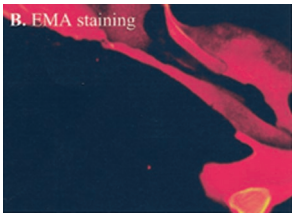
J Am Soc Nephrol 15: 2243–2245, 2004

This Month's Highlights

BASIC SCIENCE

Cell and Transport Physiology

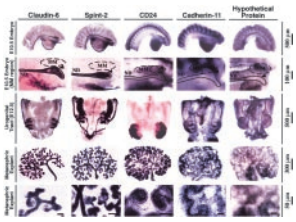
Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells
Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in opossum kidney cells



Statins: Balancing Benefit with Toxicity. The papers by Verhulst *et al.* and Sidaway *et al.* examine the effects of statins in kidney cell culture systems. There is no doubt about the importance of statins in primary and secondary prevention of cardiovascular events, and more recently in slowing the progression of chronic kidney disease. Nevertheless, the side effects of these agents can be catastrophic, especially when they are used at inappropriately high doses or in combination with other drugs that potentiate their toxicity. In the epithelial cell culture systems, statins interfere with endocytosis and processing of albumin. While these *in vitro* effects may explain the "tubular" proteinuria that has been observed with high doses of statins, it is important that these class- and dose-related and effects be kept in perspective with the well described beneficial effects of these agents on cardiovascular outcomes and progression of chronic kidney disease. Rajiv Agarwal details these issues in the accompanying editorial. **Page 2249**

Genetics and Development

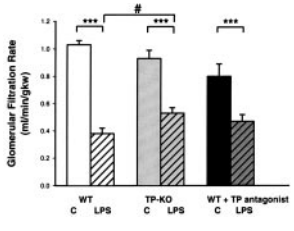
Identifying the molecular phenotype of renal progenitor cells



Cell surface molecules for isolation of renal progenitor cells. The kidney arises from the ureteric bud and metanephric mesenchyme. Under the influence of the ureteric bud, progenitor cells in the metanephric mesenchyme are induced to form new nephrons. However, there are no cell surface markers that can be used to identify renal progenitor cells. Challen *et al.* used cDNA microarray analysis and a membrane protein prediction program to identify 21 genes that are preferentially expressed in uninduced metanephric mesenchyme. Some of the genes encode cell surface molecules, such as CD24 and cadherin-11, which could be used to isolate renal progenitors by fluorescence-activated cell sorting (FACS). Isolation of live progenitor cells with FACS will permit future functional characterization of progenitor cells. The unique approach of identifying cell surface molecules in uninduced mesenchyme brings us a step closer toward identifying and isolating stem cells in fetal and adult kidneys. **Page 2344**

Hemodynamics and Vascular Regulation

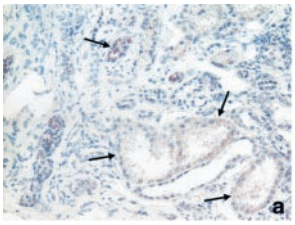
Thromboxane receptor mediates renal vasoconstriction and contributes to acute renal failure in endotoxemic mice



Thromboxane receptors in acute renal failure of septicemia – a promising therapeutic target? Despite a huge research effort treatment of septicemia in general, and particularly of acute renal failure of septicemia, has remained frustrating and continues to be a challenge to the clinical nephrologist. Treatment remains mostly supportive and not causal despite recent evidence for the roles e.g. of oxidative stress, NO and coagulation abnormalities (protein C) in the genesis of organ damage as well as of NO and vasopressin in the genesis of systemic hemodynamic abnormalities of septicemia. A paradoxical discrepancy is found between systemic vasodilatation and hypotension on the one hand and intense renal vasoconstriction on the other hand. In the genesis of renal vasoconstriction and ARF a causal role of thromboxane A_2, the major vasoconstrictor of the cyclooxygenase pathway, had been suspected for a long time. The study of Boffa *et al.* carried this issue one step further by combining classical pharmacology (TXA_2 receptor blockade) and genetic approach (wild type *versus* TXA_2 receptor knock out mice). The evidence of a causal role of TXA_2 in the genesis of renal vasoconstriction, and to some extent also of organ damage (ARF), is convincing. Why is this important? ARF in septicemia is certainly multifactorial. The fallacy of using non-specific blunt approaches was illustrated by the counterproductive results of global blockade of NO. The hope is to identify specific therapeutic targets. This study is an important step in this direction, although it is presumably naïve to assume that one single intervention will ever provide the golden bullet to prevent the renal complications of septicemia. **Page 2358**

Pathophysiology of Renal Disease and Progression

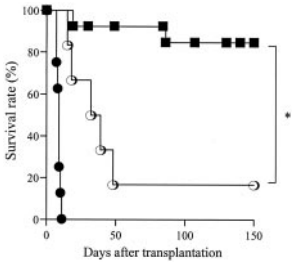
Bradykinin decreases plasminogen activator inhibitor-1 expression and facilitates matrix degradation in the renal tubulointerstitium under angiotensin-converting enzyme blockade



ACE Inhibition of Bradykinin Pathways Promotes Matrix Remodeling. Using a cyclosporine-based model of renal interstitial fibrosis, it was found that fibrosis is decreased or prevented by angiotensin converting enzyme inhibition (ACEi). Interestingly, however, angiotensin receptor blockade did not have a similar effect. Since ACE also degrades bradykinin (BK), the authors investigated whether BK mediates an antifibrotic effect. *In vivo* studies indicated that ACEi led to a decrease in kidney PAI-1 and an increase in kidney proteolytic activity, at a time when tPA mRNA expression had returned to normal. *In vitro* studies indicated that BK suppressed PAI-1 mRNA expression. These suggested that ACEi stimulates an increase in proteolysis by decreasing levels of the proteolytic inhibitor, PAI-1. These findings point to a novel mechanism by which ACEi may attenuate renal fibrosis, emphasizing its effects on promoting proteolytic pathways rather than suppression of matrix synthetic pathways. **Page 2404**

