Kidney International, Vol. 45 (1994), pp. 398–402

Glomerular perm-selective function

ANDREA REMUZZI and GIUSEPPE REMUZZI

"Mario Negri" Institute for Pharmacological Research and Division of Nephrology and Dialysis, Ospedali Riuniti di Bergamo, Bergamo, Italy

The glomerular capillary wall functions as an efficient barrier that restricts the passage of plasma proteins and allows a high flow rate of filtration for plasma water and small solutes. Experimental studies have confirmed the theoretical predictions that circulating macromolecules are retained within the lumen of glomerular capillaries because of their size, shape and electrical charge [1–6]. The selective function of the glomerular capillary wall allows an almost complete restriction of large proteins and albumin while low molecular weight proteins are almost freely filtered and reabsorbed at tubular level [7, 8]. Glomerular permeability to circulating macromolecules has been extensively studied in the last few years, both by experimental studies and clinical investigations, with the aim of elucidating the mechanisms by which the glomerular membrane loses its selective function during development of most glomerular diseases. More recently additional interest in this area has been generated by the observation that the use of angiotensin converting enzyme (ACE) inhibitors in experimental models of glomerular dysfunction and in patients, beside reducing blood pressure, prevents or lessens urinary protein excretion. Experimental research in this field has focused on the mechanisms by which such pharmacological treatment can restore, at least partially, the selective function of the glomerular barrier [9–12].

The objective of this communication is to review some recent developments in experimental and clinical research on glomerular selectivity that illustrate new aspects of the glomerular charge- and size-selective function. In particular, recent studies are reviewed that indicate the distribution of restrictive sites on the glomerular basement membrane (GBM) to the filtration of albumin. Since recent evidence indicates that epithelial cells, in addition to GBM, exert a major role in determining the selective function of the glomerular capillary wall, other studies are discussed which aimed to clarify whether there was a correlation between changes in permselective function and quantification of structural changes of glomerular cells as assessed using morphometrical techniques. Observations on the filtration of test macromolecules with different configuration are also presented since they provide new insights on the effects of molecular configuration on the filtration of test macromolecules. Theoretical analysis of experimental results obtained with these test macromolecules has been carried out to determine membrane permeability parameters in both the normal state and in a model of glomerular injury in the rat. Both theoretical analyses are reviewed because they indicate that glomerular size-selective function is more restrictive than that estimated previously by experimental and human studies.

The functional nature of the glomerular filtration barrier

The glomerular membrane effectively restricts the passage of plasma proteins as a function of their size and of their electrical charge [13–16]. However, the precise location within the glomerular capillary wall of that barrier and the factors that determine size and charge selectivity are still not well-defined. Several studies have been undertaken to investigate the location of the filtration barrier for circulating proteins. Original observations [17, 18] noted that albumin and IgG were retained at the endothelial level of the lamina densa of the GBM. Bendayan and coworkers [19, 20], by immunohistochemical staining, provided experimental evidence that albumin distribution within the GBM in the physiological state is determined by two distinct restrictive sites, one at the endothelial basal membrane, the other on the endothelial side of the lamina densa. According to other studies, these restrictive sites are lost in diabetic rats and in the nephrotic syndrome in humans. Furthermore, these investigators reported that localization of electrically modified albumin within the GBM is a function of its charge [21]. An electrostatic anionic barrier seems to be localized at the level of the lamina rara interna and externa, while the lamina densa acts more as a size-selective filter. These confirm previous observations on the deposition of electron-dense tracers within the GBM [15]. Similar results have been obtained by other investigators using immunocytochemical localization of albumin, IgG and transferrin in normal rats combined with *in situ* drip fixation of kidney tissue [22]. According to these authors the central and outer zones of the GBM act as charge restrictive barrier, while a more generalized size restriction of the whole GBM is suggested by the continuous localization of uncharged proteins throughout its depth. Taken together these investigations would suggest that under normal circumstances the selective permeability of the GBM is based on an efficient barrier acting on both the charge and size of circulating macromolecules.

