**This Month’s Highlights**

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

*Stimulation of Proximal Tubule Cell Apoptosis by Albumin Bound Fatty Acids Mediated by Peroxisome Proliferator Activated Receptor*

**Tubulotoxic Effects of Proteinuria: The Lipid Connection Is Strengthened.** There is currently little doubt that sustained high-grade proteinuria has damaging renal effects. While the mechanisms involved continue to unfold, a link between proteinuria-induced tubular responses and interstitial inflammation has been documented. Several years ago, studies by Kees-Folts and Schreiner implicated protein-bound fatty acids in this cascade. In the study reported by Arici *et al.*, an important relationship is documented between fatty acid–bearing albumin and tubular cell apoptosis. This effect appears to be mediated through activation of the peroxisome proliferator-activated receptor gamma (PPARγ), which is a nuclear receptor that initiates gene transcription following ligand-dependent activation. Fatty acids are known to be PPARγ ligands. Since the important structural connection between tubulointerstitial disease and renal insufficiency is tubular destruction, the ability of albumin-bound fatty acids to activate PPARγ and initiate apoptosis in proximal tubular cells could represent an important pathophysiologic pathway. Furthermore, this study gives cause for some reflection about the consequences of pharmacologic use of PPARγ agonists in the treatment of type II diabetes. Much more clearly remains to be learned about the effects of PPARγ and its activation by various ligands within the kidney.

**Immunology and Pathology**

*Cloning of Rat Homologue of Podocin: Expression in Proteinuric States and in Developing Glomeruli*

**Another Step Closer to Defining a Functional Role for Podocin in Diseases of the Podocyte.** Podocin is mutated in humans with autosomal recessive and sporadic forms of steroid-resistant nephrotic syndrome. Podocin is a membrane protein that has been found to be part of a large macromolecular complex that also contains nephrin, CD2AP, and other proteins important in podocyte function. Kawachi *et al.* cloned rat podocin and studied its expression in animals with experimental glomerulonephritis. Rats are particularly useful for such studies because the administration of puromycin or anti-nephrin antibodies produces a lesion resembling human minimal change disease with proteinuria. In normal rats, podocin was located in the podocyte foot processes near the slit diaphragms, which are the major barrier to glomerular filtration. However, in rats with proteinuria, podocin was redistributed to the cytoplasm. These results suggest that the localization of podocin near the slit diaphragms is important for maintaining the integrity of the glomerular filtration barrier. Interestingly, podocin was also found in the brain, where it may be involved in maintaining the blood-brain barrier.

*Membrane Expression of Proteinase 3 Is Genetically Determined*

**If ANCA Is Pathogenic, How Come Disease Activity Doesn’t Correlate Well with Antibody Levels?** Although the role of ANCA in renal vasculitides such as Wegener’s is still controversial (See editorial by Falk, *J Am Soc Nephrol* 13: 1977–1979, 2002), the proposed mechanism for its pathogenicity involves binding to neutrophil membrane–expressed antigens such as PR3 and MPO, inducing neutrophil localization and activation in the microcirculation. However, disease expression is quite variable and not well correlated with ANCA antibody levels. In this issue of *JASN*, Kettridge *et al.* test the hypothesis that it is genetically determined membrane expression of the ANCA antigens that accounts for this variability rather than antibody levels. They report significantly higher expression of PR3 on neutrophil membranes in patients with Wegener’s compared with normal patients and good evidence that this expression is genetically determined. No attempt is made to correlate membrane antigen expression with disease activity, but the results do add another factor to our understanding of the role of ANCA in disease and may provide a useful clinical marker of disease activity or susceptibility.
Molecular Medicine, Genetics and Development

Spectrum of Mutations in the Gene for Autosomal Recessive Polycystic Kidney Disease

