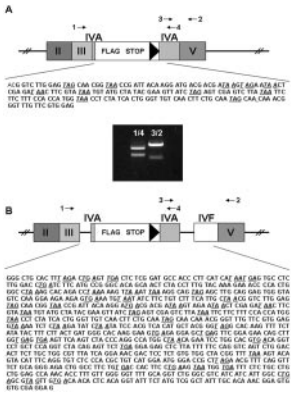
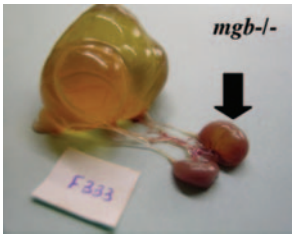
J Am Soc Nephrol 18: 353–355, 2007

This Month's Highlights

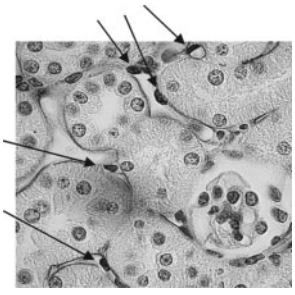
Basic Science Articles



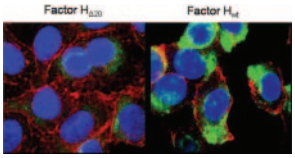
Thick Ascending Function and NKCC2 Isoforms. Three different splice-isoforms of the Na/K/2Cl cotransporter (NKCC2/BSC1) are expressed along the thick ascending limb of Henle (TAL). The functional consequences of the existence of three different isoforms of NKCC2 are unclear. NKCC2A is expressed in the TAL and macula densa. Oppermann *et al.* used NKCC2A-deficient mice to define its role in their report in this issue of *JASN*. Baseline plasma renin concentration and the effect of high- or low-salt diet on plasma renin concentration were similar in NKCC2A+/+ and −/− mice. However, macula-dependent inhibition of renin secretion in response to saline infusion was markedly reduced. The tubuloglomerular feedback function curve was left-shifted in NKCC2A−/− compared with wild-type mice. These results suggest that NKCC2A activity is required for salt-sensing by the macula densa in the high Cl concentration range. Co-expression of both high and low affinity isoforms of NKCC2 may permit transport and Cl-dependent TGF regulation to occur over a wider Cl concentration range, and could permit different pharmacologic approaches to affect TAL functon. *See Opperman et al., pages 440–448.*



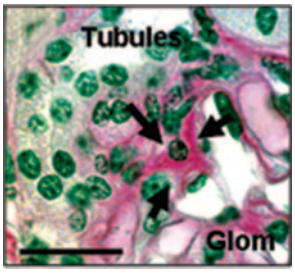
New Mouse Model of Obstructive Uropathy. Congenital urinary tract obstruction is a major cause of chronic renal failure in infants, but the molecular pathogenesis is poorly understood. Obstruction of the lower urinary tract in boys is commonly due to posterior urethral valves and bladder outlet obstruction. Singh and colleagues report the first rodent model of spontaneous *in utero* obstructive uropathy that develops chronic renal failure. The *mgb* mouse carries a new insertional mutation that results in megabladder, hydrouteronephrosis, and progressive renal failure. The abnormalities are inherited as an autosomal recessive trait, and males are more severely affected than females. The primary abnormality appears to be a defect in the differentiation of the detrusor smooth muscle in the bladder. Although posterior urethral valves are absent, the phenotype of the *mgb* mouse functionally resembles humans with congenital obstruction of the lower urinary tract. Identification of the gene that is disrupted in the *mgb* mouse should provide new insights into bladder development and the pathogenesis of obstructive uropathy. *See Singh et al., pages 461–471.*



Can Blocking a Nucleotide Receptor Protect the Glomerulus from Immune Injury? P2Y1 is a "metabotrophic" nucleotide receptor expressed on a variety of cell types including lymphocytes, platelets, and all three glomerular cells. It is essential to ADP-induced platelet aggregation and thrombosis, but it also plays a role in many other processes. Hohenstein *et al.* sought to define a physiologic role for P2Y1 in glomerulonephritis by inducing nephrotic nephritis in P2Y1 knockout mice. They report a rather dramatic protective effect of P2Y1 deficiency on virtually all parameters of disease, including survival, which is independent of alterations in the immune response. Although the authors speculate that the absence of P2Y1 expression may have had the most benefit in preserving capillary endothelial integrity and facilitating repair, the data do not establish the mechanism of the effect. However, the degree of protection conferred by P2Y1 deficiency suggests that ways to block its activity may offer a fruitful approach to suppressing the glomerular response to immune injury and perhaps slowing progression. *See Hohenstein et al., pages 494–505.*