Other components of the glomerular capillary wall are also likely to play a crucial role in determining the permselective function of glomerular membrane [23–27]. Daniels and coworkers have documented that protein permeability of GBM *in vitro* is much higher than that of intact glomeruli, suggesting a major contribution of endothelial and epithelial cells in glomerular

filtration of proteins [24]. In addition the same authors, measuring the passage of tracer macromolecules across intact or cell free glomerular membranes *in vitro*, have indicated that epithelial cells are the major determinants of the size- and charge-selective properties of the glomerular capillary wall [23]. It is also generally acknowledged that effacement and fusion of epithelial cells podocytes is associated with an altered size selective function of glomerular membrane [25, 28]. However, the mechanisms by which epithelial cell podocytes exert a filtration barrier function for macromolecules have not been completely elucidated.

Ultrastructural changes associated with glomerular permselective dysfunction

Experimental studies in laboratory animals and in humans, using neutral dextrans as tracer macromolecules, indicate that the glomerular capillary wall acts as a membrane perforated by pores having a continuous distribution of radii. The mean radius of the pore-size population has been estimated to be around 50 Å in both rats and humans [29, 30]. This hypothetical description of the glomerular capillary wall is not based on data derived from ultrastructural analysis of the glomerular membrane but rather represents a quantitative description of intrinsic membrane permeability properties to macromolecules. At the moment it is not yet clear which components of the glomerular barrier effectively exert the selective barrier to the passage of circulating macromolecules. The GBM, by its physicochemical composition, plays an important role in determining both glomerular charge- and size-selectivity. Detailed characterization of different GBM proteins and their role in this selective function is a complex task that is currently under investigation. In order to determine whether changes in GBM structure are associated with functional alterations, studies have also been undertaken with the aim of measuring simultaneously GBM thickness and protein filtration.

The epithelial podocytes, with their slit diaphragms, could also play an important role in the glomerular permselective function. This suggestion is based on the observation that fusion or effacement of foot processes of the epithelial cells is associated with abnormal protein filtration and loss of size-selective function [25, 28].

Quantification of structural changes of glomerular membrane components has been performed using morphometric analysis. GBM thickness, the number of epithelial slit pores per unit length of GBM and epithelial filtration slit width have been assessed and compared with measurements of albumin and IgG fractional clearance. Kiberd provided convincing results that, in a model of murine lupus nephritis, structural changes of the glomerular capillary wall are related to abnormal filtration of albumin and IgG [31]. In this model, albumin and IgG fractional clearances correlated significantly with the number of epithelial slits per unit length of GBM, and with GBM thickness. Interestingly, however, no significant correlation between the width of filtration slits, and fractional clearances of albumin and IgG was observed. Fogel and coworkers [32] also reported that in passive Heymann nephritis, the rat model of membranous nephropathy, GBM width is increased, compared to normal controls, and the number of slit pores per μm of GBM is significantly decreased. In contrast it has been reported that GBM thickness in subtotal nephrectomized rats is decreased, rather than increased, as compared to controls [33]. We have recently performed similar measurements with the aim of investigating whether differences in proteinuria correlate with changes in glomerular capillary wall structure in male MWF/Ztm rats treated with an ACE inhibitor [34]. In treated animals the spontaneous development of proteinuria, was completely prevented. Despite the important difference in urinary protein excretion rates, however, untreated and treated animals showed comparable GBM thickness as well as comparable epithelial slit frequency. Similar observations were reported by Guasch and coworkers in human pathological conditions, minimal change nephropathy and focal glomerulosclerosis [35]. In this study abnormal increases in albumin and IgG fractional clearance were associated with a decreased frequency of epithelial filtration slits. However, despite abnormal fractional clearances of albumin and IgG, no statistically significant differences was observed in GBM thickness between controls and nephrotic groups. These results would indicate that changes in epithelial podocyte structure, but not in GBM thickness, are related to abnormal filtration of circulating proteins.

Altogether these results indicate that structural alterations of the glomerular capillary are not invariably related to abnormal filtration of circulating proteins. In different pathological conditions, in rats and in patients, different mechanisms seem to lead to different structural and functional changes of the glomerular capillary wall. Thus, more comprehensive studies must be performed in the near future to document in more detail the structural alterations of the glomerular capillary wall and their actual relationship to the loss of selective function and abnormal protein filtration.

