.). Scintillation was produced by mixing 2 ml of aqueous sample with 7 ml of Aquasol (New England Nuclear, Pilot Chemicals Division, Boston, Mass. and shaking to form a stiff gel.

A detailed discussion of the chromatographic procedures employed in this study, as well as of the method of preparation of tritiated dextran, is given elsewhere (9).

**Calculations**

Single nephron glomerular filtration rate:

$$\text{SNFF} = (\text{TF/P})_\text{IN} \cdot V_{\text{TF}},$$

(3)

where $(\text{TF/P})_\text{IN}$ and $V_{\text{TF}}$ refer to tubule fluid/plasma inulin concentration ratio and tubule fluid flow rate, respectively. Single nephron filtration fraction:

$$\text{SNFF} = 1 - \frac{C_{\text{PA}}}{C_{\text{PF}}},$$

(4)

Initial glomerular plasma flow rate:

$$Q_A = \frac{\text{SNFF} \cdot \text{SNFF}^*}{\text{SNFF}},$$

(5)

Mean glomerular transcapillary hydraulic pressure difference:

$$\Delta P = P_{\text{GC}} - P_r.$$

(6)

**Calculation of membrane parameters.** After the analysis of Deen et al. (19), the glomerular capillary network is taken to be a single rigid tube of equivalent surface area, $S$. The system is considered to have three components: water, impermeable plasma proteins, and a partially permeable nonelectrolyte (dextran). $J_w$ and $J_s$ are the local fluxes of water and dextran, respectively, from glomerular capillary to Bowman’s space, the latter assumed to be a well-mixed compartment having dextran concentration $C_{SB}$. Of importance, $J_s$, $J_w$, the glomerular capillary plasma flow rate, $Q$, and the intracapillary dextran and protein concentrations, $C_s$ and $C_P$, respectively, are functions only of the position along the capillary, $r$. Mass balances on each of these three components are given by:

$$\frac{dQ}{dr} = -S \cdot J_w(r),$$

$$Q(0) = Q_A,$$

(7)

$$\frac{d(QC_F)}{dr} = 0,$$

$$Q(0)C_F(0) = Q_A C_{PA},$$

(8)

$$\frac{d(QC_S)}{dr} = -S \cdot J_s(r),$$

$$Q(0)C_S(0) = Q_A C_{SA}.$$  

(9)

As shown by Eq. 7, the rate of change of plasma flow along the idealized capillary is balanced by the volume flux, $J_w$, across the capillary wall. Eq. 8 states that the capillary wall is essentially impermeable to the major plasma proteins, while Eq. 9 represents the balance between changes in the mass flow of the dextran along the capillary and the local net transcapillary dextran flux, $J_s$. These equations assume that radial concentration gradients within a glomerular capillary may be neglected, an approximation which has recently been shown to be valid (23).

To relate these overall mass balances for water, protein, and dextran for the glomerular capillary network to measurable quantities, Eqs. 7–9 may be combined with expressions for $J_w$ and $J_s$ derived either from theories based on restricted transport through small pores or the Kedem-Katchalsky equations.

According to the Kedem-Katchalsky formulation $J_w$ and $J_s$ are given as follows (8, 9):

$$J_w = \frac{k(\Delta P - \Delta \pi)}{S} (\Delta P - \Delta \pi),$$

(10)

$$J_s = \omega RT(C_s - C_{SB}) + (1 - \sigma)J_w C_{SB}.$$  

(11)

diffusion convection

It is assumed in Eq. 10 that the dextran concentration is small enough that its osmotic contribution to volume flow is negligible compared to that of the plasma proteins. In Eq. 11 the terms representing diffusive and convective transport of solute have been identified. For definition of symbols see Glossary of Symbols. Alternatively, using isoporous theory,

