

# Influence of Molecular Configuration on the Passage of Macromolecules across the Glomerular Capillary Wall

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**ABSTRACT** 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 several physical properties of aqueous solutions containing either dextran or ficoll. It was found that dextran is best represented as a prolate ellipsoid with axial ratios of 4, 9, and 16 for 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 seven Munich-Wistar rats. Fractional clearances of dextran were found to be greater than those of ficoll, the difference 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.

## INTRODUCTION

The transglomerular passage of macromolecules is known to be influenced by molecular size and net charge as well as by the determinants of the glomerular filtration rate of water (Brenner et al., 1977; Deen et al., 1977; Rennke and Venkatachalam, 1977 *b*, 1978). Much of the evidence supporting these conclusions has been derived from measurements of fractional clearances of test macromolecules such as dextran or polyvinylpyrrolidone (PVP). In these

studies, the urinary clearance of the test solute is compared to that of a reference solute (usually inulin), which is freely filtered across the glomerular capillary wall. If neither the test nor reference solute is secreted or reabsorbed, the ratio of the clearance of the test solute to that of the reference solute (the fractional clearance) is equal to the ratio of the concentration of test solute in Bowman's space to that in plasma water.

It has regularly been found in these studies that the fractional clearances of proteins are much lower than those of dextran or PVP of the same effective molecular size (Renkin and Gilmore, 1973; Brenner et al., 1977; Deen et al., 1977; Rennke and Venkatachalam, 1977 *b*, 1978). One factor which has been shown to be at least partly responsible for this difference in fractional clearances is the net charge of the molecule. Due to the presence of fixed negative charges on the glomerular capillary wall, polyanions such as serum albumin are restricted to a greater extent than uncharged molecules. This electrostatic effect has been demonstrated using charged forms of dextran (Chang et al., 1975 *a*; Bohrer et al., 1978), as well as proteins of differing net charge (Rennke et al., 1975, 1978 *a*; Rennke and Venkatachalam, 1977 *a*).

It has also been suggested (Renkin and Gilmore, 1973; Rennke and Venkatachalam, 1977 *b*, 1978) that the observed differences in fractional clearances between proteins and these other polymers may reflect differences in molecular shape or configuration of these macromolecules in solution. To examine this possibility, we compared fractional clearances of two uncharged macromolecules of distinctly different molecular configuration in the rat. One of the macromolecules which we employed was dextran, a slightly branched polymer of glucopyranose, which is believed to exist as a random coil in solution (Granath, 1958). The other macromolecule, ficoll, is a highly cross-linked copolymer of sucrose and epichlorohydrin. Due to the high degree of cross-linking, ficoll is expected to have a more rigid structure in solution, thus more closely resembling that of a number of plasma proteins. In the first part of this study, we sought to evaluate differences in effective shape between these two polymers, using measurements of the physical properties of aqueous solutions containing either dextran or ficoll. The data obtained from these measurements were used to determine the ratio of major-to-minor molecular axes of prolate ellipsoid models which best describe the dextran and ficoll molecules. In the second part of this study, the filtration rates of dextran and ficoll across glomerular capillaries were compared by measuring fractional clearances of these macromolecules in Munich-Wistar rats.

## METHODS

### *Physical Chemistry Studies*

Narrow molecular weight fractions of dextran with effective Stokes-Einstein radii of 22, 32, and 40 Å were prepared by repeated fractionation of Dextran T10, T20, and T40, respectively (Pharmacia Fine Chemicals, Uppsala, Sweden), on Sephadex G-100 gel columns using 0.05 N ammonium acetate (pH, 7.0) as eluant. Samples of dextran (1 ml, 10–15 g/dl) were applied to the gel column and narrow fractions (10-ml volume) centered at each of the effective radii mentioned above were collected and

dried by lyophilization. The gel columns (total volume ~ 250 ml) were calibrated with several proteins and narrow molecular weight fractions of dextrans as described previously (Chang et al., 1975 *b*). Narrow molecular weight fractions of ficoll of the same effective radii were prepared by hydrolyzing high molecular weight ficoll (Ficoll 70, Pharmacia Fine Chemicals) and then fractionating as described above. The hydrolysis was performed by dissolving 5 g of ficoll in 20 ml of H<sub>2</sub>O + 0.25 ml of 1N HCl and heating to 100°C for 5 min. This mixture was then cooled, adjusted to pH 7.0 with NaOH, lyophilized, and then fractionated.