Effect of molecular configuration on glomerular filtration of macromolecules

The size-selective function of the glomerular membrane has been extensively investigated measuring glomerular filtration of neutral test macromolecules [9–12, 29, 30, 35–37]. If a test macromolecule is filtered at glomerular level, but neither secreted nor reabsorbed by the tubule, its urinary clearance is a direct measure of its glomerular filtration. In this condition, the urinary clearance of such a macromolecule, factored by the clearance of a freely filtered molecule (like inulin), represents the filtrate-to-plasma concentration ratio, usually termed fractional clearance or "sieving coefficient" of the glomerular capillary wall. It has been demonstrated that neutral dextrans are filtered at glomerular level with negligible reabsorption at tubular level [2]. Because of this property and because of their relative safety in patients, these molecules have been used to determine the sieving properties of the glomerular capillary wall. We and others have determined the sieving coefficient of the glomerular membrane in experimental and human studies measuring the clearance of neutral dextran molecules of varing sizes. These studies illustrate that fractional clearances of neutral macromolecules are useful in determining size-selective defects in experimental animals and in human glomerular diseases, and they can be used to investigate the effect of treatment of glomerular dysfunction with pharmacological interventions aimed at ameliorating glomerular size-selective function [10–12]. Despite numerous studies focusing on the relation

between glomerular filtration of neutral dextrans and that of proteins, the test macromolecules have a molecular configuration that is far from being globular, but are rather elongated in shape (most plasma proteins are globular. This limitation induced some investigators to assess whether other neutral macromolecules (like Ficoll), more globular in shape, have a different rate of filtration across the glomerular membrane. Deen and coworkers measured fractional clearance of Ficoll of graded sizes in normal Munich-Wistar rats [38] and showed that sieving coefficients for all radii studied were significantly lower than that measured in the same study for neutral dextran macromolecules. In the normal Munich-Wistar rat, the mean fractional clearance for a dextran macromolecule of 35 Å in radius (approximately the molecular radius of albumin) averaged 0.09 while the fractional clearance of Ficoll molecules of the same size averaged only 0.008. More recently, we measured fractional clearance of Ficoll of graded sizes in normal and in diabetic Sprague-Dawley rats after long-term observation [39]. As in the normal Munich-Wistar rats, fractional clearances of these molecules in normal Sprague-Dawley rats were significantly lower than corresponding fractional clearance values of neutral dextrans previously measured [30]. Thus, in this strain of rats fractional clearance of dextran molecules of 35 Å in radius averaged 0.17 [30] and that of Ficoll of same size averaged only 0.020 [39].

Since fractional clearance of albumin in the normal rat is estimated to be around 0.003 [7], it is understandable that earlier studies, using neutral dextran, suggested a more prominent role of charge- than of size-selectivity for albumin exerted by the glomerular membrane. The new data obtained with Ficoll, however, show that a large portion of albumin restriction must derive from the size-selective function of the capillary wall. This would imply that both charge- and size-selectivity defects must be responsible for abnormal albumin filtration in experimental and human glomerular diseases.

Theoretical analysis of glomerular size-selective function

The glomerular size-selective function has been mainly derived from the measurement of fractional clearance of neutral test macromolecules. Theoretical and experimental observations [2, 4, 6] indicated that the membrane passage of macromolecules is affected by changes in the hemodynamic conditions of the glomerular capillaries. Changes in the determinants of glomerular ultrafiltration may increase or decrease the filtration of a test macromolecule. Thus, an increase in protein concentration in the afferent arteriole or in the ultrafiltration coefficient increases macromolecule filtration while a decrease in afferent plasma flow or transmembrane hydraulic pressure difference decreases macromolecule filtration. This implies that, when glomerular filtration of test macromolecules is used to investigate glomerular size-selective function, with concomitant changes in glomerular hemodynamics, it is impossible to separate the extent to which the filtration of solute markers is influenced by effective changes in glomerular membrane permeability properties and which changes are the result of alterations in local hemodynamic conditions. In the last fifteen years mathematical models of glomerular size-selective function have been developed and used to separate these two effects and allow estimation of effective changes in glomerular membrane permeability to macromolecules. These models are based on the application of the pore theory to solute transport across the glomerular membrane and consider the changes in local concentration of test macromolecules [4, 29]. Thus, they allow an analysis of intrinsic membrane permeability parameters in terms of the radii of hypothetical pores assumed to perforate the glomerular capillary wall.

