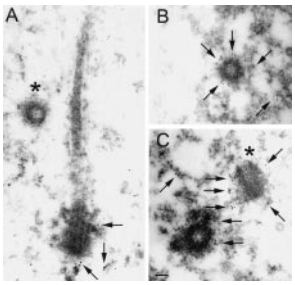
This Month's Highlights

BASIC SCIENCE

Genetics and Development



The Autosomal Recessive Polycystic Kidney Disease Protein Is Localized to Primary Cilia with Concentration in the Basal Body Area

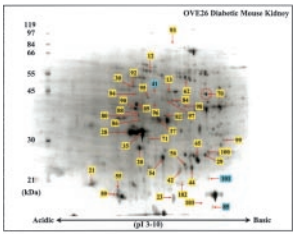
Localization of the ARPKD Protein in Renal Cilia. Autosomal recessive polycystic kidney disease (ARPKD) produces renal failure in infants and children and is caused by mutations of PKHD1. PKHD1 encodes a large membrane protein called fibrocystin (or polyductin). The function of fibrocystin is not known, but its structure resembles cell surface receptors. Wang *et al.* produced antibodies against fibrocystin and localized the protein in the primary cilia of renal epithelial cells. Fibrocystin was located along the shaft of the cilia and was concentrated in the region of the basal body, which anchors the cilia in the cell. These results are interesting because polycystin-1 and polycystin-2, the proteins that are mutated in autosomal dominant PKD, are also located in renal cilia. Cilia are hairlike organelles that project from the apical cell surface into the tubule lumen. They are believed to function as mechanosensors of urine flow that regulate renal cell proliferation and differentiation. Together with a recent study from Ward *et al.*, this study supports the hypothesis that abnormalities of ciliary function cause both dominant and recessive forms of PKD. *Page 592*

Immunology and Pathology

Lymphatic Neoangiogenesis in Human Kidney Transplants Is Associated with Immunologically Active Lymphocytic Infiltrates

Lymphatic Neoangiogenesis: A New Concept in Allograft Rejection. Kerjaschki *et al.* present evidence to demonstrate a novel mechanism by which formation of new lymphatic vessels may play a role in human kidney allograft rejection. It is highly significant that the proliferating lymphatic vessels, characterized by Ki-67 and podoplanin double immunolabeling, are associated with nodular (infiltrates) of mononuclear leukocytes. Moreover, the investigators show that these mononuclear infiltrates are positive for the chemokine CCR7. Immunoelectron microscopy localized SLC/CC21 (a ligand for CCR7) and podoplanin in close proximity on lymphatic endothelial cell membrane. Since recombinant SLC/CC21 binds to immobilized podoplanin protein, the investigators propose that this complex can induce a local inflammatory response by attracting CCR7-positive monocytes, thereby leading to cellular rejection. If substantiated, this injury process underlying rejection may be amenable to specific therapeutic intervention. *Page 603*

Pathophysiology of Renal Disease and Progression

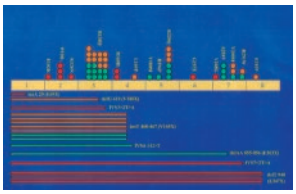


Alterations in the Renal Elastin-Elastase System in Type 1 Diabetic Nephropathy Identified by Proteomic Analysis

Proteomic Analysis of Diabetic Kidneys. The investigators have compared kidney protein expression levels between normal and diabetic mice by MALDI-TOF on a small number of samples. Proteomic approaches are an important emerging technology and hold promise for identification of new disease mechanisms. These are technically demanding and resource intensive studies, and it continues to be an interpretative issue in studies such as these as to whether small sample sizes permit differentiation between normal, stochastic variation in expression of specific molecules and variation that represents biologically or pathogenetically important differences. The significance of the increase in elastin expression and variation of elastase and elastase inhibitor expression identified in this study will need to be established in subsequent studies. In any case, this study may serve as a resource for comparison to other proteomes from normal and diseased kidneys. *Page 650*

CLINICAL SCIENCE

Human Genetics

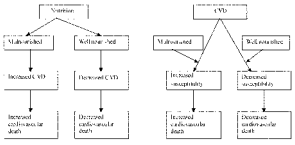


Patients with Mutations in NPHS2 (Podocin) Do Not Respond to Standard Steroid Treatment of Nephrotic Syndrome

Is It Time to Genotype All Patients with FGS before Treatment? This paper is an elegant illustration of the rapid movement from "bench to bedside" in podocyte biology. The discovery of mutations in nephrin, a slit diaphragm protein, as the underlying cause of congenital nephritic syndrome a few years ago has stimulated an era of renewed interest in the podocyte in glomerular diseases, a topic we reviewed in *JASN*'s December 2002 installment of Frontiers in Nephrology.