To ensure that the dextran and ficoll used for the physical chemistry studies were the same as the tritiated polymers used in the animal studies, these narrow fractions were subjected to the same labelling procedure (see below) with the exception that nonradioactive chemicals were used.

Viscosities were determined in a Cannon-Ubbelohde (Cannon Instrument Co., State College, Pa.) capillary viscometer for which the kinetic energy correction term was found to be negligible. All measurements were performed at 37°C in a constant temperature bath ( $\pm 0.01^\circ\text{C}$ ). The solutions (dextran or ficoll in 0.9 g/dl saline) were filtered through a Millipore filter (0.45  $\mu\text{m}$  pore size, Millipore Corp., Bedford, Mass.) and dilutions were carried out in the viscometer. The viscosity of each fraction was measured at five or more concentrations in order to determine the intrinsic viscosity. Solution densities were determined at 37°C using a Mettler-Paar densimeter (model DMA 45, Anton Paar, Austria) and partial specific volumes were calculated using standard methods (Svedberg and Pedersen, 1940).

Molecular weights were estimated using the effective Stokes-Einstein radii determined from gel chromatography. The relationship between effective Stokes-Einstein radius and weight-average molecular weight which was provided by Pharmacia Fine Chemicals was derived from the data of Granath (1958) and Laurent and Granath (1967).

#### *Animal Studies*

Adult Munich-Wistar rats weighing 180–313 g were anesthetized with inactin (100 mg/kg) (Promonta, Hamburg, West Germany) and prepared for clearance measurements as described previously (Myers et al., 1975). Initial studies were performed to test the validity of equating fractional clearances of ficoll obtained for the kidney as a whole, expressed as the urine-to-plasma concentration ratio of ficoll divided by the same ratio for inulin [ $(U/P)_{\text{ficoll}}/(U/P)_{\text{inulin}}$ ], with those for a single glomerulus, expressed as the Bowman's space-to-plasma concentration ratio of ficoll divided by the same ratio for inulin [ $(BS/P)_{\text{ficoll}}/(BS/P)_{\text{inulin}}$ ], as has been done previously for dextrans (Chang et al., 1975 *b*). This test was accomplished as follows: ficoll molecules of narrow size distribution were tritiated as described below and characterized with respect to average Stokes-Einstein radius on a Sephadex G-100 gel chromatography column. A 0.4-ml priming infusion, containing nonisotopic inulin (7 g/dl) and tritiated ficoll (<300 mg/dl, sp act  $\approx 50 \mu\text{Ci/ml}$ ), 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 for the duration of each experiment. During this infusion period, two or three 15-min urine samples were collected from a catheter in the left ureter for measurement of urine flow rate and inulin and ficoll concentrations. At the midpoint of each urine collection period, fluid was also collected from accessible Bowman's capsules (30–60 nl/collection), and 100  $\mu\text{l}$  of blood was withdrawn from the femoral artery for determination of ficoll and inulin concentrations.

As discussed below, fractional urinary clearances of ficoll and dextran are the same

as fractional clearances of these molecules measured for single accessible glomeruli in the same kidney (i.e., ficoll and dextran molecules are neither secreted nor reabsorbed). It is therefore justifiable to rely on urinary clearances to assess the permselective characteristics of all glomeruli in a single kidney, using homologous series of dextran or ficoll molecules of widely varying molecular size. These experiments were performed in seven hydropenic rats in which 0.4 ml of a solution of nonisotopic inulin in isotonic saline (6 g/dl) was infused intravenously 60 min prior to the fractional clearance measurements, followed immediately by a constant infusion of the same solution at the rate of 1.2 ml/h. 0.4 ml of an isotonic saline solution containing tritiated dextran or ficoll of wide molecular size distribution (concn <200 mg/dl, sp act  $\approx$  25  $\mu$ Ci/ml; see below 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., Millis, Mass.). To determine the transit time ( $\tau$ ) 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. Urine collection was initiated  $\tau$  min ( $\sim$  2–3 min) after initiation of the continuous femoral, arterial blood collection and terminated  $\tau$  min after the end of the blood collection period. 40–100  $\mu$ l of the femoral arterial blood plasma and 15–100  $\mu$ l of the urine collected in a given period were each mixed with 1 ml of distilled water and chromatographed on Sephadex G-100. Additional aliquots of urine and blood from each period were used for subsequent determinations of inulin concentration.