These models were originally developed assuming the glomerular membrane to be perforated by pores of uniform radius [4]. This assumption did not completely reflect the behavior of solute transport at glomerular level. Many experimental and human diseases are characterized by the abnormal passage of large neutral test macromolecules (larger than 60 Å in radius) and by a concomitant reduction in the filtration of small molecules [29, 40]. For these reasons theoretical models have been extended to allow consideration of the glomerular membrane as a barrier perforated by a continuous population of pores of different sizes [29, 30]. These models, known has heteroporous models, have been successfully applied to the analysis of fractional clearance data in experimental and in clinical studies. Among them, two models of the glomerular membrane pore size distributions have been used most frequently, the so called "isoporous plus shunt" model and the "lognormal" distribution model. The first considers the membrane as perforated by two pore populations, one represented by restrictive pores with uniform radius and another represented by pores, few in number but large in size, that offer no resistance to the passage of the test macromolecules, and represent a shunt pathway for macromolecules. The two populations are described, respectively, by the radius (r_o) and the rate of movement of filtrate through the shunt if plasma protein were absent (ω_o).

The lognormal distribution model is based on the assumption that the pore size distribution is the logarithmic transformation of the normal probability distribution function. The parameters that describe this distribution (u and s) are, respectively, the values of the mean and the standard deviation of the corresponding normal distribution. A summary of membrane pore-size parameters calculated using fractional clearance values of dextran molecules and the two different pore-size distributions is shown in Table 1. As seen in the table, theoretical analysis based on the isoporous plus shunt model suggested that in the experimental animal and in the human condition the radius of selective pores is respectively around 45 Å and 55 Å, while the shunt pathway differs by about one order of magnitude (1×10^{-4} and 1 to 10×10^{-3}) between the two conditions. Using the isoporous plus shunt model pore-size distribution, patients affected by various form of glomerular diseases showed only slight changes in pore-size parameters. A similar pattern is shown by consideration of pore-size distribution according to the lognormal probability function. Membrane parameters obtained using this model indicate that the major component of pore-size distribution has a peak at 42 Å and 55 Å, respectively for experimental animals and humans under normal conditions, and that the spread of the pore-size population is higher in the rat than in humans (Table 1). Comparing data obtained in normal and in pathological conditions in humans, it appears that the mean pore size decreases in the disease state and the spread of the distribution increases. These theoretical models have been recently used also to investigate effective changes in

Table 1. Membrane pore-size parameters in experimental animals and humans derived from fractional clearance of neutral dextran and Ficoll

Species	Condition	Tracer	Model	Pore-size parameters		Reference
Rat	Normal	Dextran	Isoporous + shunt	r_o = 48–44 Å	$\omega_o = 0.1 - 5.0 \times 10^{-3}$	[1, 2]
Human	Normal	Dextran	Isoporous + shunt	r_o = 57 Å	$\omega_o = 1.3 - 1.8 \times 10^{-3}$	[3, 4]
Human	Glom. disease	Dextran	Isoporous + shunt	r_o = 52–56 Å	$\omega_o = 2.5 - 11.3 \times 10^{-3}$	[3–7]
Rat	Normal	Dextran	Log normal	u = 42–43 Å	s = 1.17 – 1.19	[8, 9]
Human	Normal	Dextran	Log normal	u = 55 Å	s = 1.10	[3]
Human	Glom. disease	Dextran	Log normal	u = 42–49 Å	s = 1.17 – 1.24	[10, 11]
Rat	Normal	Ficoll	Isoporous + shunt	r_o = 29 Å	$\omega_o = 0.5 \times 10^{-3}$	[2]
Rat	Normal	Ficoll	Log normal	u = 6–14 Å	s = 1.46 – 1.64	[2, 12]
Rat	Glom. disease	Ficoll	Log normal	u = 24 Å	s = 1.35	[12]

Abbreviations are: r_o and ω_o, pore-size parameters for the isoporous plus shunt model; u and s, pore-size parameters for the log normal distribution.

membrane sieving properties induced by pharmacological treatments in experimental and human studies [10, 11, 41]. In general these theoretical analyses show that loss of glomerular membrane selective function is associated with the appearance of large pores that allow an increased filtration of circulating proteins.

