is underreported in TESS, most notably substance abuse and poisoning fatalities. During the quinquennium 1985–1990, about one-fifth of the calls to poison centers were not included in TESS,[4] so the trends in the report might not be as robust as they might have been if data collection had been more universal. TESS data are collected during telephone consultations; thus, bedside confirmation and data collection are not necessarily conducted by specialists in poison information. However, because calls are initiated by the general public, health-care professionals, and emergency first responders, the data collected provide a broader narrative of poisoning exposures than those from traditional health-care databases. Data quality may improve as data are collected and documented by specialists in poison information during the evaluation of the exposure and determination of the potential toxicity and therapeutic needs. It is also worth bearing in mind that the trend of the use of ECR in the United States may not necessarily reflect trends in Europe and the rest of the world.

Newer techniques for removal of toxins, such as Molecular Adsorbent Recirculating System (MARS), although still not widely available, may eventually become more common and replace HD as the modality of choice for removal of certain toxins. Efficacy of MARS in the removal of protein-bound drugs such as phenytoin, diltiazem, and theophylline has been described in case reports, but its availability remains limited.

The epidemiological trend of extracorporeal toxin removal in the United States has been changing, as has the profile of drugs removed by these techniques. With the use of newer techniques and change in drugs used in medical therapy, the trends will continue to evolve, with nephrologists playing a central role in the use of these therapeutic modalities.

DISCLOSURE
The authors declared no competing interests.

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Interstitial fibrosis: tubular hypothesis versus glomerular hypothesis

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The pathogenesis of renal interstitial fibrosis leading eventually to renal failure is highly debatable. Whereas the so-called tubular hypothesis, involving an increased tubular uptake of potentially toxic substances that induce a variety of cytokines, growth factors, and profibrogenic factors, is based to a large extent on cell-culture studies, the glomerular hypothesis is based mainly on careful morphological observations. Unraveling the pathways appears to be extremely complex, but *in vivo* studies appear to offer the most reliable results.

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Most if not all glomerular diseases involving extracapillary injury progressively develop extensive fibrotic processes, leading to nephron destruction and terminal renal failure. Two hypotheses have been put forward to account for this evolution. The first proposes that the primary event is tubular: the increased amount of protein that gains access to the proximal tubule, which results in increased protein trafficking in the proximal tubule cells, is toxic for the cells, thus triggering a number of inflammatory and fibrotic pathways. The second proposes that the primary event is glomerular: the formation of glomerular crescents leads to encroachment on the glomerular–tubular junction and subsequent tubular degeneration. Two recent studies provide additional data in this context.

Motoyoshi *et al.*[1] (this issue) induced massive glomerular proteinuria in a mouse model, mating mosaic megalin kidney knockout mice with a transgenic mouse, NEP25, in which podocytes

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expressing the transgene CD25 can be damaged by exposure to the immunotoxin LMB2 binding to CD25.[2] Ten days after exposure to LMB2, these mice showed mild glomerular injury, and only 5% of the glomeruli showed modest to severe changes. Similarly, the mice showed mild tubulointerstitial changes with occasional tubule dilatation, protein casts, and rare fibrosis. The megalin-expressing cells preferentially accumulated albumin and immunoglobulin, and these cells also showed upregulation in the expression of the tubule injury markers heme oxygenase-1, monocyte chemoattractant protein-1 (MCP-1), and apoptosis. The inevitable conclusion of the authors is that the increased reabsorption of proteins, notably high–molecular weight proteins, triggers events that can lead to tubule injury.

In a similar study, Theilig *et al.*[3] reached an apparently opposite conclusion. In this study, glomerulonephritis was induced in mosaic kidney-specific megalin knockout mice by injection of anti-mouse glomerular basement membrane serum, and the mice were analyzed 18 days later. The mice developed crescentic glomerulonephritis and tubulointerstitial disease with tubular dilation and casts, but also with atrophy, degeneration, and collapse. From a morphological analysis, the authors concluded that the tubulointerstitial changes were related directly to glomerular changes extending into the proximal tubular junction. They also concluded that excessive uptake of protein in megalin-expressing segments had no major impact on the development of tubulointerstitial disease. The authors suggested that the findings that cell proliferation and the inflammatory proteins transforming growth factor-β (TGF-β), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelin-1 were increased in megalin-expressing cells might be due to stress-protective functions rather than disease-induced mechanisms.

