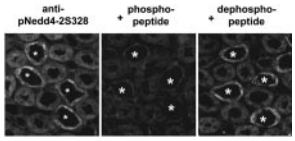
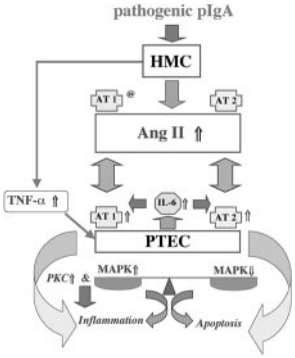
This Month's Highlights

Basic Science Articles

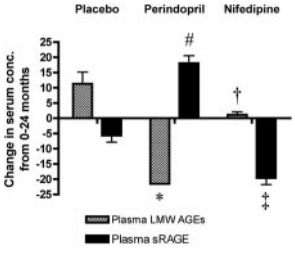


Aldosterone—The Queen of the Hormones. Stimulation of Na^+ transport by aldosterone was described 40 yr ago by classic studies by Jean Crabbe, Alex Leaf, and Isidore Edelman. The mechanisms of action were hotly debated and have only recently yielded to modern molecular techniques. Flores *et al.* provide the latest information in this issue of *JASN* with their description of the phosphorylation events that underlie the immediate response to aldosterone. Sgk1 is a Ser/Thr kinase that has been shown to be an "aldosterone-induced protein," and now we know that a proximate target for its effect is the Nedd4-2 protein. The latter effectively regulates the dwell time of the Na^+ channel complex in the apical membrane, and thus overall Na^+ channel activity. Understanding these mechanistic details has merit in its own right and in the identification of one of the critical junctures in regulation of Na^+ channel, but it may also open the door to better understanding of clinical conditions associated with "Na^+ avidity" in the aldosterone-sensitive distal nephron. *See Flores et al., pages 2279–2287.*



Glomerular-Tubular Crosstalk—A Role in Inflammation, Too? Two areas of increasing interest in renal pathophysiology are the role of intrarenal renin-angiotensin systems (RAS) and mechanisms underlying progressive tubulointerstitial injury in inflammatory glomerulopathies. In the current issue of *JASN*, Chan *et al.* describe a novel glomerulotubular interaction in IgA nephropathy leading to upregulation of local proximal tubular RAS, which may mediate tubular inflammation and apoptosis in this condition. This group had previously found that exposure of cultured mesangial cells to IgA led to increased expression of cytokines and angiotensin II. In their new studies, they found that while direct incubation with IgA had no effect on cultured proximal tubule cells, incubation with the conditioned media from IgA-activated mesangial cells led to sequential and temporally distinct upregulation of AT1 and AT2 angiotensin II receptors, which mediated tubular inflammatory and apoptotic responses, respectively. These results raise intriguing issues about glomerular-tubular crosstalk in inflammation and heighten awareness of potentially disparate roles of angiotensin II in tubulointerstitial injury at different times in the disease process. *See Chan et al., pages 2306–2317.*

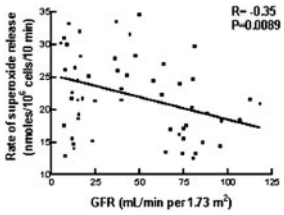
The Heartbreak of Hyperphosphatemia. Dealing with phosphate issues in the kidney failure setting is a source of daily frustration and serious morbidity and mortality in the ESRD population. While the new generation of phosphate-binders adds to the armamentarium, the simple fact is that the ambitious goals for serum phosphate control, as described in Kidney/Dialysis Outcomes Quality Initiative (KDOQI) guidelines, are not achieved in the majority of ESRD patients. The paper by Yamagata *et al.* describes a totally novel approach to affecting the membrane trafficking of the renal sodium phosphate co-transporter that affects the steady state level of the transport protein in the apical membrane. While affecting renal phosphate reabsorption in ESRD is moot, the possibility of developing a similar approach to downregulating intestinal phosphate reabsorption would be an interesting advance and certainly would provide a novel approach to dealing with a very difficult clinical problem. *See Yamagata et al., pages 2338–2345.*