4 With the infusate volume and dextran concentration employed in these studies, plasma dextran concentration was less than ~10 mg/100 ml, or less than ~5 nmol/cm³ assuming a number-average mol wt of ~10⁶ g/mol. This concentration can be used to estimate the osmotic pressure due to the dextran, given by $\sigma RT\Delta C_s$, where $\sigma$ is the reflection coefficient, $R$ and $T$ are the gas constant and absolute temperature, respectively, and $\Delta C_s$ is the transmembrane dextran concentration difference. Assuming as an extreme case that $\sigma$ = 0 and $\Delta C_s$ = 5 nmol/cm³, $\sigma RT\Delta C_s < 0.2$ mm Hg. This confirms the assumption that the osmotic contribution of dextran to volume flow is negligible.
the expressions for \( J_s \) and \( J_k \) based on total glomerular capillary surface area, \( S \), are given by (8, 9):

\[
J_s = \frac{S'}{S} k' (\Delta P - \Delta x) = \frac{K_f}{S} (\Delta P - \Delta x),
\]

\[
J_k = \frac{S'}{S} \frac{D_x \xi_0}{l} [C_S - C_{SB}]
\]

diffusion

\[
+ \chi_0 J_s C_s \left[ \frac{1 - (C_{SB}/C_S) \exp (-\gamma)}{1 - \exp (-\gamma)} \right]
\]

convection

\[
\frac{S'}{S} \frac{D_x \xi_0}{l} [C_S - C_{SB}],
\]

where \( S' \) is the area of the glomerular capillary network occupied by pores, a small fraction \((S'/S)\) of the total capillary surface area. \( K_f \), the ultrafiltration coefficient, is given by (8, 9):

\[
K_f = k \cdot S = K_f \cdot S' = \frac{r_0^5 S'}{8 \mu l}.
\]

The ultrafiltration coefficient, \( K_f \), and the other membrane parameters \( r_0 \) and \( S'/l \) (for the model based on pore theory) and \( u_S \) and \( \sigma \) (for the model based on the Kedem-Katchalsky equations) were obtained by solving Eqs. 7-9 numerically (8, 9, 19) using the experimentally measured quantities: \( Q_A \), \( \Delta P \), \( C_{FA}, C_{FB}, C_{SB}/C_{SA} \) (fractional clearance), and dextran radius, \( a \).

RESULTS

General. Rats with NSN appeared healthy. Edema formation was not detected. The kidneys were of normal size and color, and all tubules, vessels, and glomeruli appeared normal at the time of micropuncture. As noted in a previous study (12), histological lesions were confined almost exclusively to the glomerular capillaries, which showed generalized and segmental proliferation of mesangial and endothelial cells with resultant obliteration of some capillary lumina. In some areas the endothelium was absent and replaced by polymorphonuclear leukocytes. Tubule morphology was normal. By immunofluorescence microscopy rabbit gamma globulin, rat gamma globulin, and rat C3 component of complement were observed in a uniform linear distribution in the capillary walls of all glomeruli examined. Renal tubule cells, tubule basement membranes, and nonglomerular vascular structures did not stain with these immunofluorescence reagents except for scattered, interrupted linear deposits of C3 component of complement in tubule basement membranes, a finding also noted occasionally in nonnephritic rats (12).

Before injection of nephrotoxic serum, mean 24-h urinary protein excretion in this strain of Wistar rats has been found by us to average 11 ± 2 mg SE (12). Induction of NSN results in moderate to marked proteinuria, as shown previously (12) and by the finding in six rats in the present study that, in the 24-h urine collections obtained just before micropuncture, protein excretion rates were all abnormally high, ranging from 21 to 450 mg/day.

The results of preliminary experiments in four NSN rats demonstrated that inulin serves as an ideal marker for water movement, in accord with recent observations in normal rats (1, 9). The ratio of inulin concentration in Bowman’s space to that in plasma water, \((BS/P)_{inulin}\), measured in eight nephrons averaged 1.04 ± 0.02 (range: 0.99–1.11).

