Generation and Evolution of Atubular Glomeruli in the Progression of Renal Disorders

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ABSTRACT
Functional nephrons can be lost through a process of glomerulotubular disconnection. Progressive development of atubular glomeruli seems to play a major role in a number of renal disorders, including glomerular diseases, ascribed to injury to the glomerulotubular junction as a result of proteinuria; however, formation of atubular glomeruli is even more common in tubulointerstitial disorders, such as obstructive nephropathy. Toxic nephropathy is also associated with the formation of atubular glomeruli, suggesting susceptibility of the glomerulotubular junction to toxic injury. Narrowing or other abnormalities of the glomerulotubular junction are described as precursors of glomerulotubular disconnection. Cystinosis represents a dramatic example of progressive injury to the glomerulotubular junction, with formation of the “swan-neck deformity” following degenerative tubular cell changes attributable to apoptosis. Significant numbers of atubular glomeruli have been reported in chronic pyelonephritis and renal allograft rejection; this suggests interstitial inflammation as a stimulus for the formation of atubular glomeruli. Because of difficulties in morphologic recognition, it is likely that glomerulotubular disconnection is an underappreciated mechanism in the progression of renal disease. A better understanding of the vulnerability of the glomerulotubular junction and its protection from injury should lead to better strategies for preserving renal function in many nephropathies.


Whether congenital or acquired and whether predominantly glomerular or tubulointerstitial in origin, the majority of advancing renal disorders are characterized by progressive nephron loss. In typical glomerular disorders, such as diabetes or IgA nephropathy, heavy proteinuria is thought to contribute to nephron injury, whereas in tubulointerstitial disorders, such as pyelonephritis or obstructive nephropathy, destruction of the nephron begins in the renal tubule. There is ample evidence that acute renal injury resulting from ischemia or toxins can also lead to progressive nephron loss. This review presents an alternative perspective on nephron loss, focusing on glomerulotubular disconnection and the formation of atubular glomeruli and agglomerular tubules. Evidence is presented to support the hypothesis that the proximal tubule is particularly vulnerable to injury, thereby predisposing the damaged nephron to decapitation.

MECHANISMS OF NEPHRON LOSS
The current view of progressive renal disease emphasizes three major types of cellular injury: Release of injurious cytokines by invading inflammatory cells, phenotypic transition of tubular epithelial cells, and fibrosis.1 Outright destruction of the nephron can progress from involvement of the glomerulus, as in FSGS, or from the tubule, as in chronic renal allograft rejection. Once the destructive process becomes advanced, the end-stage kidney has a monotonous appearance of glomerular sclerosis, tubular atrophy, and interstitial fibrosis, which complicates identification of the original renal disease or injury. The appearance of atubular glomeruli in diseased kidneys was highlighted in the 1930s in elegant microdissection studies by Oliver and Luey,2 who conclusively demonstrated the presence of glomerulotubular disconnection in kidneys from patients with terminal Bright’s disease, which we now call chronic glomerulonephritis (Figure 1). They noted that proximal tubules are subject to disruption, which may result in fragmentation of the tubule into multiple small cysts the size and diameter of the original tubule.2

During the middle of the 20th century, attention shifted from remnants of damaged nephrons to the remaining intact nephrons and their adaptation.3,4 This was followed in the 1990s by a series of articles by Marcussen5–7 that reemphasized the importance of atubular glomeruli in a wide variety of clinical and experimental forms of renal disease:
Rather than microdissection, serial sections were used to show the discontinuity between glomeruli and tubules (Figure 2). Because of the time-consuming nature of either microdissection or serial sectioning, the formation of atubular glomeruli has been underappreciated in renal pathology. As shown in Table 1, glomerulotubular disconnection has thus far been described in proteinuric disorders, tubulointerstitial disorders, congenital metabolic disorders, and toxic nephropathies.