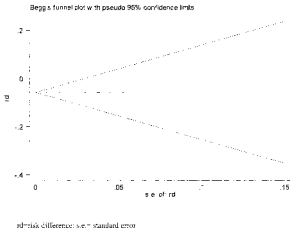
What followed was the discovery of a whole series of new, podocyte-specific proteins and attempts to link mutations in these to nephrotic syndrome. One such protein is podocin. Thongboonkerd *et al.* report that about 25% of patients with steroid-resistant FGS exhibit mutations in the gene for podocin, which correlates well with failure to respond to immunosuppressive therapy and failure to recur in transplants, clearly differentiating these patients from the typical treatment-resistant patients with idiopathic FGS that is believed to be caused by a lymphocyte-derived circulating permeability factor. This result not only clarifies the pathogenesis of what is apparently a fairly common form of FGS, but it also raises the obvious question of whether we should be genotyping patients with FGS before even considering therapy. This question is discussed in more detail in an accompanying editorial by Niaudet later in this issue. *Page 722*

Epidemiology and Outcomes



Malnutrition and Atherosclerosis in Dialysis Patients

Another Strike against Malnutrition as the Link between Low Albumin and Mortality in Dialysis Patients. It has been hypothesized that inflammation is a risk factor that is associated with increased risk of malnutrition and atherosclerosis among patients with CKD, termed the MIA hypothesis. Beddhu *et al.* tested this hypothesis by examining the association between markers of malnutrition at the inception of renal replacement therapy, low BMI and urinary creatinine excretion, and cardiovascular morbidity and mortality among over 50,000 incident hemodialysis and peritoneal dialysis patients. Interestingly, while both measures were associated with increased risk of all-cause mortality, the authors found, after controlling for multiple confounders including baseline serum albumin, no association between risk of cardiovascular disease and low BMI and only a weak association among individuals in the lowest quartile of urinary creatinine excretion. A low BMI was noted among nearly 8% of the cohort. Given the size of the cohort and the relatively high prevalence of low BMI, this is an unexpected result and it challenges the malnutrition component of the MIA hypothesis. Of note, the authors report that mean urinary creatinine excretion but not serum albumin increased as BMI increased from <18.5 kg/m^2 (low) to 18.5 to 24.9 kg/m^2 (normal) and then to ≥ 25 kg/m^2 (high). Since low serum albumin is an inflammatory as well as a nutritional marker, the lack of a strong association between BMI and serum albumin suggests that individuals with increased levels of inflammatory burden may have been present in each BMI group. As noted by the authors, these findings warrant further investigation into the independent contributions of inflammation and malnutrition to the risk of atherosclerotic cardiovascular disease among dialysis patients. *Page 733*



N-Acetylcysteine for the Prevention of Radiocontrast-Induced Nephropathy: A Systematic Review of Prospective Controlled Trials

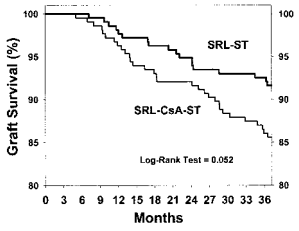
N-Acetylcysteine for Contrast Nephropathy? Maybe Not. Kshirsagar *et al.* report a meta-analysis of the current evidence that N-acetylcysteine prophylaxis for radio contrast nephropathy is beneficial. On the basis of their analyses, the authors report that the supporting evidence for its use is scant at best. We increasingly expect our primary care colleagues to identify early chronic kidney disease and to implement appropriate measures to preserve renal function, including managing the renal risks attendant to contrast radiography. As a consequence, nephrologists in community practice can expect increasing inquiries from primary care physicians and radiologists about the stratification of risk and prevention of contrast-related nephropathy. On the basis of the results of Kshirsagar *et al.*, unequivocal evidence-based recommendations for the routine used of N-acetylcysteine cannot be made at present. One implication of these results, as noted by the authors, is that further research is needed. As recently pointed out by Strippoli *et al.*, the production of clinical trials in nephrology may lag behind that of other medical subspecialties. An accompanying editorial by de Zeeuw and de Graeff pointed out the important role that clinically relevant questions have in generating new clinical trials. Surely the need to provide a firm basis for the evidence-based management of contrast-related nephropathy among the growing population of patients with chronic kidney disease meets that standard. *Page 761*

Mineral Metabolism and Bone Disease

Calcium, Phosphate, and Parathyroid Hormone Levels in Combination and as a Function of Dialysis Duration Predict Mortality: Evidence for the Complexity of the Association between Mineral Metabolism and Outcomes

Calcium, Phosphate, and PTH: How to Do the Numbers. This timely article addresses the methodologic problems presented in evaluating the possible causal associations of disordered calcium, phosphorus, and parathyroid hormone metabolism with clinical outcomes in dialysis patients. Consideration of each of these variables individually has produced conflicting results. In this article, the association of the eight possible high/low combinations of these three variables and the confounding effect of duration of time on dialysis on patient survival are presented in a detailed multivariable analysis. *Page 770*

Transplantation



Long-Term Benefits with Sirolimus-Based Therapy after Early Cyclosporine Withdrawal

Looks Like Early Calcineurin Replacement with Rapamycin May Improve Long-Term Graft Survival. Since 1995, several new drugs have been approved for maintenance immunosuppression to prevent allograft rejection in renal transplant recipients. While these drugs have resulted in significant reduction of acute rejection rates, it has so far been unclear whether they will result in improved long-term graft function and survival. Kries *et al.* report the results of a 3-yr follow-up of the original rapamycin-cyclosporine withdrawal study (Johnson *et al.*: *Transplantation* 72: 777–786, 2001). They show that graft function, as measured by calculated GFR and slope of GFR, continues to be better in the group receiving rapamycin that had cyclosporine withdrawn 3 mo posttransplant. More interestingly, graft survival appeared to be trending toward better in the cyclosporine-withdrawal group. With the caveat that more long-term data are required, these results are perhaps the first indication that some of the new immunosuppressive strategies involving calcineurin inhibitors minimization, avoidance, and/or withdrawal may translate to improved long-term outcome of renal transplants. *Page 809*