Studies with dextran of narrow molecular size distribution. Fig. 1 summarizes data comparing \((BS/P)_{dextran}\) ratios, normalized to the simultaneous \((BS/P)_{inulin}\) ratios, with final urine/plasma \((U/P)_{dextran}\) ratios, again normalized to the simultaneous \((U/P)_{inulin}\) ratios. As can be seen, fractional dextran clearance ratios obtained for single glomeruli from four NSN rats, plotted on the ordinate of Fig. 1, were essentially the same as ratios measured for the kidney as a whole, plotted on the abscissa. These data were obtained for dextran ranging in molecular radius from 18 to 28 Å. For all paired measurements, the ratio of \((BS/P)_{dextran}/(BS/P)_{inulin}\) to \((U/P)_{dextran}/(U/P)_{inulin}\) averaged 1.02 ± 0.02, a value not significantly different from unity \((P > 0.2)\). These findings demonstrate that in NSN rats, as in normal rats (9), dextran are neither secreted nor reabsorbed by the renal tubules, and also suggest that fractional dextran clearances are homogeneous from glomerulus to glomerulus within a single kidney.

Studies with dextran of wide molecular size distribution. This evidence that fractional dextran clearances for the kidney as a whole provide an accurate measure of dextran permeation across capillaries of a single glomerulus makes it possible to characterize the glomerular transport of dextrans of widely varying molecular weights.
molecular size in each of eight NSN rats, since sufficient quantities of blood and urine can be collected to permit chromatographic separation of the polydisperse dextran into constituent narrow molecular size fractions. Fractional dextran clearance profiles can therefore be constructed for each rat, based on simultaneous clearances of dextrans ranging in molecular radius from ~18 to 42 Å. The relationship between the fractional clearance of dextran, given by the ratio \((U/P)_{dextran}/(U/P)_{inulin}\), and effective dextran radius for eight NSN rats during hydropenia is given in Fig. 2 (open circles). Values are expressed as means±1 SE. For comparison, the fractional dextran clearance profile recently obtained by us (9) in seven normal rats under similarly hydropenic conditions is also shown (Fig. 2, solid circles). Whereas in normal rats, restriction to dextran transport does not occur until the effective radius equals approximately 21 Å, in NSN rats restriction to transport is evident over the entire range of dextran radii studied. Since there is not measurable restriction to the transport of inulin (~14 Å) in NSN rats, the present findings suggest that restriction to neutral macromolecules in NSN becomes manifest at some radius above 14 but below 18 Å. As shown in Fig. 2, fractional dextran clearances decrease progressively with increasing molecular size, values for NSN being lower for any given molecular size than in normal rats. Differences between NSN and normal rats disappear at effective dextran radii >40 Å, where the fractional clearances for both groups approach zero. Fractional clearances for dextrans of varying molecular size obtained from individual NSN rats are shown in the left-hand portion of Table I.

Table II summarizes individual and mean values for several indices of single nephron function during hydropenia in the eight NSN animals. Despite the induction of a moderately severe form of NSN, mean values for body weight, kidney weight, mean femoral arterial blood pressure (\(\Delta P\)), and systemic hematocrit and protein concentration (C\(P_a\)) were essentially the same as values reported by us for non-nephritic Wistar rats (24–29). Moreover, the values for these quantities, as well as the other indices of single nephron and microvascular function summarized in Table II, are in close agreement with values obtained in two previous studies of rats with NSN (12, 30). Mean values for SNGFR (Table II) were similar to values obtained in normal Wistar rats (9, 24–29), as were values for whole kidney GFR, averaging 26±3 ml/min and 0.8±0.08 ml/min, respectively. As noted by us in previous studies of NSN rats, there was generally close agreement of SNGFR values from nephron to nephron in individual rats, although considerable variation was observed from rat to rat. On the average, values for SNFF were appreciably lower (0.31±0.02), and \(Q_x\) higher (89.5±13.9 ml/min) in these NSN rats than values generally noted in non-nephritic Wistar rats (24–29). SNFF in NSN rats was reduced despite the fact that glomerular capillary hydraulic pressure, \(P_{GC}\) (Table II), and the mean transcapillary hydraulic pressure difference, \(\Delta P\),