Following clearance measurements with one of the polymers, its infusion was stopped and sufficient time ( $\sim$  3 h) was allowed for the plasma activity to return to background. The clearance measurements were then repeated using the other polymer, with the order of infusion of the two polymers being random.

#### *Preparation of Tritiated Dextran and Ficoll*

The dextran and ficoll molecules were tritiated using a reaction procedure described previously (Chang et al., 1975 *b*). Briefly, the dextran or ficoll was oxidized by mixing 1 g with 0.5 g NaIO<sub>4</sub> in 5 ml of water for 1–2 h. The dextran or ficoll was then separated from the NaIO<sub>4</sub> on a Sephadex G-100 gel column and reacted with 100 mCi of tritiated sodium borohydride (Amersham Corp., Arlington Heights, Ill.) at pH 8.0 for 1 h. Next, 0.2 g of nonisotopic NaBH<sub>4</sub> was added and allowed to react for an additional 3 h. The solution was then adjusted to pH 7.0, lyophilized, and the tritiated dextrans or ficolls were isolated on a gel column.

#### *Calculations*

Intrinsic viscosities ( $[\eta]$ ) were calculated from the following:

$$[\eta] = \lim_{c \rightarrow 0} \frac{\eta - \eta_0}{\eta_0 c} = \lim_{c \rightarrow 0} \frac{\eta_{sp}}{c}, \quad (1)$$

where  $\eta$  is the solution viscosity,  $\eta_0$  is the solvent viscosity,  $c$  is the concentration, and  $\eta_{sp}$  is the specific viscosity. Intercept of plots of  $\eta_{sp}/c$  vs.  $c$  determined by linear regression yielded the intrinsic viscosity. Confidence intervals at the 95% level for the intrinsic viscosities averaged  $\pm 6.1\%$  and never exceeded  $\pm 10\%$ .

The configuration of dextran and ficoll was estimated using the approach first presented by Scheraga and Mandelkern (1953). In this approach, the macromolecules are modelled as rigid particles whose hydrodynamic properties are expressed in terms

of equivalent prolate ellipsoids. Combining an equation which describes the viscosity of a dilute suspension of prolate ellipsoids with one describing the frictional coefficient (obtained from sedimentation or diffusion data) for such particles, Scheraga and Mandelkern demonstrated that the ratio of major-to-minor axes,  $a/b$ , could be uniquely related to various solution properties through a parameter which they called  $\beta$ . This parameter can be calculated as follows:

$$\beta = NS[\eta]^{1/3} \eta_0 / M^{2/3} (1 - \bar{V}\rho), \quad (2)$$

where  $N$  is Avogadro's number,  $S$  is the sedimentation coefficient,  $M$  is the molecular weight,  $\bar{V}$  is the partial specific volume, and  $\rho$  is the solvent density. Values of the sedimentation coefficient,  $S$ , were calculated by using the following:

$$S(\text{dextran}) = 0.020 M^{0.504}; \quad (3)$$

$$S(\text{ficoll}) = 0.0086 M^{0.586}. \quad (4)$$

Eqs. 3 and 4 were obtained using linear regression on data in the literature (Laurent and Granath, 1967) which had been corrected to 37°C. The correlation coefficients for the linear regression fits for dextran and ficoll were 0.998 and 0.997, respectively.

## RESULTS

### *Physical Chemistry Studies*

Table I summarizes the results of measurements of the physical properties of solutions of dextran and ficoll. As shown, values of the intrinsic viscosity increase sharply with increasing molecular size for dextran, whereas the intrinsic viscosity of ficoll increases only slightly. The values of the partial specific volume,  $\bar{V}$ , are independent of molecular size and are essentially the same as reported by others for both dextran and ficoll (Granath, 1958; Laurent and Granath, 1967). As expected, weight-average molecular weights,  $M$ , increase as the effective size of the molecules increase, with the increase for dextran and ficoll being similar. The variation in sedimentation coefficient,  $S$ , with effective radius is also similar for dextran and ficoll.