GLomerULOTUBULAR DISconnection

In a review, Lindop et al.8 presented evidence that certain characteristics of the glomerulotubular junction predispose it to injury. Most notable are disorders in which the glomerulotubular junction, the “neck” of the nephron, becomes progressively narrowed. Such a lesion is described in homotransplanted dog kidneys undergoing acute rejection.9 This is accompanied by leukocyte infiltration surrounding the lesion, which is attenuated by cortisone treatment.9 Leukocyte infiltration at the glomerulotubular junction has also been described in human renal allografts, associated with adhesion of the tip of the glomerular tuft to the origin of the tubule.10 In patients with chronic renal allograft rejection, 18% of glomeruli are atubular.11 Scanning electron microscopy of atubular glomeruli shows their Bowman’s capsules to be lined with podocytes that are continuous in some places with the capillary tuft.12 Cohen et al.13,14 reported progressive stenosis of the glomerulotubular junction in both pigs and rats with radiation nephropathy. These lesions are characterized by thinning of the tubular epithelial cells and progress to glomerulotubular disconnection with consequent formation of atubular glomeruli.14 Significantly, although it does not affect development of the stenotic lesion itself, treatment with an angiotensin-converting enzyme inhibitor prevents formation of atubular glomeruli.14 In rats with passive Heymann nephritis, treatment with an angiotensin-converting enzyme inhibitor prevents glomerulotubular disconnection and the formation of atubular glomeruli, possibly by decreasing proteinuria-induced apoptosis at the glomerulotubular junction.15 Studies showing that formation of atubular glomeruli is amenable to therapeutic manipulation are potentially important.

The most dramatic example of stenosis of the glomerulotubular junction is the “swan-neck deformity” described in nephropathic cystinosis (Figure 3).16 This is a progressive lesion that does not develop until after 6 mo of life and follows the accumulation of lysosomal cystine crystals in the tubular cells of the glomerulotubular junction.17 Intracellular glutathione is reduced in proximal tubular cells of children with cystinosis, and this is associated with reduced ATP levels after hypoxic stress and increased susceptibility to apoptosis.18 Increased apoptosis of proximal tubular cells in cystinosis seems to result from lysosomal cystine storage19,20 and leads to formation of atubular glomeruli (J.G. Thoene, MD, Biochemical Genetics Laboratory Di-
Table 1. Formation of atubular glomeruli

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Species</th>
<th>Model/Disorder</th>
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<td>Human</td>
<td>Chronic renal disease (Bright disease)</td>
<td>ATG and aglomerular tubules</td>
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<td>Chronic renal disease (Remnant kidney)</td>
<td>More ATG than sclerotic glomeruli</td>
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<td>Rat</td>
<td>Chronic renal disease (Remnant kidney)</td>
<td>Misdirected filtrate causes ATG</td>
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<td>Human</td>
<td>Congenital nephrotic syndrome</td>
<td>Persistence of fetal glomeruli leads to ATG</td>
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<td>Human</td>
<td>Diabetes</td>
<td></td>
<td>17% ATG</td>
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</tr>
<tr>
<td>Human</td>
<td>Diabetes</td>
<td></td>
<td>70% GTJ abnormalities in proteinuric patients with diabetes</td>
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<tr>
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<td>IgA nephropathy</td>
<td>GTJ stenosis associated with periglomerular fibrosis</td>
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<td>Glomerular “tip lesions” in 64%</td>
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<tr>
<td>Rat</td>
<td>Passive Heymann nephritis</td>
<td>ATG associated with increasing proteinuria, prevented by lisinopril</td>
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<td>Dog</td>
<td>Allograft rejection, acute</td>
<td>Narrowing of GTJ; inhibited by cortisone</td>
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<tr>
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<td>18% ATG; 19% sclerotic glomeruli</td>
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<td>Human</td>
<td>Allograft rejection, chronic</td>
<td>Up to 60% ATG</td>
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<td>Chloroform nephropathy</td>
<td>Increased renal tubular injury and greater proportion of cuboidal parietal epithelial cells in Bowman’s capsule in males versus females</td>
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<tr>
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<td>Cystinosis</td>
<td>ATG in child with cystinosis</td>
<td>J.G. Thoene (personal communication)</td>
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<td>Swan-neck deformity at GTJ</td>
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<td>Apoptosis in proximal tubular cells</td>
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<td>60% ATG</td>
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<td>40% ATG; enalapril decreased proteinuria and glomerular sclerosis, but not fraction of ATG</td>
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<td>Human</td>
<td>Obstructive nephropathy</td>
<td>Proximal tubular diverticula and “beading”</td>
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<td>Mouse</td>
<td>Obstructive nephropathy</td>
<td>ATG in neonate</td>
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<td>Obstructive nephropathy in children</td>
<td>Renin present in ATG in fibrotic areas</td>
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<td>Obstructive nephropathy, pyelonephritis</td>
<td>6 to 31% ATG</td>
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<td>ATG</td>
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<td>Radiation nephropathy</td>
<td>Progressive narrowing of GTJ</td>
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<td>Rat</td>
<td>Radiation nephropathy</td>
<td>Narrowing of GTJ and ATG prevented by captopril</td>
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<td>Human</td>
<td>Renal artery stenosis</td>
<td>50% ATG</td>
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<td>Toxic</td>
<td>Rat</td>
<td>Adriamycin nephrosis</td>
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<td>80% ATG</td>
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<td>Lithium nephropathy</td>
<td>30% ATG</td>
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*ATG, atubular glomeruli; GTJ, glomerulotubular junction.

rector and Active Professor Emeritus of Pediatrics, University of Michigan, Ann Arbor, MI, personal communication, May 11, 2007).