**FIGURE 2** Comparison of fractional dextran clearances plotted as a function of effective dextran radius for NSN rats (○) and for a group of non-nephritic normal hydropenic control rats (●) reported previously (9). Values are expressed as means±1 SE. See text for details of curve A.
Similar findings were efferent arteriolar and shown in typically found together with transcapillary ends of the glomerular filtration at 12.9±2.8 mm Hg and Kf 0.684±0.06) averaged i.e. when filtration pressure equilibrium was not achieved, so that a significant force for ultrafiltration existed throughout the glomerular capillary network in NSN rats. This finding, in agreement with that reported previously for NSN rats (12, 30), contrasts with results for normal hydropenic rats, where filtration pressure equilibrium ($\pi_E/\Delta P = 1$) has been demonstrated consistently in our laboratory (24–29). When filtration pressure equilibrium is not achieved, i.e. when $\pi_E/\Delta P < 1$, a unique value of the glomerular capillary ultrafiltration coefficient ($K_f$) can be calculated (19, 31). In the seven NSN rats in which all of the determinants of glomerular ultrafiltration were measured (Table II, left), equilibrium did not obtain. $K_f$ for these animals averaged 0.026±0.004 nl/(s·mm Hg), a value similar to that reported previously by us for NSN rats (12, 30) and approximately one-third that found in the normal Wistar rat (9, 29, 31).

To determine the parameters characterizing the glomerular capillary wall ($r_0$ and $S'/l$ for pore theory and $\sigma$ and $\sigma$ for the Kedem-Katchalsky equations), and assess the relative contributions of diffusion and bulk flow to total dextran transport, measurements of fractional dextran clearances and glomerular pressures and flows were repeated in five NSN rats after volume expansion with iso-oncotic rat plasma. This maneuver has previously been shown to produce marked increases in QA, which in turn result in significant downward displacement of the fractional dextran clearance profiles (9). The extent of this displacement allows calculation of the parameters governing bulk flow and diffusion of dextrans across the glomerular capillary wall (8, 9). As shown in the right-hand portion of Table II, plasma loading achieved the desired effect of producing large increases in QA. As shown by the individual animal data in the right-hand portion of Table I, alterations primarily in QA induced by plasma loading resulted in highly significant reductions in the fractional clearance of all but the largest dextrans studied.

These large increases in QA resulted in significant decreases in SNFF (hence $\pi_E$) and the ratio $\pi_E/\Delta P$, as expected if $K_f$ remains unchanged by plasma volume expansion. This was indeed the case, $K_f$ for these five rats averaging 0.029±0.003 nl/(s·mm Hg), the paired difference from hydropenia not being significant statistically ($P > 0.5$). This insensitivity of $K_f$ to large changes in QA is in accord with previous theoretical (23) and experimental findings in normal rats (31), suggesting that plasma volume expansion alters neither

<table>
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<tr>
<th>Rat no.</th>
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<th>22Å</th>
<th>24Å</th>
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<td>0.11</td>
<td>0.07</td>
<td>0.045</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Mean ±1 SE

Paired difference from hydropenia

| Mean | 0.90 | 0.86 | 0.81 | 0.73 | 0.63 | 0.50 | 0.38 | 0.28 | 0.2 | 0.14 | 0.09 | 0.05 | 0.025 |
| ±1 SE | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.01 | 0.01 | 0.01 | 0.005 | 0.005 | 0.005 |

$P$ value

Table I
(U/P)$_{dextran}$/ (U/P)$_{insulin}$ Ratios for Dextrans of Varying Molecular Size
Measured in NSN Rats during Hydropenia and after Plasma Volume Expansion