Before we discuss the apparent discrepancy between the two studies, it is worth taking a brief look at the arguments underlying each hypothesis.

The tubular hypothesis can be traced to a paper by Risdon and co-workers,[4] who first showed in human renal biopsies 40 years ago that progression to renal failure correlated more closely with tubular than with glomerular damage. Further evidence was derived from the close correlation between the levels of proteinuria and disease progression (reviewed by Abbate *et al.*[5]). The bulk of evidence in favor of a toxic role of reabsorbed proteins was obtained *in vitro* with the use of proximal tubular cells in culture. When exposed to a variety of plasma proteins, proximal tubular cells secrete cytokines such as endothelin-1, MCP-1, RANTES, interleukin-8, and fractalkine. Secreted cytokines appear to be released essentially at the basolateral pole, suggesting that they may indeed be involved in interstitial inflammation. They probably recruit and stimulate interstitial macrophages, which, under the influence of growth factors and profibrogenic factors such as TGF-β, transform interstitial cells into myofibroblasts. TGF-β may also be secreted by proximal tubular cells. The mechanisms of protein uptake have not been studied in detail, and, in particular, the expression of megalin and cubilin in cell-culture studies is often not documented. In contrast, the mechanisms involved in cytokine induction have been actively explored. Exposure of various cells to albumin activates nuclear factor-κB (NF-κB) via a pathway involving protein kinase C–dependent generation of peroxide, mitogen-activated protein kinases (including p38, ERK1, and ERK2), and STAT. As Figure 1[5] illustrates, autocrine loops may exist, amplifying the inflammatory response. Finally, glomerular-produced growth factors and/or cytokines may reach the tubule. *In vitro*, these cytokines upregulate their receptors and induce basal secretion of MCP-1 and RANTES. *In vivo* evidence relating increased protein trafficking to interstitial inflammation and fibrosis is limited. Production of MCP-1 and activation of the NF-κB pathway have been described in five-sixths nephrectomy and passive Heymann's nephritis. Similar observations have been reported in patients' biopsies. It has also been reported that knockdown of key components of the putative pathway (for example, MCP-1 or NF-κB) improved interstitial inflammation. These experiments establish a link between interstitial inflammation and cytokine production, but they do not provide evidence directly linking these findings to proteinuria. The latter relies on pharmacological studies using angiotensin-converting enzyme inhibitors, which decrease proteinuria, inhibit the production of MCP-1 and the activation of NF-κB, and limit the accumulation of cells in the interstitium.

The glomerular hypothesis (reviewed by Kriz and LeHir[6]), sometimes referred to as the overload hypothesis, relies almost entirely on careful morphological analysis of various models of glomerular diseases. It proposes that inflammatory or degenerative processes of the glomerulus invariably decrease podocyte density, resulting in naked areas of glomerular basement membrane to which parietal epithelial cells may adhere. Such adhesions of the tuft to the glomerular capsule result in misdirected filtration through a podocyte-deprived filtration barrier. This results in the formation of the so-called proteinaceous crescents, which progressively transform into cellular and fibrocellular crescents and encroach on the glomerular tubular junction, resulting in atubular glomeruli and aglomerular tubules (Figure 1).[6] Also, misdirected ultrafiltration may indeed occur and dissect tubular epithelial cells away from the tubular basement membrane. Key for this theory is the observation that a preserved tubule within damaged parenchymal and stromal tissue can be traced to a normal glomerulus. Dynamic experiments to further document this pathway are not easy to conceive. It has, however, been shown with the use of various tracers that misdirected ultrafiltration did occur.[7]

Of course, the two hypotheses are not mutually exclusive, and the objective at present is to define their role in a given pathological context. The paper by Motoyoshi *et al.*[1] and the paper by Theilig *et al.*[3] present data of significance in this context. First, both clearly show that megalin-dependent endocytosis significantly impacts the production of various markers of tubular injury, including proinflammatory/profibrotic components or adhesion molecules such as MCP-1 and heme oxygenase for Motoyoshi *et al.*[1] and TGF-β, ICAM-1,