As discussed above, the shapes of dextran and ficoll can be estimated from measurements of various solution properties. The results of such calculations are given in the last two columns of Table I. Shown for each effective size of dextran and ficoll is the value of  $\beta$  as calculated in Eq. 2. The maximum error in  $\beta$  due to experimental errors in the various input quantities was estimated to be ~8%.<sup>1</sup> These values of  $\beta$  were used to determine the ratio of major-to-minor molecular axes,  $a/b$ , of equivalent prolate ellipsoids (Scheraga and Mandelkern, 1953). As can be seen, values of this axial ratio increase dramatically with size for dextrans, averaging 4, 9, and 16 for effective radii of 22, 32, and 40 Å, respectively. These findings indicate that dextran behaves as an

<sup>1</sup> The error in  $\beta$  was estimated using the following equation:

$$\text{Error in } \beta = \Delta[\eta](\partial\beta/\partial[\eta]) + \Delta M(\partial\beta/\partial M) + \Delta S(\partial\beta/\partial S) + \Delta(1 - \bar{V}\rho)(\partial\beta/\partial(1 - \bar{V}\rho)),$$

where  $\Delta[\eta]$ ,  $\Delta M$ ,  $\Delta S$ , and  $\Delta(1 - \bar{V}\rho)$  are the estimated errors in each of these parameters. Experimental errors of 5% were assumed for  $[\eta]$  and  $M$ , 2% for  $S$ , and 1% for  $(1 - \bar{V}\rho)$ .

elongated ellipsoid in solution.<sup>2</sup> Ficoll, on the other hand, is more closely approximated as spherical since the axial ratios are 1–2 for all three sizes. The effective volume of the dextran molecules, including tightly bound water, was calculated to be 1.9, 1.3, and 1.0 ml/g corresponding to degrees of hydration of 1.3, 0.7, and 0.4 g H<sub>2</sub>O/g dextran for effective radii of 22, 32, and 40 Å, respectively. Ficoll was estimated to have a higher degree of hydration with values of 1.7, 2.5, and 2.4 g H<sub>2</sub>O/g ficoll for molecules with effective radii of 22, 32, and 40 Å, respectively. The effective molecular volumes for these same three sizes of ficoll were calculated to be 2.4, 3.2, and 3.1 ml/g.

#### Animal Studies

Studies with ficoll molecules of narrow size distribution performed in three rats demonstrated that  $(BS/P)_{\text{ficoll}}/(BS/P)_{\text{inulin}}$  ratios were essentially the same as simultaneously measured fractional clearance ratios obtained for the kidney as a whole  $[(U/P)_{\text{ficoll}}/(U/P)_{\text{inulin}}]$ . Values for the ratio  $[(BS/P)_{\text{ficoll}}/(BS/P)_{\text{inulin}}]/[(U/P)_{\text{ficoll}}/(U/P)_{\text{inulin}}]$  for eight such comparisons averaged  $0.99 \pm 0.03$  (SE). These findings indicate that ficoll is neither secreted nor reabsorbed by the renal tubules. Similar conclusions have previously been reached for dextran (Chang et al., 1975 b).

TABLE I  
PHYSICAL PROPERTIES OF DEXTRAN AND FICOLL

Polymer	Effective radius	$[\eta]$	$\bar{V}$	$\bar{M}$	$S$	$\beta \times 10^6$	Axial ratio
	Å	dl/g	ml/g	g/mol	$10^{-13}$ s		
Dextran	22	0.09	0.61	9,500	2.02	2.18	4
	32	0.16	0.62	21,000	3.02	2.38	9
	40	0.26	0.62	33,000	3.79	2.57	16
Ficoll	22	0.06	0.67	9,000	1.80	2.11	1
	32	0.08	0.67	23,500	3.17	2.08	1
	40	0.09	0.67	41,000	4.34	2.13	2

$P)_{\text{inulin}}]/[(U/P)_{\text{ficoll}}/(U/P)_{\text{inulin}}]$  for eight such comparisons averaged  $0.99 \pm 0.03$  (SE). These findings indicate that ficoll is neither secreted nor reabsorbed by the renal tubules. Similar conclusions have previously been reached for dextran (Chang et al., 1975 b).

