Glomerular Permeability: New Concepts

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In a healthy person, the body's total blood volume passes through a complex system of glomerular capillaries more than 20 times each day in the essential process of selective filtration of plasma. One of the more remarkable characteristics of this physiology is that, although more than 7,000 g of plasma albumin flow past the filtering surfaces of the glomeruli, minute amounts of albumin escape through the capillary wall to appear in the urine. Thus, in a normal child the 24-hour urinary albumin excretion varies between 1.7 and 22.9 mg/day, demonstrating the remarkable selectivity of the glomerular filter. In healthy persons, the total urinary protein excretion, which is traditionally evaluated, is about 100 mg/m²/24h, and includes plasma albumin, a smaller amount of other plasma proteins, and a major component of proteins that originate from secretions of the kidneys and the urogenital tract. Urinary protein excretion may be increased in adolescents, after strenuous exercise, and during fever, emotional stress, and cold temperatures.

The nephrotic syndrome of childhood is a relatively common and very frustrating disease; multiple recurrences plague about 80% of patients and may continue into adult life.

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The anatomical structure and biochemical composition of the glomerular capillary walls ultimately determine the permeability of the capillaries to plasma proteins.

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The endothelial cell layer contains fenestrations (poles) of about 50 nm in diameter and its surfaces are coated with sialoproteins. The glomerular basement membrane (GBM) consists of a lucent subendothelial layer; the lamina rara interna (LRI); a central electron dense layer, the lamina densa (LD); and a lucent subepithelial zone, the lamina rara externa (LRE). In humans, the normal width of the GBM is about 250 to 300 nm. Relatively recent biochemical and immunochemical studies of the GBM have revealed its complex structural components, including unique collagens IV and V, large glycoproteins, laminin, fibronectin, and nidogen (entactin), acidic proteins such as amyloid P, and heparan sulfate proteoglycan. The precise arrangement of these constituents remains unclear. The most current accurate model presents a network of collagen filaments coated with laminin and nidogen, interacting with them, and extending into the lamina rara to interact with heparan sulfate proteoglycans and fibrinogen (Figure 2). Heparan sulfate proteoglycan molecules are arranged primarily in parallel rows within the LRE and LRI and have been demonstrated and quantitated by staining with positively charged (cationic) probes such as poly-ethyleneimine and cuproline blue (Figure 3). These cationic molecules are believed to contribute significantly to an electrostatic (charge) barrier of the GBM, which tends to inhibit negatively charged molecules of all sizes from passing through the GBM. Heparan sulfate molecules also interact strongly with collagen, laminin, and other constituents of the GBM; changes in their concentration or charge density may thus be critical to the maintenance of the size-selective as well as the charge-selective characteristics of the capillary wall. The heavy coating of the glomerular epithelial cell surfaces with a negatively charged sialic acid-rich glycoprotein (podocalyxin) (depicted in Figure 2) is also thought to contribute to the electrostatic filtration barrier function.

Recognition of the effect of interrelationships between molecular size, shape, and charge on the filtration of plasma proteins across the GBM have been largely derived from many outstanding studies using molecular probes of different size, shapes, and charge
Figure 1. Electron micrograph of a portion of a normal glomerular capillary. Note the epithelial cell foot processes (Fp) and the bridging filtration slit membrane (arrow-f). The glomerular basement membrane consists of the well-defined semilucent lamina rara externa (LRE), the homogenous lamina densa (LD), and a less well-defined inner lucent zone, the lamina rara interna (LRI). The endothelium (END) lines the lumen (L), and over much of the circumference is attenuated and contains fenestrations (arrows) of about 50 to 80 nm diameter (original magnification x100,000). Reproduced with permission from Kurtzman NA. Seminars in Nephrology 1986; 6(4):371-388.

Figure 2. Schematic diagram of the major structures and constituents of the glomerular capillary wall. The glomerular polyanion (GPA-podocalyxin) is represented over the surfaces of the epithelial and endothelial cells and the filtration slit membranes (FM). Heparan sulfate proteoglycan (HSPG) is distributed primarily in the lamina rara externa (LRE) and interna (LRI). Fibronectin (F) is thought by most investigators to be distributed primarily within the LRI. Collagen fibris (IV and V) are present primarily within the lamina densa (LD) but extend into the LRE and LRI where the fibrils may be coated with laminin (L) and HSPG. Reproduced with permission from Kurtzman NA. Seminars in Nephrology 1986; 6(4):371-388.

such as ferritin, dextrans, enzymes, etc. The studies have confirmed the concept of size selectivity of the glomerular filter and demonstrated, for example, that neutral dextran molecules of increasing molecular radius are progressively restricted in their transit across the GBM into the urine (Figure 4). A curiosity of the curve for filtration fraction of neutral dextrans was that about 15% of molecules with a radius of 35 Å were filtered. This was unexpected because, as described earlier, very little plasma albumin of a similar radius (35 Å) appears in the urine. An explanation was continued on page 596.


