# This Month's Highlights

## Cell and Transport Physiology

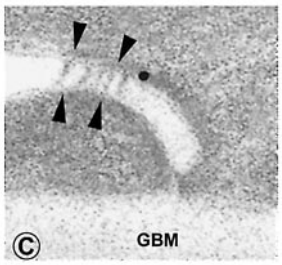
*Role of NHERF-1 in Regulation of the Activity of Na-K ATPase and Sodium-Phosphate Co-transport in Epithelial Cells*

**Why Does Parathyroid Hormone Affect Tubular Functions Like Acidification?** Some years ago, Weinman's group purified a novel protein they called sodium-hydrogen exchanger regulatory factor (NHERF). NHERF is now known to be part of a gene family (NHERF-1 and NHERF-2) of docking proteins that assemble multi-protein signaling complexes, including ezrin, the Na/H exchanger present at the proximal tubule apical membrane (NHE3), and protein kinase A through their multiple PDZ domains. These protein-signaling complexes facilitate the phosphorylation of NHE3 by activated PKA, thereby inhibiting its activity. This is a general phenomenon insofar as biochemical association of CFTR with the NHERF PDZ1 domain has also been reported by several groups, and the importance of this interaction for apical sorting of CFTR in polarized epithelia has been demonstrated. In this issue, Weinman's group extends the reach of NHERF-1 by showing that it is also needed for PTH-mediated phosphorylation of Na/K ATPase, but the mechanism for retrieval of the phosphate transporter NaPi IIa from the apical membrane in response to cAMP does not require NHERF. **Page 1711**

## Hormones, Growth Factors, Cell Signaling, Cell Biology and Structure

*A Novel Protein, Densin, Expressed by Glomerular Podocytes*

**A Brain Protein Densin Now Shows up in the Podocyte: Is Nephrotic Syndrome a Thought Disorder?** The discovery that congenital nephrotic syndrome is due to a mutated podocyte-specific protein nephrin launched a new era of focus on the podocyte and its proteins in the pathogenesis of glomerular diseases. The paper by Holthofer *et al*. in this issue of *JASN* represents the latest in the series of new podocyte proteins discovered that have stimulated and sustained this area. Using a mass fingerprint analysis technology, they discover that proteins precipitated by anti-nephrin antibodies include densin, a molecule previously localized only in the brain. Densin seems linked to nephrin in the podocyte. In the brain, densin seems important in cell adhesion, polarity, and shape, all functions important in normal podocyte physiology and altered in glomerular diseases. It seems likely that densin plays a role in maintaining glomerular barrier function, which is altered when a plethora of antibodies, permeability factors, and cytokines interact with still unknown targets on the podocyte. Densin may well be one of these — stay tuned! **Page 1731**




## Hemodynamics, Hypertension and Vascular Regulation

*Chymase Is Upregulated in Diabetic Nephropathy: Implications for an Alternative Pathway of Angiotensin II–Mediated Diabetic Renal and Vascular Disease*

**Inhibition of ACE May Not Be Good Enough in Diabetic Nephropathy.** There is no doubt that in clinical and experimental diabetic nephropathy AngII plays a crucial role in the genesis of renal damage. What is less certain, however, is the pathway through which AngII is generated within the kidney. While an important role in cardiovascular research has been amply documented for chymase, an AngII-generating enzyme that is not inhibited by ACE inhibitors, its role in renal disease had remained elusive. In the study of Huang *et al.*, chymase antigen was markedly overexpressed in the kidneys of diabetic patients, particularly those with concomitant hypertension. Although information on renal chymase activity is not given, the data are suggestive of an important role of chymase. If this hypothesis is correct, it does have important clinical implications, because ACE inhibitors (ACEi) do not abrogate chymase-dependent generation of AngII. Angiotensin receptor blockers or even the combination of ACEi and ARB would then be the answer. On the horizon are specific chymase inhibitors that may open further novel and fascinating therapeutic alternatives. **Page 1738**

## Molecular Medicine, Genetics and Development

*Autosomal Dominant Progressive Nephropathy with Deafness: Linkage to a New Locus on Chromosome 11q24. and*

*Identification of the First Gene Locus (SSNS1) for Steroid-Sensitive Nephrotic Syndrome on Chromosome 2p*

**Mapping Genes for Nephrotic Syndrome.** Since mutations of the nephrin gene were identified five years ago as the cause of congenital nephrotic syndrome of the Finnish type, there has been steady progress in the mapping and cloning of additional genes responsible for inherited nephrotic syndrome. Mutations of podocin, $\alpha$-actinin-4, and a second FSGS locus on chromosome 11 have been identified. In this issue of *JASN*, two new studies illustrate the continued progress in this field. In a Brief Communication, Ruf *et al.* describe the mapping of a locus for steroid-sensitive nephrotic syndrome. This group had previously reported 15 families with autosomal recessive nephrotic syndrome in which renal biopsies showed minimal change disease. By performing linkage analysis in a single consanguineous family, they were able to map the disease gene to the short arm of chromosome 2. The same gene locus appears to be involved in two additional families. Prakash *et al.* identify a new syndrome of autosomal dominant nephropathy with sensorineural hearing loss. Affected individuals present with hematuria, proteinuria, hypertension, and variable degrees of renal failure. Interestingly, the renal biopsies show characteristics of both FSGS and Alport syndrome. Linkage analysis of 39 members of a single family excluded the known nephrotic syndrome genes and identified a new locus on the long arm of chromosome 11. Although neither of the disease genes has been cloned, their eventual identification promises to advance our understanding of glomerular biology and the pathogenesis of nephrotic syndrome. **Page 1897 (Ruf *et al.*) and 1794 (Prakash *et al.*)**