Fig. 1 summarizes the results of fractional clearance measurements of dextran and ficoll carried out in random order in seven Munich-Wistar rats. Fractional clearances of dextran always exceeded values for ficoll, the mean difference between dextran and ficoll being significant ( $P < 0.05$ ) for radii  $> 22$  Å. Since dextran and ficoll are not secreted or reabsorbed, these findings indicate that the more elongated dextran molecules are filtered to a greater extent across glomerular capillary walls than are the more spherical ficoll molecules of the same effective radius.

#### DISCUSSION

The effect of molecular shape or configuration on the movement of macromolecules has been investigated in vitro using gels, synthetic membranes, or

<sup>2</sup> The intrinsic viscosity of narrow fractions of the anionic form of dextran, dextran sulfate, was found to be essentially the same as those of neutral dextran, indicating that the shapes of these two forms of dextran are probably not much different. Values for  $\beta$  and thus axial ratios could not be calculated for dextran sulfate, however, since sedimentation data are not available.

porous glass cubes. Laurent and co-workers (1963, 1975) have studied the sedimentation of various proteins and linear polymers through gel matrices of hyaluronic acid. They found that for molecules of equivalent Stokes-Einstein radii, the linear, random coil polymers had a greater sedimentation rate through the gel matrix than the globular proteins. They postulated that these differences in sedimentation rates are due to differences in molecular configuration among these various macromolecules within the gel matrix. In another study, Schultz and co-workers (1978) measured osmotic reflection coefficients of dextrans and proteins, using track-etched polycarbonate membranes. They found that, at any given molecular size, the dextrans have a lower reflection coefficient than the proteins, indicating less restriction to transport of dextrans than proteins across these membranes. Colton and co-workers (1975) have investigated the diffusion of macromolecules within finely porous glass cubes. They found that narrow molecular weight fractions of polystyrene, a linear

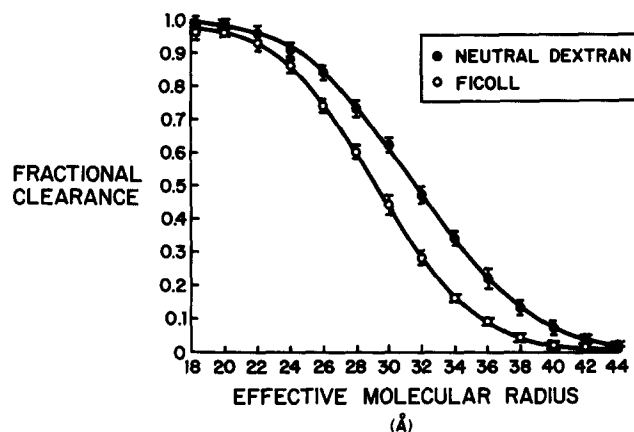


FIGURE 1. Fractional clearances for dextran and ficoll obtained in seven Munich-Wistar rats.

polymer, have a much greater diffusivity than proteins of the same effective Stokes-Einstein radii.

The present study demonstrates that differences in molecular shape or configuration are also important in the glomerulus. It was found that the fractional clearances of dextrans, which appear to be elongated ellipsoids, are greater than those of the nearly spherical ficoll molecules of the same effective size. In agreement with this finding are the results of Rennke and co-workers (1978 *b*) who compared the fractional clearance of dextran with a neutral form of horseradish peroxidase of the same effective molecular radius. They found that the fractional clearance of dextran was some eightfold greater than that of the globular protein. These results suggest that the globular structure of many circulating proteins may contribute to their retention within the circulation, as do their overall size and net negative charge.

In contrast to the results presented in Table I, Ogston and Woods (1953) estimated the axial ratio of dextrans to be less than 10 for molecules in the molecular weight range from 14,000 to 3,300,000. This difference in axial

ratios is most likely due to a difference in the degree of branching between the dextrans studied by Ogston and Woods (1953) and those examined in the present study. As pointed out by Granath (1958), Ogston and Woods (1953) studied a rather highly branched dextran of the Birmingham strain, whereas Pharmacia dextrans, produced by the *Leuconostoc mesenteroides* B512 bacteria, have a lesser degree of branching. Granath (1958) demonstrated that this difference in branching can cause significant differences in the solution properties of these dextrans.

