Competition for organic anion transporters in chronic renal disease

To the Editor: In their mini review, Meyer and Hostetter[1] review recent evidence that uremic toxins such as indoxyl sulfate and *p*-cresyl sulfate are produced by colonic bacteria and suggest that suppressing their production might benefit patients with renal failure.

Evidence that uremic solutes are secreted, rather than filtered, using organic anion transporters[2,3] may create a new paradigm in treating patients with chronic renal failure.

Smith wrote, 'In tubular excretion … apparently all substances share a common element in one of two transport systems … This is presumably a result of competition … since it is freely reversible'.[4] The possibility that many drugs compete for the secretion of indoxyl sulfate or other uremic toxins broadens greatly the range of drugs that should be used with caution in patients with uremia or less-advanced stages of renal failure. Rather than focus on guidelines that depend on estimated glomerular filtration rate, prescribing for patients with chronic renal failure should take into consideration possible competition for organic anion transport.

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The Authors Reply: Like Dr Lowenstein,[1] we are intrigued by the possibility that impaired secretion of toxic compounds contributes to uremic illness. Competition for tubular transport may cause both natural waste solutes and pharmaceutical metabolites to accumulate out of proportion to the reduction in glomerular filtration rate (GFR). As Dr Lowenstein notes, the assumption that some of these secreted compounds are toxic can explain why uremic symptoms are not closely correlated with creatinine and other GFR markers. James Shannon, a student of Homer Smith, who became Director of the NIH, raised these points many years ago and concluded, 'The answer to this question must await the further identification of those substances which make up the unknown portion of the urinary constituents'.[2] So far, however, we have compiled only a limited catalog of secreted compounds and know very little about their individual effects.

In addition to their transport across the renal tubules, the transport of organic ions across other barriers may be involved in uremic illness. For example, hepatic clearance of some drugs is reduced in end-stage renal disease patients due at least in part to impaired hepatic transport of organic ions.[3] Impaired organic ion transport across the blood–brain barrier could contribute to uremic encephalopathy.[4] The organic ion transporters are widely distributed and the accumulation of transported solutes due to kidney failure could therefore interfere with multiple physiological processes.

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Interstitial mononuclear infiltrates in murine α3(IV)-NC1–induced nephropathy: harbingers of renal failure?

To the Editor: Whereas the noncollagenous domain 1 of α3(IV) collagen (α3(IV)-NC1) is the major target of Goodpasture autoantibodies in anti-glomerular basement membrane (GBM) glomerulonephritis, DBA/1 mice immunized with α3(IV)-NC1 develop massive albuminuria progressing to nephrotic syndrome. Kidney histopathology shows fine granular GBM deposition of immunoglobulin G and C3, GBM thickening with 'spike' reaction, subepithelial electron-dense deposits, and podocyte foot process effacement, but minimal glomerular inflammation.[1–3] These clinical and morphological findings recapitulate human membranous nephropathy rather than anti-GBM glomerulonephritis. This unexpected phenotype may be due to a subepithelial planted antigen, consistent with the fine granular deposition of exogenous antigen in the capillary loops.[3] An elegant recent study comprehensively characterized tubulointerstitial infiltrates of macrophages and CD4(+) T helper (Th)1 and Th17 cells in the late stages of α3(IV)-NC1–induced nephropathy.[1] This may reflect a true

autoimmune response against α3(IV) collagen occurring in all mouse (but not human) tubular basement membranes. Alternatively, mononuclear interstitial infiltrates may be secondary to nephrotic-range proteinuria. Of note, the predominant inflammatory cells in human membranous nephropathy are interstitial monocytes/macrophages and CD4(+) T cells.[4] Moreover, their numbers correlate with renal impairment at the time of biopsy and progressive renal impairment over 5 years, suggesting that progression toward renal failure in membranous nephropathy may be driven mainly by cell-mediated immunity.[4] Future studies expanding on the findings of Hopfer *et al.* are needed to determine whether interstitial mononuclear infiltrates are indeed harbingers of renal failure in membranous nephropathy.

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The Authors Reply: In their letter[1] and in a recent publication,[2] Borza and Fogo report that DBA/1 mice immunized twice with recombinant human noncollagenous domain 1 of α3(IV) collagen (α3(IV)-NC1) developed severe nephrotic syndrome. Histological examination revealed membranous glomerulonephritis (GN) with only a few glomerular crescents. The protocol deployed in our studies[3,4] uses four immunizations instead of two. After a stage of membranous GN, mice rapidly progress to a necrotizing crescentic GN accompanied by tubulointerstitial damage with massive infiltration of macrophages and, to a lesser extent, T cells. In our study, two immunizations were also not sufficient to induce crescentic GN (unpublished). Thus, continuous immunizations appear to be necessary for the switch to crescentic GN.

Borza and Fogo suggest that the interstitial infiltrates may be a true autoimmune response against mouse tubular basement membranes. In contrast, we favor the hypothesis that α3IV-NC1–specific T cells are the driving force triggering the switch from membranous to crescentic GN. As recently proposed by Heymann *et al.*,[5] antigen from damaged glomeruli may spread into the interstitium and become available for antigen presentation, causing local T-cell activation and subsequent recruitment and activation of macrophages. We think that this mechanism is more likely because the glomerular basement membranes show extensive alterations while the tubular basement membranes don't. In our view, the biphasic course of our animal model with a rapid increase of mononuclear cells in the context of crescentic GN rather than a chronic accumulation does not support the concept of mononuclear cells as a harbinger of renal failure in membranous GN.

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Association between dialysis schedule and mortality in maintenance hemodialysis

To the Editor: This is with reference to the recent article by Zhang *et al.*[1] that studied the association between the dialysis schedule and the day of the week of all-cause mortality in maintenance hemodialysis (HD) patients. We undertook a retrospective analysis of all chronic HD patients (treated for >6 months) dialyzed in a single UK region (Northern Ireland, population = 1.8 million) in order to study this relationship. All deaths between 2007 and 2011 were recorded ($n = 247$; mean age = 70.2 years; 62.7% males). The mean duration of HD was 55 months (range 6–296 months) and the commonest primary renal diagnosis was diabetic nephropathy (22%). We found a relative increase in mortality on the first dialysis schedule day, i.e., Monday for Monday–Wednesday–Friday (MWF) schedule and Tuesday