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<th>(U/P)<em>{dextran}/(U/P)</em>{inulin}</th>
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<th>20Å</th>
<th>22Å</th>
<th>24Å</th>
<th>26Å</th>
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The permeability properties nor the surface area of the glomerular capillary wall in either NSN or normal rats. Membrane parameters derived from pore theory. As discussed in more detail elsewhere (8, 9), the membrane parameters $K_f$, $r_0$, and $S'/l$ are related by Eq. 14, where $\mu$, the viscosity of water at 37°C, has a value of 0.007 poise. Thus, given Eq. 14 and the experimentally determined value of $K_f$, specification of $r_0$ also provides a value of $S'/l$. To determine $r_0$ from mean values of $\Delta \overline{P}$, $Q_a$, $C_{PA}$, $K_f$, and the mean values of the $(U/P)_{dextran}/(U/P)_{inulin}$ ratios in hydropenia for various effective solute radii, Eqs. 7–9 are solved iteratively, using Eqs. 12 and 13 in the manner described previously (8, 9). Values of $r_0$ computed in this manner for dextrans of varying molecular size are shown in Fig. 3A. Curves are shown for NSN rats and for a group of non-nephritic control rats studied previously (9). Over the range of effective dextran radii studied,
### TABLE II
**Summary of Several Measures of Single Nephron and Microvascular Function**

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<th>Rat no.</th>
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<th>PT</th>
<th>PC</th>
<th>CPA</th>
<th>CPE</th>
<th>(\delta A)</th>
<th>(\delta E)</th>
<th>SNGFR</th>
<th>QA</th>
<th>SNFF</th>
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<tr>
<td></td>
<td>(\bar{P})</td>
<td>(\delta P)</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>ml/100 ml</td>
<td>ni/min</td>
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<td>146.7</td>
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Overall Mean: 207 ± 10

Paired difference from hydropenia

Mean ± 1 SE

*P* value

Chang, Deen, Robertson, Bennett, Glassock, and Brenner
**in NSN Rats during Hydropenia and after Plasma Volume Expansion**

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<th>$\gamma_E$</th>
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Glomerular Permselectivity to Neutral Dextran in Glomerulonephritis 1281
$r_0$ was found to be relatively independent of dextran size, averaging approximately 50 Å both in NSN and non-nephritic control rats. In contrast, $S'/l$ in NSN rats is approximately $\frac{1}{3}$ of that in normal rats, an effect attributable to the marked fall in $K_f$ in NSN in the absence of a substantial change in $r_0$ (Eq. 14). Since $S'/l$ is proportional to $r_0^{-2}$ (Eq. 14), it follows that as dextran radius falls, $S'/l$ must necessarily decrease even more dramatically than $r_0$ rises, as shown in Fig. 3B.

Membrane parameters derived from the Kedem-Katchalsky equations. In addition to $K_f$, the membrane parameters required to characterize the glomerular capillary wall according to the Kedem-Katchalsky approach are $\omega S$, the product of solute permeability ($\omega$) and total capillary surface area ($S$), and $\sigma$, the reflection coefficient. In this case, the membrane parameters for dextran transport, $\omega S$ and $\sigma$, are regarded as independent, so that glomerular pressures and flows and fractional dextran clearances from two states, hydropenia and plasma volume expansion, are needed to evaluate these two unknowns. Values for $\omega S$ and $\sigma$ were calculated as described previously (8, 9) by iterative solution of Eqs. 7–9, using Eqs. 10 and 11. The dependence of $\omega S$ on effective dextran radius is illustrated in Fig. 4A. Values for NSN rats are again compared to values obtained previously in non-nephritic rats (9). As can be seen, $\omega S$ decreases markedly with increasing molecular size, falling by some two orders of magnitude over the range of dextran radii studied, values for NSN rats always being lower than in normal rats. These findings suggest that for the largest dextrans, in both groups of rats, diffusion is no longer an important mechanism for transport across the glomerular capillary wall. Fig. 4B illustrates the relationship between dextran size and the reflection coefficient, $\sigma$. $\sigma$ increases in essentially a linear manner with increasing dextran radius, values for NSN rats being greater than in normal rats, over the entire range of dextran radii studied. There is little selective restriction by the capillary wall to transport of the smallest dextrans, for which $\sigma$ is small. In contrast, for the largest dextrans $\sigma$ approaches 1 in both groups of rats, denoting the progressive reduction in dextran transport by bulk flow (see Eq. 11).