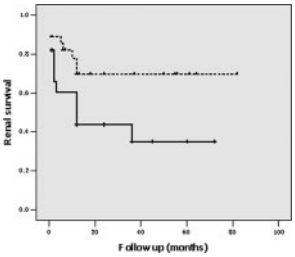


Factor H and the Pathogenesis of HUS—One Step Closer to Understanding the Mechanism. Considerable progress has been made in understanding the many circulating and cell-bound complement regulatory proteins (CRP), particularly their roles in the pathogenesis of hemolytic-uremic syndrome (HUS). In non–Shiga toxin–induced HUS, microangiopathy reflects complement-mediated endothelial injury due to abnormalities in Factor H, a circulating CRP that regulates the alternative pathway C3 convertase, thus preventing excess spontaneous or induced complement activation. Most patients with non–Shiga toxin–induced forms of HUS exhibit either genetic deficiencies or mutations in the C-terminus of the Factor H gene associated with loss of efficient complement regulation. In this study, Heinen and colleagues extend these observations by showing that mutated Factor H protein actually exhibits normal regulatory activity in solution but loses that ability in the conformation it assumes when acting at the endothelial cell surface. This finding is another step in the march from gene to protein to therapeutic intervention in patients with HUS and Factor H abnormalities. *See Heinen et al., pages 506–514.*

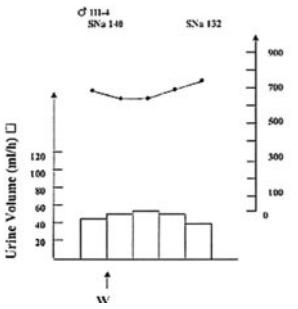


Diabetic Nephropathy: Is NO/VEGF Uncoupling the Mechanism? Studies of diabetic nephropathy (DN) have been hampered because most animal models lack many of the morphologic features of human DN. In this paper, Nakagawa and colleagues report detailed studies of the lesions that develop when diabetes is induced in mice that lack the gene for endothelial nitric oxide synthase (eNOS). Similar to the recent report by Zhao *et al.* (*J Am Soc Nephrol* 10: 2664–2669, 2006), these mice develop the full array of diabetic glomerular lesions with clinical manifestations that include hypertension and proteinuria. However, in this study Nakagawa *et al.* further show that the inability of the eNOS knockout mice to produce nitric oxide (NO) is associated with an increase in vascular endothelial growth factor (VEGF), a major angiogenic cytokine known to participate in DN. The significance of these observations is two-fold. They confirm the utility of this model for future studies of the pathogenesis of DN, and they support a provocative new hypothesis regarding the potential roles of NO and VEGF, in conjunction with hyperglycemia, in causing diabetic lesions. *See Nakagawa et al., pages 539–550, and the editorial by Quaggin, pages 364–366.*