To predict theoretically the influence which molecular configuration has on the filtration of macromolecules through porous barriers, a model for the molecules must be chosen. The results of the present study suggest that ficoll may be represented as a spherically symmetrical molecule; compared to dextran, it is expected to have a relatively rigid structure due to the high degree of cross-linking. The most appropriate model for dextran, however, is less apparent. Dextran may be represented as a rigid prolate ellipsoid, as suggested by the results of this study, or it may be described as a flexible molecule (Granath, 1958), which is able to undergo deformation and can therefore change its shape. Irrespective of the molecular model chosen, there are two possible mechanisms whereby molecular configuration can affect the filtration of macromolecules through fluid-filled pores. The first relates to the ability of a molecule to enter a pore in the membrane, and the second relates to the resistance to movement which the molecule encounters once it has entered a pore. The first effect, usually termed "steric partitioning," accounts for the fact that the concentration of solute molecules within a pore is less than that in the bulk solution adjacent to the membrane, even at equilibrium. This is so because molecules are not able to intersect the pore wall and therefore cannot occupy all of the volume within the pores.

The solute concentration in a pore, divided by that in bulk solution, is equal to the steric partitioning coefficient ( $K$ ), which for spherical molecules is given by:

$$K = (1 - \lambda)^2, \quad (5)$$

where  $\lambda$  is the ratio of molecular radius to pore radius. As can be seen from Eq. 5,  $K$  approaches zero as the molecule approaches the size of the pore, and approaches unity for very small molecules. Values of  $K$  for prolate ellipsoids can be calculated<sup>3</sup> from relations derived by Giddings and associates (1968). The partitioning coefficient for dextrans so obtained are compared with those for ficolls (the latter calculated from Eq. 5) in the second and third columns of Table II assuming a pore radius of 50 Å. As can be seen, the values of  $K$  for the rigid ellipsoid model of dextran are calculated to be lower than those for ficoll of the same effective radius. On this basis, dextran is therefore predicted to be filtered to a lesser extent than ficoll, an effect opposite to that observed

<sup>3</sup> Values of  $K$ , the partitioning coefficient, were obtained by numerical integration of Eq. 16 in Giddings et al. (1968). This equation was integrated by a double application of Simpson's rule. Step-sizes for the integration were decreased until the value of  $K$  was within 0.001 of the previously calculated  $K$  value.



in this study. If the alternative model for dextran molecules, the random coil, is chosen, partitioning coefficients can be calculated as described by Casassa (1967), with the results shown in the last column of Table II. As shown, the steric partitioning coefficient for random coil polymers are even lower than those for rigid molecules of the same effective size. These results make it highly unlikely that steric partitioning accounts for the greater fractional clearance of dextran than ficoll.

The second mechanism which may account for the observed shape effect is that related to the enhanced resistance to movement which a molecule experiences once it has entered a pore. This enhanced resistance is due to the hydrodynamic effects of the pore walls, and its magnitude is expected to be a function of several parameters including the molecular shape. Unfortunately, it is possible at the present time to calculate such resistances only for rigid spherical particles, and not for other shapes such as ellipsoids. Although it is not yet possible to predict theoretically the effect of the difference in shape between dextran and ficoll, our findings suggest that the movement of ficoll

TABLE II  
STERIC PARTITIONING COEFFICIENTS FOR DEXTRAN AND  
FICOLL

Effective radius	Ficoll (rigid sphere)	Dextran (rigid ellipsoid)	Dextran (random coil)
$\bar{A}$			
22	0.31	0.10	0.06
32	0.13	0.02	0.003
40	0.04	0.009	0.0002

within the glomerular capillary wall is restricted more severely than that of dextran, thereby resulting in a lower fractional clearance of ficoll than dextran.

In summary, this study provides evidence for a role of molecular configuration in determining the fractional clearance of neutral macromolecules. Dextrans, which behave as elongated molecules, were found to be filtered to a greater extent than ficolls, which are more nearly spherical. It is suggested that this difference in fractional clearances is due, not to steric partitioning, but to the greater resistance to movement of ficoll than dextran within the capillary wall. The precise hydrodynamic basis for this difference in resistance remains to be determined.

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