ACE Inhibition in Diabetic Nephropathy—It's Not All Hemodynamic. There is increasing evidence that drugs that interfere with the renin-angiotensin system afford renoprotection by a variety of mechanisms. One of the most intriguing recent observations is that these agents may block accumulation of advanced glycation endproducts (AGE) in diabetes. The paper by Forbes *et al.* in this issue of *JASN* and the related editorial by Raymond Harris describe a novel potential mechanism underlying the ability of angiotensin-converting enzyme (ACE) inhibitors to decrease circulating and tissue levels of AGE. Recent studies have indicated that the AGE receptor (RAGE) has multiple splice variants, and in untreated diabetes there is a selective decrease in a truncated, soluble form of the receptor (sRAGE) that is secreted and binds AGE. ACE inhibitor treatment increased expression of sRAGE, while decreasing expression of full-length RAGE. By demon-

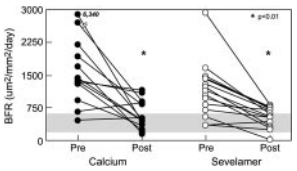
strating that ACE inhibitor–induced increases in sRAGE expression and serum levels correlated with decreased AGE levels in both experimental animals and in patients with type I diabetes, Forbes *et al.* have identified an additional possible therapeutic target of our most-used renoprotective drugs in diabetes. *See Forbes et al., pages 2363–2372, and Harris, pages 2251–2253.*

Clinical Science Articles



Leukocyte Priming in Chronic Kidney Disease. Chronic low-grade inflammation and systemic oxidative stress are increasingly being recognized as cardiovascular risk factors in patients with chronic kidney disease (CKD). However, the nature and source of excess inflammation and oxidative stress in CKD remains to be defined. In this issue of *JASN*, Sela and colleagues have examined the priming of polymorphonuclear leukocytes (PMNL) to release the reactive oxygen species superoxide anion as well as the enzyme myeloperoxidase in a cohort of patients with CKD including dialysis patients. All patients with CKD exhibited evidence of increased PMNL priming compared with healthy subjects, with the greatest alterations occurring in dialysis patients. Of interest, an inverse association was found between PMNL priming and estimated GFR. This study provides strong evidence to support the hypothesis that PMNL are at least partly responsible for maintaining a chronic low-grade inflammatory state with elevated systemic oxidative stress in patients with kidney disease. However, a mechanistic understanding of how loss of kidney function leads to PMNL priming remains to be determined. *See Sela et al., pages 2431–2438.*

Fish Oil Doesn't Help the Transplanted Kidney—The Pros and Cons of Meta-Analysis. Meta-analysis is a tool that allows quantitative summarization of multiple individual trials which individually may provide conflicting evidence derived from populations that may or may not be relevant to the patient at hand. The end product is not a test of a hypothesis about a treatment, but an estimate of the benefit, or lack thereof, of that treatment. Tatsioni and his colleagues illustrate the utility of meta-analysis in this issue of *JASN* with a report on the effects of omega-3 fatty acid supplementation on outcomes of kidney transplantation. The authors executed a well-described literature search, abstracted information from the studies meeting their inclusion criteria, and performed weighted analyses to derive a summary measure of the aggregate trial experience. They conclude that the available data does not support posttransplant omega-3 fatty acid therapy. A meta-analysis can only include information from identified studies, and a major concern with any systematic review is that the conclusions may be influenced by a publication bias toward positive studies. This is not a major issue with a negative conclusion like that reported by Tatsioni *et al.* A recent policy implemented by *JASN*, in collaboration with other leading kidney journals, should help reduce the risk of publication bias even with positive results. In the future, *JASN* will only publish clinical trials that were registered at outset in one or more available registries. Future meta-analyses and systematic reviews can use these registries to identify relevant trials regardless of their conclusions and publication history. *See Tatsioni et al., pages 2462–2470.*



Does Sevelamer Increase the Safety Net in Renal Osteodystrophy Treatment? Renal osteodystrophy remains a significant problem in children with ESRD. Unfortunately, its treatment may be associated with new morbidities such as adynamic bone disease and vascular calcification. In the study by Salusky *et al.*, the effects of calcium carbonate and sevelamer phosphate binders were compared in a group of children on peritoneal dialysis with severe hyperparathyroidism and bone biopsy evidence of osteitis fibrosa. After 8 mo, either therapy used in combination with thrice weekly vitamin D sterols, adjusted to target serum PTH, calcium, and phosphorus levels, improved histologic and biochemical measures of secondary hyperparathyroidism while avoiding adynamic bone disease. In the sevelamer-treated group, serum calcium remained closer to the lower range of normal, allowing for progressive increases in vitamin D doses, whereas significantly more calcium carbonate-treated patients developed episodes of hypercalcemia. We await with interest comparative data on the incidence of vascular calcifications between the two phosphate-binder groups. *See Salusky et al., pages 2501–2508.*