New Mutations that Cause Polycystic Kidney Disease. Autosomal recessive polycystic kidney disease (ARPKD) is a genetic disorder that produces renal failure in infants and children. ARPKD is caused by mutations of the PKHD1 gene located on chromosome 6. The international ARPKD Consortium here reports 34 new mutations found by screening 90 ARPKD patients. Their study effectively doubles the number of known mutations of PKHD1 and permits some preliminary genotype-phenotype correlations. The rate of detection of mutations is only 61%, which is probably due to the enormous size of the gene and the insensitivity of SSCP analysis. Mutations were found throughout the gene. However, a missense mutation in exon 3 that changes a threonine to a methionine was identified in multiple unrelated individuals, indicating that it represents a mutational hotspot. Individuals who carried two mutations that truncated the PKHD1 protein died shortly after birth, whereas individuals with missense mutations had less severe disease. The results suggest that complete loss of PKHD1 produces severe disease and that missense mutations may produce partially functional protein.

Pathophysiology of Renal Disease

Crystal Retention Capacity of Cells in the Human Nephron: Involvement of CD44 and its Ligands Hyaluronic Acid and Osteopontin in the Transition of Crystal-Binding into a Nonadherent Epithelium

Once Calcium Crystals Form, Why Do They Stick to Cells to Make a Stone? In medieval times, bladder stones were removed by a method called “Celsan,” after Celsus’ description in De Medicina. We are still, to some extent, in the Dark Ages when it comes to the pathophysiology of idiopathic calcium nephrolithiasis. We do know that hypercalciuria may result from genetic mutations altering tubular function and that hyperoxaluria may cause supersaturation and oxidative stress on tubular cells. Natural inhibitors, such as bikunin and osteopontin, modulate crystallization and may also be involved in crystal attachment to cells. In this issue, Verhulst et al. use primary cultures of human proximal and collecting duct cells to examine the factors responsible for attachment of calcium oxalate monohydrate (COM) crystals. Their results suggest that crystal retention may occur by calcium binding to CD44, osteopontin, and hyaluronidase that would be preferentially expressed on the surface of damaged human proximal tubule cells, although other studies (see below) identify a role for osteopontin in protecting from calcium crystal formation. The implication is that tubular damage causes stones, and stones cause tubular damage.

Mineral Metabolism and Bone Disease

Osteopontin Is a Critical Inhibitor of Calcium Oxalate Crystal Formation and Retention in Renal Tubules

A Natural Inhibitor of Calcium Stone Formation Lives up to Its Promise. Osteopontin is a multifunctional macromolecule that is secreted by most cells and involved in a diversity of biologic processes. In the kidney, OPN from tubular cells has been implicated as a chemoattractive molecule in interstitial cellular infiltrates and progressive fibrosis in several renal diseases. However, before its role in inflammation was discovered, OPN was known to be a potent inhibitor of calcium crystal formation in vitro. In this study, Wesson et al. make use of an OPN knockout mouse made hypoxaluric with ethylene glycol to document a clear and powerful role for OPN in protecting the kidney tubules from calcium crystal formation in vivo. This is the first study to clearly establish the renoprotective role of OPN in renal stone formation in intact animals and suggests possible new approaches to stone disease involving modulation of OPN expression in the kidney.
Dialysis

Cardiac Valve Calcification as an Important Predictor for All-Cause Mortality and Cardiovascular Mortality in Long-Term Peritoneal Dialysis Patients: A Prospective Study