**DISCUSSION**

As shown by us previously (12, 30), the method of induction of NSN employed in this study produces a uniform lesion confined solely to the glomerular capillary network, as evidenced by light, immunofluorescence, and electron microscopy. Kidneys appeared normal at the time of micropuncture despite morphological evidence of glomerular injury, and glomerular filtration rates (single nephron and whole kidney) were not significantly different from values reported previously in non-nephritic control rats (24–29). Although filtration rates were normal in NSN rats, single nephron filtration fraction (SNFF) and efferent arteriolar oncotic

![Figure 4](https://example.com/figure4.png)

**Figure 4.** (A) The relationship between $\omega S$, the product of solute permeability and total glomerular capillary surface area, and effective dextran radius, $a$, assuming that $\omega S$ and $\sigma$ were unchanged by plasma volume expansion. Values are shown for both NSN and non-nephritic control rats. (B) The relationship between $\sigma$, the solute reflection coefficient, and effective dextran radius, $a$; values again shown for both groups of rats.
pressure ($\pi_E$) were lower than values typically observed in control rats (24-30), despite mean glomerular transcapillary hydraulic pressure differences ($\Delta P$) in excess of normal. This resulted from a marked fall in $K_f$, on average to a value essentially identical to that reported previously for NSN rats (12, 30), 0.026 nl/ (s mm Hg), or one-third that found for the normal rat (9, 29, 31). Thus, as noted previously (12, 30), the mean net ultrafiltration pressure was nearly three times greater in NSN rats than in controls, averaging 16.5 mm Hg in the former compared with a maximum estimate of approximately 4-6 mm Hg in non-nephritic hydropenic control rats (24-29).

We have previously demonstrated that the glomerular lesion in NSN is relatively uniform from nephron to nephron, based on morphological findings and the small coefficients of variation for measurements of SNGFR and $P_f$ among different nephrons in a given animal (12, 30). In addition to similar evidence for homogeneity of structure and function in the present study, the close correspondence of fractional dextran clearances for single glomeruli and the kidney as a whole (Fig. 1) provides further support for the view that the renal lesion in this model of NSN is uniform. This functional homogeneity permits characterization of dextran transport for a representative glomerular capillary from measurements of whole kidney fractional dextran clearances and measurement of pressures and flows made in a number of separate tubules and capillaries. Since these pressures and flows have recently been shown, both theoretically (8) and experimentally (9), to be capable of strongly influencing these fractional dextran clearance profiles, the present study represents the first opportunity to examine the relative contributions of changes in these hemodynamic factors, as well as of changes in the permeability properties of the glomerular capillary wall, in bringing about the markedly abnormal fractional dextran clearances found in NSN (Fig. 2).

The effects on dextran transport of changes solely in the determinants of SNGFR measured in NSN rats are illustrated by curve A in Fig. 2. This curve was computed from the measured mean values of $Q_A$, $\Delta P$, $C_{PA}$, and $K_f$ in NSN rats during hydropenia, assuming that the parameters $\omega S$ and $\sigma$ were unchanged from values reported by us previously for control rats (9). Of the quantities measured, only $\Delta P$, $Q_A$, and $K_f$ differed appreciably from values typically observed in normal Wistar rats, $\Delta P$ and $Q_A$ being far higher than normal and $K_f$ being markedly reduced. For