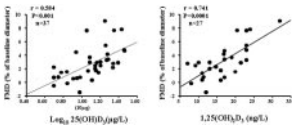
Clinical Science Articles



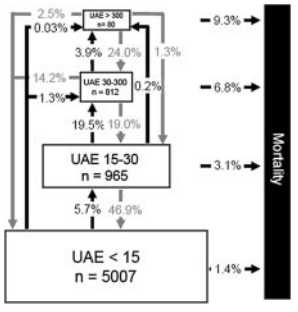
Pauci-Immune Crescentic Glomerulonephritis—You Don't Have to Have ANCA to Get It. The entity of rapidly progressive crescentic glomerulonephritis without immune deposits was described first in 1978 before its association with antineutrophil cytoplasmic autoantibodies (ANCA) was identified and the potential role of ANCA in pathogenesis explored. Since then it has been appreciated that some small percent of patients with a similar clinical and pathologic syndrome, usually about 10%, do not have detectable ANCA—an observation relevant to the issue of whether ANCA antibodies are the pathogenetic agents in this disease. However, since ANCA were discovered, these patients have largely been overlooked. In this paper, Chen *et al.* provide a detailed clinical and pathologic analysis of 28 ANCA-negative Chinese patients with pauci-immune crescentic glomerulonephritis, a surprising 33% of the total, and note that these patients often have more severe disease and a worse prognosis than their ANCA-positive counterparts. Is this a different disease caused by another mechanism? Is it the same disease, thus demonstrating that ANCA alone are not necessary to cause it? The paper not only provides useful clinical data but also underscores the fact that we still do not have a full understanding of the pathogenesis of pauci-immune rapidly progressive crescentic glomerulonephritis. *See Chen et al., pages 599–605.*



Spectrum of Nephrogenic SIADH. Most physicians are familiar with the syndrome of inappropriate antidiuretic hormone (SIADH) as a common cause of hyponatremia. However, some patients who appear to have SIADH have undetectable circulating antidiuretic hormone (ADH) levels. Recently, a gain-of-function mutation of the vasopressin V2 receptor (V2R) was identified as a cause of a nephrogenic SIADH-like syndrome. This disorder produces hyponatremia and has been named the nephrogenic syndrome of inappropriate antidiuresis (NSIAD). NSIAD was first described in male infants, consistent with the localization of the V2R gene on the X chromosome. Decaux *et al.* describe a large family with NSIAD caused by a missense mutation of the V2R gene. In contrast to the original report, the diagnosis was first made in an elderly affected male. He was initially thought to have SIADH but failed to respond to tolvaptan, a V2R antagonist. Affected males had hyponatremia, and most women with the mutation had an abnormal response to water loading. The one female with a normal phenotype appeared to have skewed X-inactivation. These findings extend the spectrum of NSIAD to include adult men and women with hyponatremia or abnormal water loading tests. *See Decaux et al., pages 606–612.*



More Support for a Role of Vitamin D Deficiency in the Vascular Disease of Dialysis Patients. ESRD patients receiving dialysis are known to have altered arterial function, which is characterized by decreased capacitive function (arterial stiffening) and diminished flow-mediated dilation. However, the etiology of these abnormalities is not well understood. There has also been increasing recognition that functional vitamin D deficiency in dialysis patients may alter mortality, also through unclear mechanisms. In this issue of *JASN*, London and colleagues examine relationships between arterial alterations and cardiovascular risk factors in a cross-sectional study of 52 stable hemodialysis patients. As with previous studies, these investigators found a high prevalence of aortic stiffness, decreased vascular distensibility, and brachial artery flow dysfunction in dialysis patients. After adjusting for BP and age, serum levels of 25-OH vitamin D3 and 1,25-OH vitamin D3 were inversely associated with aortic stiffness and positively associated with brachial artery dilation. These results suggest that vitamin D deficiency may be a culprit in arteriosclerosis and endothelial dysfunction in patients on hemodialysis. Whether administration of vitamin D can improve these abnormalities remains to be discovered in prospective controlled trials. *See London et al., pages 613–620.*



Does BMI Have a Role in Progression of Diabetic Nephropathy? The report by Brantsma *et al.* in this issue addresses risk factors for progressive kidney disease by describing the occurrence or regression of albuminuria in nondiabetic adults during follow-up of 4.2 yr. As a biomarker for early kidney injury, albuminuria had a variable course, similar to much earlier observations from the Modification of Diet in Renal Disease trial, where GFR slopes included a substantial number that were close to or greater than zero. In addition, factors associated with both the appearance and regression of albuminuria after controlling for baseline kidney function are largely related to BP control and hyperglycemia. Finally, baseline body mass index (BMI) was associated with progression to albuminuria in the multivariate analyses. However, BMI change was not associated, despite univariate associations between changes in BMI and changes in albuminuria. The clinical relevance of these observations is clear, particularly for high-risk individuals, and these observations suggest that, in these populations, attention to maintenance of normal body weight, blood pressure, and blood sugar are important primary and secondary prevention goals. *See Brantsma et al., pages 637–645.*