Cardiac Calcification — A Predictor of High Mortality in Dialysis Patients. Calcification of coronary arteries and the aorta of ESRD patients, detected by electron beam computed tomography, has focused attention on the prevalence and consequences of deposition of calcium in soft tissues and in cardiac valves. In this study, Wang et al. have reported on these phenomena in prevalent peritoneal dialysis patients in Hong Kong. Among 192 patients (mean duration of peritoneal dialysis; 39 mo), 62 patients (32%) had calcification of either the aortic or mitral valves or both. The one-year survival was 70% and 93% for those with and without calcification. The RR of all-cause mortality and cardiac mortality were 2.50 and 5.39, respectively. Those with cardiac calcification also had a higher prevalence of atherosclerotic disease than those without calcification (44% versus 29%). Those with both valvular calcification and atherosclerosis had a much higher mortality rate than did those with one complication only or with neither complication. The mechanism does not appear to be due to the direct effect of valve stenosis or insufficiency. The role of atherosclerotic disease is probably not different than that in the general population, whereas that associated with valvular calcification may be associated with a more general process of vascular calcification, leading to less compliant blood vessels, higher pulse wave velocity, and death due to the adverse cardiac effects of these hemodynamic factors. On the other hand, both might be related to an unidentified confounder. In any case, further research is required to address this prevalent condition, which is predictive of poor survival.

Epidemiology and Outcomes

Kidney Transplantation in the Elderly: A Decision Analysis

More Cadaver Kidneys Are Going to Elderly Recipients — But Is This a Good Idea? The rate of cadaveric and living kidney donation increased over the past decade in the United States from 10,418 in 1990 to 13,590 in 1999. Despite the 30% increase in graft donation, this represents an overall decline in graft availability from one kidney for every five incident patients in 1990 to one for every seven patients in 1999. Furthermore, the allocation of donated kidneys to individuals aged 60 years and older increased from 9% to 23% of available kidneys. The article by Jassal et al. in this issue of JASN is an important contribution to the evaluation of the appropriateness of this increased allocation of kidneys to older recipients. The authors conducted a decision analysis to examine the cost-benefit tradeoff of allocation of cadaveric kidney transplantation for elderly individuals and found that the cost of extended life expectancy, measured by “quality-adjusted years” was favorable between 65 and 80 years of age. As pointed out by the authors, this finding establishes only one of the boundaries of an assessment of the appropriateness of organ allocation to elderly individuals.

Cancers of the Kidney and Urinary Tract in Patients on Dialysis for ESRD: Analysis of Data from the United States

The Risk of Urinary Tract Cancer Is Increased in ESRD Independent of Acquired Renal Cysts. Stewart et al. have analyzed the risk of kidney and bladder cancer in over 800,000 ESRD patients followed by the USRDS, EDTA, and ANZDATA renal registries. The authors report substantially increased risk for both cancers compared with the general populations of the three regions. This report confirms previous observations, and it is an important illustration of how data from the multiple population-based registries throughout the world can be used to identify important associations. For example, the authors report substantial heterogeneity of cancer risk across primary causes of renal disease, raising the possibility that disease-specific factors rather than factors common to ESRD, like acquired cystic disease of the kidney, may be responsible for the increased occurrence of kidney cancer in these patients.
Transplantation

Kidney Allograft and Patient Survival in Type I Diabetic Recipients of Cadaveric Kidney Alone Versus Simultaneous Pancreas/Kidney Transplants: A Multivariate Analysis of the UNOS Database

Does Simultaneous Pancreas Transplantation Improve Renal Survival in Type I Diabetic Patients? Apparently Not. The manuscript by Bunnapradist et al. reports data based on registry data analysis examining the outcome of renal allografts in two groups of type I diabetic recipients: recipients of kidneys alone or recipients of simultaneous pancreas transplantation (SPK). The results show that SPK was associated with better renal allograft survival as compared with kidney alone, despite a higher rate of renal allograft rejection in the SPK group. This observation was explained by favorable donor and recipient factors in the SPK group. After controlling for these factors, SPK provided no protective or detrimental effect on renal allograft or patient survival. The study is important because it provides hard evidence that, when circumstances of retrieval and distribution are taken into account, short-term renal allograft outcomes for type I diabetic recipients are not different in kidney alone versus kidney-pancreas transplant recipients. These data are helpful for nephrologists and transplant surgeons because they help in planning the best strategy for renal replacement in diabetic patients.