The theoretical analysis so far described, however, is based on the assumption that solute molecules are spherical in shape. The test macromolecules adopted in the above-mentioned studies (neutral dextrans) are not spherical in shape but rather characterized by an elongated shape with a random-coil configuration [38]. We have already discussed the ability of Ficoll molecules to behave more like an ideal probe for determining glomerular pore size than the conventionally used dextrans. For these reasons fractional clearance of Ficoll was recently used to compute membrane pore-size parameters and to compare them with values calculated for dextran molecules [38, 39]. As reported in Table 1, new measurements of size-selective function in normal rats performed using Ficoll indicate that mean pore size is much smaller than that derived from dextran clearances. Using the isoporous plus shunt model, it was calculated that the restrictive pores have a radius of only 29 Å for normal rat and a mean pore size, calculated with the lognormal distribution model, less than 15 Å in radius. This is confirmed by our observation that the mean pore radius of the lognormal distribution for the Sprague-Dawley rat averaged 42 Å using dextran fractional clearances and only 18 Å for Ficoll fractional clearance [30, 39]. Thus, a completely different picture is shown by these theoretical analyses. Since albumin, the major urinary protein of glomerular origin, has a size of 35 Å it appears that it can not be filtered through the majority of the membrane pores on the basis of its relative size. This indicates that a charge-selective defect of the glomerular capillary wall may cause important changes in albumin filtration only if associated with a size-selectivity defect. These observations change previous considerations on the relative importance of charge- and size-selectivity and better define the absolute quantification of glomerular size-selective function in the experimental animal. On the basis of these results it appears that the use of Ficoll fractional clearance in humans would give additional useful information on the glomerular barrier. However, to what extent it would affect computation of pore-size parameters in the normal condition and in glomerular diseases is not known at the moment. To obtain such results the limitations connected with the use of these tracer molecules in man must first be overcome.

Conclusions

In the last few years efforts have been devoted to the detailed study of the structural and functional nature of glomerular selective function in the hope to identify the mechanisms responsible for altered permeability of the glomerular capillary wall to circulating macromolecules. Since this condition characterizes several glomerular diseases that progress to end-stage renal failure, it is believed that a better understanding of the causes responsible for proteinuria will lead to development of new therapeutical interventions aimed at reducing glomerular injury and retarding the onset of renal failure [42]. The functional nature of changes in the selective properties of the glomerular capillary wall that follows glomerular injury have been explored by studies of endogenous albumin distribution which revealed that the barrier normally localized in the subendothelial area of the GBM is lost in proteinuric glomerular disease, while other studies indicate a crucial role for epithelial cell slit diaphragms. No details exist which define the structural nature of the barrier which opposes the passage of macromolecules from the capillary lumen into the urinary space under normal conditions. The transmembrane passage of non-reabsorbable dextrans has been used to probe the passage of circulating macromolecules and proteins. Interpreting dextran data on the basis of the pore theory allowed an understanding of the intrinsic membrane properties that prevented the passage of macromolecules in normal circumstances and their selective alterations in glomerular disease. However, more recent studies showed that the use of dextrans as filtration probes does not fully explain the relatively high sieving coefficient of normal animals in the absence of proteinuria. Charge-selectivity has been advocated as a possible explanation, since albumin is negatively charged. This does not apply, however, to the G class of immunoglobulins that are mainly neutral proteins. In this context data generated by the use of a different filtration probe (that is, Ficoll), that difuses less than dextrans due to its spherical configuration, offers a better way to analyze the consequences of glomerular injury on barrier permeability to macromolecules. Models based on the application of the pore theory to solute transport across the glomerular membrane are becoming more sophisticated in recent years. Combining the use of new probes with more reliable models will allow, in the near future, a more close definition of the functional nature of altered permselectivity in glomerular diseases.

Reprint requests to Dr. Andrea Remuzzi, Biomedical Engineering Laboratory, "Mario Negri" Institute for Pharmacological Research, Via Gavazzeni, 11, 24100 Bergamo, Italy.