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The frequent recurrence of nephrotic syndrome in children following renal transplantation suggests that a circulating factor was involved.

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provided by the observation that the addition of negative charges to the dextran molecules (dextran sulfate), which does not affect molecular size, resulted in a striking change in the shape of the curve for fractional clearance (Figure 4, lower curve). The filtration of negatively charged dextran molecules was restricted at all molecular sizes, as compared with neutral dextran, and molecules of 36 Å and larger were totally restricted and did not appear in the urine. These data suggested that the GBM permeability of plasma albumin, which is negatively charged (isoelectric point 5.1), was modulated by negative charges within the membranes. These concepts have been amply confirmed in the past ten years.

What is the relevance of these observations in laboratory animals to the problem of proteinuria and nephrotic syndrome in children? The first suggestion that an alteration of GBM charges might be present in the nephrotic syndrome in humans resulted from fractional clearance studies of the tracer molecule polystyrene-polyvinyl pyrrolidone (PVP) by Robson et al.6 who compared normal and nephrotic children. They showed that when the molecular radius of each fraction of the PVP excreted in the urine was plotted against the glomerular clearance (simultaneously determined inulin clearance), small molecules had high clearances and larger PVP molecules were virtually excluded from the urine of normal children. Surprisingly, in nephrotic children, the relative clearance of PVP molecules, equivalent in size to albumin (radius about 35 Å) was not increased, but rather decreased, as compared with the controls. It was proposed that these findings were best explained by losses of anionic charges in the GBM in the primary nephrotic syndrome. Subsequent physiologic studies by Myer's group7 in adult patients with minimal change nephrotic syndrome, using fractional dextran clearances, have both confirmed and denied these early results. Their more recent studies suggest that changes in pore size within the GBM, an alteration of the size-selective barrier, were the more important abnormality occurring in the GBM in nephrotic patients8.

Morphologic cytochemical studies in one rare form of the nephrotic syndrome in infants (congenital nephrotic syndrome) support the concept of an alter-
nation of the charge barrier in this proteinuric state. It was shown that a marked decrease in the number of stained heparan sulfate proteoglycan molecules within the lamina rara externa of the GBM occurred in that condition, presumably as a consequence of decreased synthesis or of increased degradation of this material by the glomerular epithelial cells. Similar studies of kidney biopsy specimens from children with minimal change nephrotic syndrome have shown no change in the anionic sites in the GBM. Thus, the evidence suggests that there are several different mechanisms involved in the maintenance of the selective permeability barrier of the GBM and that multiple alterations may occur, which are expressed as albuminuria and clinical nephrotic syndromes.

The nephrotic syndrome of childhood is a relatively common and very frustrating disease; multiple recurrences plague about 80% of patients and may continue into adult life. In addition, a significant number of patients continue to die of complications, particularly overwhelming infection, and another significant population eventually develop renal failure. The pathogenic mechanism(s) involved remains unknown. The success of therapy with adrenocortical steroids, and cytotoxic agents such as cyclophosphamide, chlorambucil, and most recently cyclosporine suggested years ago that some alteration of cellular immunity might be involved in the pathogenesis of this disease. The frequent (20% to 30%) incidence of recurrence of nephrotic syndrome in children with the disease following renal transplantation suggested that a circulating factor was probably involved in at least some cases. Intense investigation has revealed many abnormalities of cellular immune system function in nephrotic patients, but the issue remains controversial. Recent studies by Schnaper et al., which have demonstrated the presence of a soluble immune
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response suppressor (SIRS) in both serum and urine of untreated nephrotic children, are particularly exciting. This substance or a similar lymphokine-like material could satisfy most of the requirements of the pathogenetic hypotheses proposed. However, there would remain the need to understand the mechanism by which such a lymphokine could in this disease suddenly alter glomerular permeability; and even more dramatically, through its reversal, allow repair and return of normal selective permeability within a few days, as is often observed clinically.

In spite of the remarkable advances made in understanding structure and function of the glomerular capillaries in recent years, it is clear that many unanswered questions remain that will continue to challenge investigators for many more years.

REFERENCES