Basic Transplantation

Mechanism of action of donor specific transfusion in inducing tolerance: Role of donor MHC molecules, donor costimulatory molecules, and indirect antigen presentation

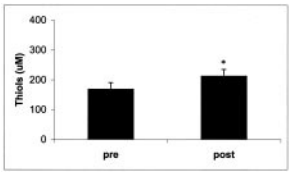


What makes donor cells tolerogenic? It is well documented that administration of donor cells promotes transplantation tolerance in several experimental models but little is known about "what is it" in donor cells that mediates this effect. In this manuscript Kishimoto *et al.* use various combinations of donor and recipient gene knockout mice to show that neither cell surface expression of MHC molecules no costimulatory molecules is necessary suggesting that indirect recognition of processed donor peptides is sufficient. They also show that the absence of indirect allorecognition renders recipients resistant to tolerance. Taken together with published reports that regulatory T cells regulatory self-MHC molecules, this report established that indirect recognition of donor alloantigen is a key mechanism of induction of tolerance by donor antigen administration. These data have clinically relevant implications for designing novel tolerogenic strategies in transplantation. **Page 2423**

CLINICAL SCIENCE

Clinical Nephrology

Oxidative stress is increased in critically ill patients with acute renal failure



Oxidative stress: A new target for decreasing the mortality in acute renal failure (ARF). Despite improvements in renal replacement therapies, the mortality rate for patients with acute renal failure remains high. In this issue, Himmelfarb and colleagues report much greater oxidative stress among critically ill patients with ARF than among patients with critical illness without ARF; those with ESRD and healthy controls. The estimates of oxidative stress were changes in plasma protein oxidation; thiol oxidation and carbonyl content. These are indirect estimates but correlate with measures of cytokine production. Hemodialysis is associated with a transient decrease in plasma thiol oxidation and has no effect on protein carbonyl content. Therapies that target increase oxidative stress in ARF appear to be a logical next step in the search for effective treatment of ARF in critically ill patients. **Page 2449**

Epidemiology and Outcomes

"Renalism": Inappropriately Low Rates of Coronary Angiography in Elderly Persons with Renal Insufficiency

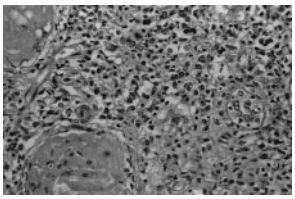
People with CKD – another undertreated minority? There is ample evidence that the presence of chronic kidney disease in a patient is associated with increased risk of receiving less medical care than comparable patients without CKD. Chertow and his colleagues illustrate the dimensions of this problem by examining coronary angiography rates among Medicare beneficiaries with and without CKD who had been hospitalized for an acute coronary syndrome. Patients with CKD were half as likely to undergo angiography and those CKD patients for whom angiography was indicated and who received an angiogram were less likely to die during follow up. It is unlikely that angiography *per se* was responsible for the reduction in risk of death and it is reasonable to speculate that the clinicians treating these patients may also be more conversant with other aspects of patient CKD care. It is also possible that the variations in care may reflect inappropriate caution and the authors speculate that the low angiography rates in CKD patients may reflect clinician concerns about radiocontrast nephropathy. Evidence for these and other explanations for avoidable variations in CKD care await further health services and outcomes studies like that of Chertow *et al.* **Page 2462**

Retinal Microvascular Abnormalities and Renal Dysfunction: The Atherosclerosis Risk In Communities Study

The eye is a window to the kidney even in non-diabetics. The association between diabetic retinopathy and CKD has been recognized for some time and has been termed the renal-retinal syndrome. The presence of retinopathy in a diabetic patient should lead to an assessment of renal function and CKD in the absence of significant retinopathy in this patient population should lead the clinician to carefully consider the possibility of non-diabetic renal disease. The report by Wong and associates from the ARIC cohort study that retinopathy in both diabetic non-diabetic populations, with and without hypertension, is associated with increased risk of developing kidney disease during six years of follow-up. Furthermore, consistent with other reports, retinopathy was an independent risk factor for the development of kidney disease after controlling for demographic characteristics and other risk factors for vascular disease. These findings support the concept that kidney disease in some individuals is linked to more diffuse dysfunction of the microcirculation that includes the eye, the heart and the kidney. **Page 2469**

Clinical Transplantation

Presence of a failed kidney transplant in patients on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance



Is leaving a failed kidney transplant contributing to morbidity in dialysis patients? Dialysis patients who previously failed a kidney transplant suffer from high morbidity and mortality. The authors of this interesting manuscript tested the hypothesis that this may be due to a chronic inflammatory state induced by the failed kidney that is usually left in place since such patients rarely undergo transplant nephrectomy. The results were intriguing in that they show that indeed the presence of a failed kidney transplant in dialysis patients is associated with markers of inflammation and anemia that tends to be resistant to erythropoietin therapy. Importantly, in a subset of patients who underwent nephrectomy, such markers were reversed. These results are clinically relevant in that they imply that transplant nephrectomy should be seriously considered in dialysis patients who had failed a transplant and have clinical and/or laboratory evidence of chronic inflammation and/or unexplained anemia resistant to therapy. **Page 2494**