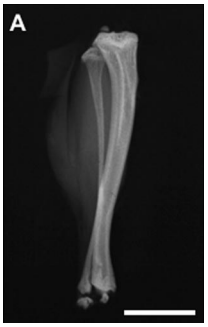
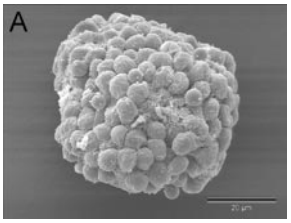
J Am Soc Nephrol 16: 3137–3138, 2005

# This Month's Highlights

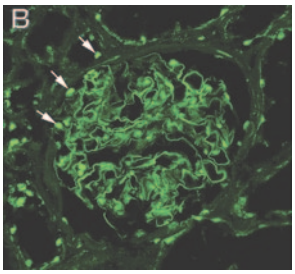
## Basic Science Articles



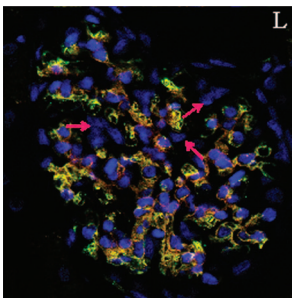

**Tripping over Calcium Channels.** $1,25(OH)_2$ vitamin $D_3$ plays a central role in regulating kidney and intestinal calcium absorption *via* channels that have recently been identified as members of the Vth subfamily of the transient receptor potential cation channel family (TRPV5). Renkema *et al.* used knockout mouse models to deftly explore the physiologic role of these channels. If the kidney form expressed in the distal tubule was knocked out, circulating $1,25(OH)_2$ vitamin $D_3$ increased and maintained calcium balance by enhancing intestinal calcium uptake. If these animals were crossed with mice that were 1$\alpha$-hydroxylase–deficient, the compensatory increase in active vitamin $D_3$ did not occur, and these mice developed hypocalcemia, hyperparathyroidism, and rickets. These studies describe interactions between intestinal, kidney, and parathyroid functions, and provide solid evidence for the localization and physiologic role of the TRPV5 channels, and the underlying importance of $1,25(OH)_2$ vitamin $D_3$ in coordinating their activity. *See Renkema et al., pages 3188–3195.*




**Gene Expression in Developing Glomeruli.** Pod-1 is a basic helix-loop-helix transcription factor expressed in developing and mature podocytes. Knockout mice lacking Pod-1 show arrested glomerular development as well as abnormalities in ureteric branching and the renal mesenchyme. To elucidate the role of Pod-1 in glomerular development, Cui *et al.* devised a new technique for analyzing gene expression in developing glomeruli. Using magnetic beads, they isolated late S-shaped bodies, capillary-loop stage glomeruli, and maturing glomeruli from mouse embryos. They then performed microarray analyses to identify differences in gene expression between glomeruli isolated from Pod-1 knockout embryos and wild-type embryos. These studies identified genes such as $\alpha$8 integrin, $\alpha$3 chain of type IV collagen, and podocin that were downregulated in the mutant glomeruli and represent potential downstream targets of Pod-1. The technique described by Cui *et al.* should be generally applicable to the characterization of knockout mice with glomerular phenotypes. *See Cui et al., pages 3247–3255.*

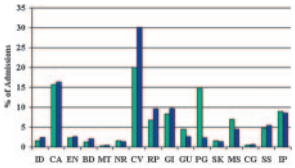



**How Do You Get Immunized to Your Own Kidney?** Remarkable progress has been made recently in anti–glomerular basement membrane (GBM) nephritis, including the molecular identification of the "Goodpasture antigen," identifying conformational antigenic changes that may confer autoimmunity and clarification of the role of GBM-reactive T cells in mediating nephritis. Still unknown, however, is exactly how one becomes immunized to antigens in the GBM. This study by Robertson *et al.* provides a provocative insight into that process. Using a rat model of T cell–mediated glomerulonephritis, they show that the first activation of B cells producing anti-GBM antibody occurs in a single "renal-draining lymph node" in the hilus of a nephritic kidney some time after the initial glomerular injury takes place. The finding suggests release of peptide antigen(s) related to the initial immunogen (epitope spreading) from the damaged kidney leading to systemic autoimmunity and a secondary anti-GBM antibody response. Though the findings are unique to this particular model, they offer a new approach to better understanding the origins of renal autoimmunity. *See Robertson et al., pages 3256–3263.*