1 An analogous computation using pore theory is not possible because of the interrelationship among $r_s$, $S'/l$, and $K_f$ (Eq. 14). That is, $K_f$ cannot be changed from the normal value to that in NSN without concomitant changes in $r_s$, $S'/l$, or both.

definition, based on the separate terms for convection and diffusion shown in Eqs. 11 and 13. In these figures, the left-hand and right-hand panels described dextran transport in normal hydropenic and NSN rats, respectively. Total dextran transport is represented by solid lines, convective transport alone by dashed lines, and diffusive transport alone by dotted lines. Since the ordinates in Figs. 5 and 6 represent single nephron dextran clearances, the solid lines approach the mean values of SNGFR as dextran size diminishes and dextran clearance approaches inulin clearance. In general, for both groups of rats, the contribution of diffusion to dextran transport, while appreciable, is less than that of convection, diffusion exceeding convection only for dextrans of 22-36 Å radius in normal hydropenia using pore theory (Fig. 5A). Based on the Kedem-Katchalsky
equations, diffusion accounts for \(~25\%\) of the total dextran transport in both groups (Fig. 6). It is of interest that whereas in non-nephritic rats, using either theory, diffusive transport is maximal for dextrans of \(~25\ \text{Å}\) radius, no such peak exists in NSN. The explanation for the occurrence of this maximum in non-nephritic rats is reviewed in detail elsewhere (9).

Using immunological or quantitative gel chromatographic techniques, several groups of workers have attempted to determine the basis for the increased urinary excretion of proteins seen regularly in patients with a variety of disorders affecting the renal glomerulus (4–7). In the most rigorous study to date, the measured changes in fractional clearances of polyvinylpyrrolidone in children with untreated idiopathic nephrotic syndrome (7) were in qualitative agreement with the present findings in NSN rats using dextrans, namely, a substantial reduction in the fractional clearance of uncharged macromolecules with effective radii less than approximately 35 Å. Similar findings have also been obtained in adult patients with various forms of glomerulonephritis (6). The similarity of fractional clearances of macromolecules in these studies by others (6, 7) to those in the present study suggests that a common mechanism of altered macromolecular transport might be involved in these disorders in man and rats. Unfortunately, since direct measurements of the glomerular pressures and flows are not yet possible in

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**Figure 5** Relationship between dextran size and single nephron dextran clearance based on pore theory and measurements during hydropenia in non-nephritic rats (A) and in NSN rats (B). Solid, dashed, and dotted lines represent total dextran transport, convective transport alone, and diffusive transport alone, respectively.

**Figure 6** Relationship between dextran size and single nephron dextran clearance based on the Kedem-Katchalsky equations and measurements during hydropenia in non-nephritic rats (A) and in NSN rats (B). Solid, dashed, and dotted lines are as in Fig. 5.
man, the degree to which changes in these quantities may be responsible for the observed alterations in fractional solute clearance profiles cannot be determined. If in these studies in man, as in the present study, changes in the glomerular pressures and flows with disease have only a modest effect on fractional solute clearances (as shown by curve A in Fig. 2), then it is likely that alterations in glomerular capillary permselectivity also occurred in the patients studied. The evidence in the present study failed to suggest an alteration in pore radius as being responsible for the decline in the fractional dextran clearance profile observed in NSN. This decline in the fractional dextran clearance profile is more readily explained by a decrease in the number of pores, or an increase in their length.

Remaining to be defined is the mechanism whereby the excretion of albumin was found to increase in NSN rats, whereas the excretion of normal dextran having the same effective radius as albumin (~36 Å) decreased. As discussed in detail in the companion report (14), this apparent discrepancy may be explained by disease-induced alterations of the fixed charge residing on the structural barrier to transport, the effect of which is to increase the permeability of the glomerular capillary wall to polyanionic, but not neutral, macromolecules.

ACKNOWLEDGMENTS

This study was supported in part by grants from the National Institutes of Health (HE14945, AM16565, and AM13888). Computer time was made available by the School of Engineering, Stanford University.

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