References

1. Chang RLS, Ueki IF, Troy JL, Deen WM, Robertson CR, Brenner BM: Permselectivity of the glomerular capillary wall to macromolecules. I. Theoretical considerations. *Biophys J* 15:887–895, 1975
2. Chang RLS, Ueki IF, Troy JL, Deen WM, Robertson CR, Brenner BM: Permselectivity of the glomerular capillary wall to macromolecules: II. Experimental studies in rats using neutral dextran. *Biophys J* 15:887–906, 1975
3. Bohrer MP, Deen WM, Robertson CR, Troy JL, Brenner BM: Influence of molecular configuration on the passage of molecules across the glomerular capillary wall. *J Gen Physiol* 74:583–593, 1979
4. Deen WM, Bohrer MP, Brenner BM: Macromolecules transport across glomerular capillaries: Application of pore theory. *Kidney Int* 16:353–365, 1979
5. Deen WM, Satvat B, Jamieson JM: Theoretical model for glomerular filtration of charged solutes. *Am J Physiol* 238:F126–F139, 1980
6. Brenner BM, Ichikawa I, Deen WM: Glomerular filtration, in *The Kidney*, edited by Brenner BM, Rector FC Jr, Philadelphia, W.B. Saunders Company, 1981, pp 289–327
7. Galaske R, Baladamus CA, Stolte H: Plasma protein handling in the rat kidney: Micropuncture experiments in the acute heterologous phase of anti-GBM-nephritis. *Pflügers Arch* 375:269–277, 1978
8. Tojo A, Hitoshi E: Intrarenal handling of proteins in rats using fractional micropuncture technique. *Am J Physiol* 263:F601–F606, 1992
9. Remuzzi A, Puntorieri S, Battaglia C, Bertani T, Remuzzi G: Angiotensin converting enzyme inhibition ameliorates glomerular filtration of macromolecules and water and lessens glomerular injury in the rat. *J Clin Invest* 85:541–549, 1990
10. Morelli E, Loon N, Meyer TW, Peters W, Myers BD: Effects of converting-enzyme inhibition on barrier function in diabetic glomerulopathy. *Diabetes* 39:76–82, 1990
11. Remuzzi A, Perticucci E, Ruggenenti P, Mosconi L, Limonta M, Remuzzi G: Angiotensin converting enzyme inhibition improves glomerular size-selectivity in IgA nephropathy. *Kidney Int* 39:1267–1273, 1991
12. Remuzzi A, Ruggenenti P, Mosconi L, Pata V, Viberti G, Remuzzi G: Effect of low-dose enalapril on glomerular size-selectivity in human diabetic nephropathy. *J Nephrol* 6:36–43, 1993
13. Farquhar MG: The glomerular basement membrane. A selective macromolecular filter, in *Cell Biology of Extracellular Matrix*, edited by Hay ED, New York, Plenum Press, 1981, pp 335–378
14. Rennke HG, Venkatachalam MA: Glomerular permeability: *In vivo* tracer studies with polyanionic and polycationic ferritins. *Kidney Int* 11:44–53, 1977
15. Kanwar YS, Farquhar MG: Anionic sites in the glomerular basement membrane. *In vivo* and *in vitro* localization to the laminae rarae by cationic probes. *J Cell Biol* 81:137–153, 1979
16. Bliss DJ, Brewer DB: Ultrastructural localization of anionic and cationic ferritin in the rat glomerular basement membrane protein-overload proteinuria. *J Pathol* 143:57–68, 1984
17. Ryan GB, Karnovsky MJ: Distribution of endogenous albumin in the rat glomerulus. Role of hemodynamic factors in glomerular barrier function. *Kidney Int* 9:36–45, 1976
18. Ryan GB, Hein SJ, Karnovsky MJ: Glomerular permeability to proteins. Effects of hemodynamic factors on the distributions of endogenous immunoglobulin G and exogenous catalase in the rat glomerulus. *Lab Invest* 34:415–427, 1976
19. Bendayan M, Gingras D, Charest P: Distribution of endogenous albumin in the glomerular wall of streptozotocin-induced rats as revealed by high-resolution immunocytochemistry. *Diabetologia* 29:868–875, 1986
20. Russo PA, Bendayan M: Distribution of endogenous albumin in the glomerular wall of proteinuric patients. *Am J Pathol* 137:1481–1490, 1990
21. Ghitescu L, Desjardins M, Bendayan M: Immunocytochemical study of glomerular permeability to anionic, neutral and cationic albumins. *Kidney Int* 42:25–32, 1992