## Pathophysiology of Renal Disease

*Induction of Renoprotective Gene Expression by Cobalt Ameliorates Ischemic Injury of the Kidney in Rats*

**Hypoxia: Could It Paradoxically Be Beneficial to the Kidney?** Despite the high proportion of cardiac output going to the kidney, the renal cortex has paradoxical areas of hypoxia and is uniquely sensitive to hypoxia/ischemia. Recently, following work on how EPO gene expression is regulated, the molecular mechanisms underlying the cellular response to hypoxia have been clarified. Hypoxia induces hypoxia-induced factor (HIF)-1$\alpha$, the concentration of which is the result of synthesis and degradation via von Hippel Lindau factor. Degradation is inhibited by cobalt. Matsumoto *et al.* pretreated rats with cobalt and found increased expression of hypoxia-induced genes such as EPO, Glut-I, and VEGF. Animals thus pretreated had strikingly better renal function after an episode of ischemia induced by renal artery clamping. Although actions of cobalt other than those on HIF-1$\alpha$ are not definitively excluded, the results may provide a window to understand how renal tissue protects itself against ischemic injury. This observation may have potential implications for cadaver kidney donation, acute renal failure, and possibly even progression of chronic renal disease. **Page 1825**

## Clinical Nephrology

*Rituximab in Idiopathic Membranous Nephropathy: A One-Year Prospective Study*

**A New and Less Toxic Therapy for Idiopathic Membranous Nephropathy? Maybe!** Despite its frequency and the multiple treatment trials in idiopathic membranous nephropathy, therapy remains imperfect and therefore controversial. The disease is believed to be mediated largely by humoral antibody/complement mechanisms. If so, a therapy that selectively targets antibody-producing B cells should be more effective and less toxic than conventional cytotoxic drug therapy. In this paper, Ruggenenti *et al.* pilot test that hypothesis by treating eight patients with idiopathic membranous nephropathy with four weekly infusions of a monoclonal antibody that depletes B cells, and they then compare them with untreated controls for 12 months. The treated patients generally did dramatically better in terms of proteinuria, progression, and renal function without significant side effects. Of course, this study is too small to provide strong evidence for the efficacy of rituximab, which was not compared with better-established therapies such as steroids/cyclophosphamide or cyclosporine. Its value is that it provides provocative data to support the conduct of the larger studies that need to be done to confirm this pilot. But in this particular disease, any promise of a new and better approach is exciting. **Page 1851**

## Dialysis

*Impact of Dialysis Dose and Membrane on Infection-Related Hospitalization and Death: Results of the HEMO Study*

**If High-Dose or High-Flux Help, It's Not by Reducing Infectious-Related Mortality.** Observational studies have suggested that higher dialysis dose and use of high-flux membranes are associated with a lower probability of infection. Allon *et al.* report, from the randomized clinical HEMO trial, that neither infection-related mortality nor infection-related hospitalization are decreased in patients allocated to either high-dose or high-flux treatments. The evidence is particularly strong for the dose

variable, where the RR of infection-related death was 0.99. On the other hand, the RR was 0.85 in the high-flux group with a 95% CI (0.64 to 1.13). The study had an 84% statistical power to detect a 25% decrease in total mortality. The power to detect a similar decrease in infection-related deaths is less, and the results should be interpreted accordingly. **Page 1863**

## Epidemiology and Outcomes

*Is a Single Time Point C-Reactive Protein Predictive of Outcome in Peritoneal Dialysis Patients?*

**Beware the Patient with Even One Elevated CRP.** The association of inflammation with decreased survival of patients with kidney failure has become well known. The serum concentration of CRP is often used as an estimate of the current inflammatory state. Despite variability in this estimate in individuals over time, Wang *et al.* have demonstrated that even a single time point estimate of CRP is predictive of outcome in peritoneal dialysis patients in Hong Kong. Using multivariate statistical techniques to control for other important prognostic variables, they found that even a 1-mg/L increase in highly sensitive CRP was associated with a 2% increase in all-cause and a 3% increase in cardiovascular mortality. **Page 1871**

## Transplantation

*Association of the Multidrug Resistance-1 Gene Single-Nucleotide Polymorphisms with the Tacrolimus Dose Requirements in Renal Transplant Recipients*

**Pharmacogenomics and Immunosuppression in Renal Transplant Recipients.** This study correlates a specific MDR1 gene single-nucleotide polymorphism (SNP) with tacrolimus pharmacokinetics in renal transplant recipients. The study was based on the fact that P-glycoprotein (P-gp), the product of the multidrug-resistance-1 (MDR1) gene, controls tacrolimus intestinal absorption. The authors studied the effect of four frequent SNPs of the MDR1 gene on tacrolimus pharmacokinetics in renal transplant recipients. At one month after introduction of the drug, they found that exon 21 SNP correlated significantly with the daily tacrolimus dose and the concentration/dose ratio. Tacrolimus dose requirements were 40% higher in homozygous than wild-type patients for this SNP. The concentration/dose ratio was 36% lower in the wild-type patients, suggesting that, for a given dose, the tacrolimus blood concentration is lower. If the results are confirmed in large prospective clinical trials and potentially expanded to other immunosuppressive drugs, such genotyping studies may in the future have applicability in individualizing immunosuppressive therapy for renal transplant recipients. **Page 1889**