The extent of injury to the tubulointerstitial compartment has been recognized for several decades as closely linked to declining renal function in glomerular diseases. In addition to secondary inflammatory injury and ischemia as mechanisms of injury in the tubulointerstitium downstream from diseased glomeruli, proteinuria itself is now recognized as a pathogenic factor and an independent risk factor for the progression of kidney disease. Reduction of proteinuria is now a major therapeutic goal in reducing risk for renal progression. Current strategies to reduce proteinuria are largely focused on treatment of the underlying glomerular disease and by alteration of glomerular hemodynamics and filtration. With improved understanding of basic mechanisms of proteinuria-induced injury, however, more refined and proximate strategies based on molecular pathogenesis of proteinuria-induced tubulointerstitial injury may be possible.

The damaging effects of proteinuria on the renal tubulointerstitial compartment involve a variety of mechanisms. These include tubular cell toxicity, when the lysosomal capacity to degrade proteins reabsorbed in excess by the tubules is overwhelmed, the downstream exposure to chemokines in tubular fluid, or the expression of surface neo-antigens and adhesion molecules with proinflammatory action. In addition, tubular epithelial cells respond to exposure to filtered serum proteins, as to other forms of injury, by undergoing epithelial-to-mesenchymal transition (EMT), with reduction of epithelial phenotype and functions and induction of increased cell motility and matrix production. Transition toward a mesenchymal phenotype has been demonstrated in epithelial and endothelial cells by in vitro as well as in vivo studies and is recognized as an important contributor to the development of fibrosis, not only in the kidney but also in lung and liver. The mechanisms involved in proteinuria-induced EMT in renal tubular cells have not been clearly identified.

As an important component of innate immunity, the complement system is activated in proteinuric states. Tang et al. in this issue of JASN examine the clinical and experimental evidence that complement activation plays a role in tubulointerstitial injury and dysfunction during proteinuria. Existing data suggest roles for both the membrane attack complex, C5b-9, and the anaphylotoxin C5a in injury and dysfunction in proteinuric states. There is also recent evidence that C3- or C5-deficient mice have reduced EMT in models of proteinuria.

The elegant studies by Tang et al. provide a new focus on another complement activation product, the anaphylotoxin C3a, and its role in altering proximal tubular epithelial cell (PTEC) phenotype in vitro and presumptively in vivo. The HKC-8 in vitro cell system is capable of activating complement and undergoing EMT on exposure to serum C3a but not C5b-9. An antagonist of the C3a receptor expressed on the cells inhibits the effect and blocks an increase in the mRNA encoding collagen I. The antagonist also blocks EMT and collagen I–induced by exposure to serum. Extending these observations in vivo in an adriamycin model of proteinuria, C3a receptor null mice develop less albuminuria, lower mortality, and less severe renal failure compared with wild-type mice. C3aR null mice also have less glomerular injury and less severe tubulointerstitial disease, as measured by tubular diameter/cell height ratio and interstitial volume, with less interstitial collagen and fewer myofibroblasts and macrophages.

Although in vitro evidence of C3aR-mediated injury induced by proteinuria in human renal proximal tubular cells reported by Tang et al. is compelling, it is difficult to define the role of complement and C3a directly at the level of the tubular epithelium in the in vivo studies, because glomeru-
Salivary Phosphorus Binding: A Novel Approach to Control Hyperphosphatemia

Garabed Eknoyan
Renal Section, Department of Medicine, Baylor College of Medicine, Houston, Texas


Hyperphosphatemia as a complication of chronic kidney disease (CKD) was recognized nearly a century ago. The central role of altered phosphate metabolism in CKD as a cause of secondary hyperparathyroidism and renal osteodystrophy was exposed as part of the elegant experimental studies that provided the basis of the “intact nephron hypothesis.” The association of high serum phosphorus levels and increased mortality of patients with ESRD first noted in 1990 has since been confirmed and extensively studied. There is now considerable evidence, convincing on balance, that elevated serum phosphorus levels are a surrogate marker of cardiovascular disease (coronary, aortic, valvular, and vascular calcification) and hard clinical outcomes (cardiovascular and all-cause hospitalization and mortality) in CKD. Accrued evidence on the systemic complications of altered phosphate homeostasis in CKD has led to the proposal of a new syndrome of mineral and bone disorders (MBD) of CKD, termed CKD-MBD, which encompasses biochemical alterations, bone abnormalities, and vascular calcification. Renewed interest in the detrimental consequences of elevated serum phosphorus and the difficulties of its management in CKD has become the center of much recent debate and controversy fueled, at least in part, by the pharmaceutical industry.

Approximately two thirds of the daily phosphorus intake is absorbed in the small intestines, and normal phosphorus homeostasis is maintained by its subsequent appropriate excretion by the kidney. With decreasing kidney function, the initial adaptive changes for maintenance of normal serum phosphorus gradually become restricted, and hyperphosphatemia occurs at GFR of <30 ml/min per 1.73 m². Available treatments for the control of phosphorus in CKD are restriction of dietary phosphorus intake, the use of phosphorus binders, and in ESRD the increased duration and frequency of dialysis. The dietary control of phosphorus has been difficult and implicated in contributing to mal-

See related article, “C3a Mediates Epithelial-to-Mesenchymal Transition in Proteinuric Nephropathy,” on pages 593–603.