22. Fujigaki Y, Nagase M, Kobayasi S, Hidaka S, Shimomura M, Hishida A: Intra-GBM site of the functional filtration barrier for endogenous proteins in rats. *Kidney Int* 43:567–574, 1993
23. De Nicola L, Wilson CB, Keiser JA, Blantz RC, Gabbai FB: Effect of angiotensin converting enzyme inhibition on renal functional reserve (RFR) in rats with chronic glomerulonephritis with and without hypertension. (abstract) *J Am Soc Nephrol* 2:517, 1991
24. Daniels BS, Hauser EB, Deen WM, Hostetter TH: Glomerular basement membrane: *In vitro* studies of water and protein permeability. *Am J Physiol* 262:F919–F926, 1992
25. Kanwar YS, Rosenzweig LJ: Altered glomerular permeability as a result of focal detachment of the visceral epithelium. *Kidney Int* 21:565–574, 1982
26. Hostetter TH, Rennke HG, Brenner BM: The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 72:375–380, 1982
27. Alfino PA, Neugarten J, Schacht RG, Baldwin DS, Dworkin LD: Glomerular size-selective barrier dysfunction in nephrotoxic serum nephritis. *Kidney Int* 34:151–155, 1988
28. Weening JJ, Rennke HG: Glomerular permeability and polyanion in adriamycin nephrosis in the rat. *Kidney Int* 24:152–159, 1983
29. Deen WM, Bridges CR, Brenner BM, Myers BD: Heteroporous model of glomerular size selectivity: Application to normal and nephrotic humans. *Am J Physiol* 249:F374–F389, 1985
30. Remuzzi A, Battaglia C, Rossi L, Zoja C, Remuzzi G: Glomerular size selectivity in nephrotic rats exposed to diets with different protein content. *Am J Physiol* 253:F318–F327, 1987
31. Kiberd BA: Murine lupus nephritis: A structural-functional study. *Lab Invest* 65:51–60, 1991
32. Fogel MA, Boyd CD, Leardkamolkarn V, Abrahamson DR, Minto AWM, Salant DJ: Glomerular basement membrane expansion in passive Heymann nephritis. Absence of increased synthesis of type IV collagen, laminin, or fibronectin. *Am J Pathol* 138:465–475, 1991
33. Dubrulle MP, Terzi F, Gubler MC, Kleinknecht C, Schaeverbeke M: Changes in thickness and anionic sites of the glomerular basement membrane after subtotal nephrectomy in the rat. *Am J Pathol* 141:1481–1489, 1992
34. Imberti O, Foglieni C, Bogdan EI, Remuzzi G, Remuzzi A: An angiotensin converting enzyme inhibitor prevents proteinuria in MWF/Ztm rats and increases hydraulic permeability but does not modify basement membrane thickness and epithelial slit pore frequency. (abstract) *J Am Soc Nephrol* 3:740, 1992
35. Guasch A, Hashimoto H, Sibley RK, Deen WM, Myers BD: Glomerular dysfunction in nephrotic humans with minimal changes or focal glomerulosclerosis. *Am J Physiol* 260:F728–F737, 1991
36. Shemesh O, Ross JC, Deen WM, Grant GW, Myers BD: Nature of the glomerular capillary injury in human membranous glomerulopathy. *J Clin Invest* 77:868–877, 1986
37. Loon N, Shemesh O, Morelli E, Myers BD: Effect of angiotensin II infusion on the human glomerular filtration barrier. *Am J Physiol* 257:F608–F614, 1989
38. Oliver JD, Anderson S, Troy JL, Brenner BM, Deen WM: Determination of glomerular size-selectivity in the normal rat with Ficoll. *J Am Soc Nephrol* 3:214–228, 1992
39. Remuzzi A, Perico N, Amuchastegui CS, Malanchini B, Mazerska M, Battaglia C, Bertani T, Remuzzi G: Short- and long-term effect of angiotensin II receptor blockade in rats with experimental diabetes. *J Am Soc Nephrol* (in press)
40. Myers BD, Winetz JA, Chui F, Michaels AS: Mechanisms of proteinuria in diabetic nephropathy: A study of glomerular barrier function. *Kidney Int* 21:633–641, 1982
41. Golbetz H, Black V, Shemesh O, Myers BD: Mechanisms of the antiproteinuric effect of indomethacin in nephrotic humans. *Am J Physiol* 256:F44–F51, 1989
42. Remuzzi G, Bertani T: Is glomerulosclerosis a consequence of altered glomerular permeability to macromolecules? *Kidney Int* 38:384–394, 1990