Introduction

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While the nephrotic syndrome has been recognized for many years as a condition causing edema associated with coagulable protein in the urine, many of the widely held paradigms explaining the relationships between proteinuria, hypoalbuminemia, hyperlipidemia and edema formation that characterize this syndrome have been recently challenged or refined. Progress has been made toward clarification of the mechanism of glomerular injury that both cause, and possibly result from proteinuria. Likewise, knowledge pertaining to the physiologic effect of changed plasma protein composition that result both from the urinary loss of specific proteins as well as from increased plasma levels of other liver-derived proteins has been extended. This issue contains articles by several investigators who have contributed greatly to refining our understanding of pathophysiologic events that occur in the nephrotic syndrome and have developed data that challenge old paradigms.

The glomerular barrier normally consists of a log normally distributed group of pores that normally restrict passage of intermediate sized plasma proteins, mostly on the basis of size. The barrier may be at the sight of the

slit diaphragm. Electron microscopy reveals potential channels in this area that are of a size compatible with pore theory obtained by gel filtration of uncharged dextrans. Glomerular endothelial cells may play a key role in maintaining the integrity of this filtration barrier as well as the structure of the glomerular basement membrane. Injury occurs to the glomerular barrier as a consequence of a variety of immunologic and non-immunologic processes. Several of these are reviewed in the body of this symposium. Nonimmunologic processes, such as the interaction between lipoproteins and mesangial cells, may recruit immunologic processes, such as macrophages. Once glomerular endothelial cells are damaged, or their physical attachment to one another is disrupted, the area available for filtration is decreased, and the selective characteristics of the glomerular capillary is altered.

Glomerular proteinuria is a consequence of the development of a small number of nonselective shunts that allow the passage of proteins of between 40 and 200 kD into glomerular ultrafiltrate and is a consequence of a development of a size-selective defect in the glomerular filtration barrier. Hormonal changes,

including increased activity of angiotensin II and decreased kinin activity, occur as a consequence of alteration in dietary protein content or composition and increase the fraction of glomerular filtrate passing through the unselective shunt pathway. Dietary protein augmentation, while necessary for the liver to increase synthesis of albumin and other plasma proteins, causes further disruption in glomerular barrier function, possibly acting through these and other hormonal mediators.

Plasma proteins lost into the urine are those that are most important in maintaining plasma oncotic pressure (71) both because of their great abundance and their relatively low molecular mass. Although they are replaced by several high molecular weight proteins, plasma % drops considerably. Following the onset of proteinuria the kidney becomes unresponsive both to the

effects of atrial natriuretic factor and to salt loading, although the relationship between this unresponsiveness and proteinuria is not yet clear. As a consequence, plasma volume may expand despite reduced plasma oncotic pressure (n). Edema generally develops in the context of plasma volume expansion in the presence of reduced

plasma %, rather than as a consequence of renal sodium reabsorption being driven to defend a contracted plasma volume.

Proteins lost in the urine each have specific functions. Some are defended by increased synthesis, but others, such as erythropoietin and IgG, are not. Urinary protein loss may cause deficiency of specific vitamins and minerals normally bound to plasma proteins, anemia as a consequence of erythropoietin and transferrin loss, excessive blood coagulability as a consequence of the loss of small anticoagulant proteins, and other hormonal deficiency states. The homeostatic responses lead to increased blood viscosity and hyperlipidemia, also promoting coagulation and atherogenesis.

Low density lipoprotein and probably other lipoproteins whose plasma concentrations are elevated as a consequence of both increased synthesis in response either to reduced plasma % or albumin concentration and from a defect in their catabolism that follows the onset of proteinuria, may bind to mesangial cells causing disruption in their function and attract macrophages to them. Macrophages may also be drawn into the renal interstitium by metabolic breakdown products of catabolized plasma proteins or lipids. These and other immune cells further perpetuate renal injury by release of enzymes, reactive oxygen species, growth factors and lymphokines. Filtered proteins may also be directly toxic to glomerular endothelial cells further exacerbating the defect in permselectivity.

These new insights provide important information about current and potential future avenues of research and clinical practice. Edema may be safely handled in patients who are not plasma volume contracted, the majority of those with the nephrotic syndrome. Both proteinuria and hyperlipidemia may play an important role in mediating disease progression. Treatment of hyperlipidemia may in part require management of proteinuria. Elucidation of the mechanisms causing renal sodium retention, alteration in hepatic gene expression, development of methods to suppress secondary immunologic reactions that occur as a consequence of proteinuric disease, and pharmacologic control of the adaptive hemodynamic and hormonal reactions to renal injury will ultimately provide more adequate therapy to patients with this syndrome than are now available.