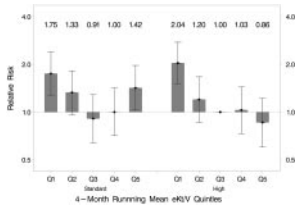



**Can We Treat the Mesangium and Spare the Patient?** The mesangium is a common site of injury in a variety of glomerular diseases such as IgA nephropathy, lupus nephritis, diabetes, and others. The systemic toxicity of most currently available immunosuppressive and anti-inflammatory drugs limits their efficacy. But what if one could selectively administer drugs directly to the site of injury in the mesangium without exposing the rest of the body? In this study, Tuffin *et al.* convincingly show that this can be done by coupling liposomes to a small fragment of a mesangial cell-specific antibody and showing that these immunoliposomes attach very selectively to mesangial cells, to be taken up by the cells without apparent consequences. When a toxin is attached to the liposome, it delivers a selective blow to the mesangium *in vivo* without systemic toxicity. The study stops short of showing that a therapeutic agent similarly delivered will have a beneficial effect on a mesangial disease process, but the stage is clearly set. *See Tuffin et al., pages 3295–3305.*

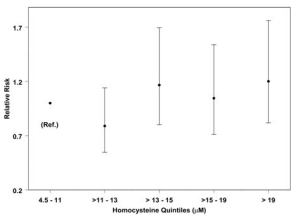
## Clinical Science Articles



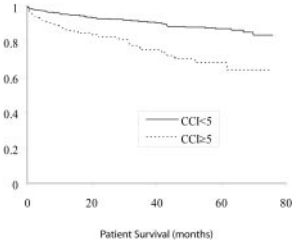

**Little Things Mean a Lot.** That acute kidney failure increases the risk of morbidity and mortality is one of the organizing concepts of acute care nephrology and considerable attention has been devoted to identifying the optimal renal replacement for the management of these patients. The report by Chertow *et al.* in this issue of *JASN* brings attention to the opposite end of the continuum of kidney injury in hospitalized patients. The authors report that even modest degrees of kidney injury are associated with increased risk of adverse outcomes during hospitalization, extending previous reports in this journal (*J Am Soc Nephrol* 15:1697–1705, 2004; *J Am Soc Nephrol* 16:195–200, 2005) and elsewhere. Although additional confirmation of these observations is clearly warranted, the possibility that much smaller perturbations in kidney function than were previously recognized may signal increased risk of adverse outcomes raises issues of immediate clinical relevance. First, should we recommend closer monitoring of kidney function for all, or for some subpopulations of hospitalized patients? Second, what clinical recommendations should be made when patients with persistent, small elevations in serum creatinine are brought to our attention? Clearly one can recommend a review of renal drug dosing and fluid balance, but are there other aspects of patient care, like nutritional support, that should be modified? Third, what recommendations should we make with respect to subsequent in-hospital monitoring and readiness for discharge? The answers to these as well as other management issues identified by cohort studies that were conducted to better define the demographic characteristics and risk profile of this patient population require evidence from well-designed clinical trials. *See Chertow et al., pages 3365–3371.*




**Toward a Better Understanding of HEMO.** Two decades' worth of observational data suggested that higher doses of delivered dialysis were associated with lower mortality rates. However, the HEMO study, a randomized, clinical trial, suggested that large differences in the equilibrated, volume-indexed urea clearance ($eKt/V_{urea}$) did not result in significant improvements in survival, cause-specific survival, nutritional status, or health-related quality of life. In this issue of *JASN*, Greene *et al.* demonstrate an eye-opening phenomenon: Within each randomized dose group in HEMO ($eKt/V_{urea}$, 1.45 and 1.05), subjects in the lowest quintile of delivered dose experienced roughly twice the 1-yr mortality rate of others who met prescribed dose targets. Indeed, the risk of death for subjects in the lowest quintile of the higher prescribed dose group was 60% higher than the risk of death for the aggregate of all subjects in the lower prescribed dose group, despite a higher mean $eKt/V_{urea}$. This study highlights the importance of intent-to-treat (rather than as-treated) analyses, and provides important insights into the strengths and weaknesses of observational studies and randomized clinical trials. *See Greene et al., pages 3372–3381.*




**Xerostomia, Pilocarpine, and Interdialytic Weight Gain.** Achieving estimated dry weight goals in patients with large interdialytic weight gains remains one of the more vexing problems in the management of hemodialysis patients. Further, the etiology of hyperdipsia in many patients remains obscure. In this issue of *JASN*, Sung *et al.* examine the hypothesis that decreased salivary flow and xerostomia (dry mouth) are important contributors. In a randomized trial, administration of pilocarpine decreased thirst and interdialytic weight gain in hyperdipsic dialysis patients. Will pilocarpine become a frontline therapy for large weight-gainers? *See Sung et al., pages 3419–3430.*




**Extending Comorbidity Analyses to Transplantion.** Although comorbid conditions are known to influence survival in dialysis patients, a role for pretransplant comorbidity on posttransplant outcome is less well established. In the study by Wu *et al.*, the investigators used the Charlson Comorbidity Index to assess the impact of pretransplant comorbid conditions on graft and patient survival in 715 renal allograft recipients. The authors found that increased comorbidity, including diabetes and heart failure, was associated with a higher incidence of patient death, both perioperatively and >3 mo posttransplantation. The findings could have broad implications for individualizing patient treatment protocols, for the design and interpretation of transplant studies, and for developing policies regarding organ distribution. *See Wu et al., pages 3438–3445.*