GLOMERULOTUBULAR JUNCTION

There are significant species differences in the location of the transition from the squamous parietal epithelial cells lining Bowman’s capsule to cuboidal epithelial cells forming the proximal tubule. The point of transition varies: Squamous cells constitute the initial proximal tubule in the rabbit, cuboidal cells extend well onto the parietal surface of Bowman’s capsule in the mouse, and in human, the transition occurs where the proximal tubule contacts the glomerular sphere. In the mouse, >80% of glomeruli in males and females contain mainly squamous parietal epithelial cells during the first 3 wk of life; however, by 7 wk, the fraction containing squamous cells decreases to 25% in males, whereas females remain at 74%. Castration of adult male mice maintains a high fraction of glomeruli with parietal squamous cells, whereas treatment with testosterone markedly decreases the fraction. Remarkably, chloroform-induced toxic nephropathy in adult mice leads to tubular necrosis in males or castrated males treated with testosterone but neither in normal females nor in castrated males. These differences correspond to a preponderance of cuboidal cells lining Bowman’s capsule in normal males and castrated males treated with testosterone, with a prepon-
derance of squamous cells in both normal females and castrated males. These observations reveal a striking correlation among susceptibility to renal tubular injury, androgen levels, and the phenotype of epithelial cells lining Bowman’s capsule. This correlation may have clinical relevance: Progression of nondiabetic renal disease is greater in men than in women.

In rabbits, as mentioned, squamous epithelial cells extend down the initial proximal tubule; these cells contain actin-like filaments and few mitochondria, which may make them more resistant to hypoxic injury. Notably, although antibodies to epithelial membrane antigen, a glycoprotein in human milk fat globules, normally bind to all parts of the human nephron except proximal tubules and glomeruli, they also bind to the sharply defined transition from squamous to cuboidal epithelium. In proteinuric diseases, the antibody binds to damaged proximal tubules, which can develop flattened, or squamous, phenotypic transformation. Squamous epithelial cells extend down the initial proximal tubule of 10% of nephrons in normal human renal tissue, whereas in nephrectomy specimens, cuboidal cells occupy Bowman’s capsule in up to 18% of nephrons. Cuboidal glomerular parietal epithelial cells may reflect a broad range of human glomerular injury, and these have been described as “prominent parietal epithelium” or as “metaplasia” associated with hypertension or hepatic disease. Cuboidal glomerular parietal epithelial cells have been described in rats after unilateral nephrectomy and in spontaneously hypertensive rats.

VULNERABILITY OF THE PROXIMAL TUBULE TO INJURY AND ENDOGENOUS DEFENSES

There is growing evidence that the proximal tubule is particularly susceptible to various forms of injury, which may explain the formation of atubular glomeruli in renal disease. Renal artery stenosis in human results in greater atrophy of proximal than distal tubules, as well as a very high proportion of atubular glomeruli (52%). Acute bilateral ureteral obstruction in rats results in a prompt increase in urinary excretion of renal tubular epithelial antigens that are derived from the proximal tubular brush border. Depletion of ATP in mouse proximal tubular cells leads to apoptosis if moderate (25 to 75% depletion) but necrosis if severe (>75% depletion). Proximal convoluted tubules are the most severely hypoxic nephron segment in the immature mouse kidney, and immortalized rat proximal tubular cells subjected to hypoxia develop progressive decrements in Bcl-2, leading to cell death by apoptosis. After ischemia/reperfusion in the rat, proximal tubular cells are

Figure 3. Microdissected nephrons from a patient with cystinosis. The first portion of each proximal tubule is markedly narrowed, illustrating the “swan-neck deformity.”

Figure 4. Correlation of GFR with the fraction of glomeruli connected to normal tubular segments 20 wk after acute ischemic injury to a solitary kidney of the rat. $R^2 = 0.79$, $P = 0.0002$. 

BRIEF REVIEW
the main source for synthesis of reactive oxygen species (ROS), which are not produced by distal tubular cells. This results in marked proximal tubular apoptosis, which can be prevented by administration of superoxide dismutase, a scavenger of ROS. Increased lipid peroxidation potential and low levels of catalase place the neonatal kidney at significantly greater risk for oxidative damage, compared with the adult. Chronic unilateral ureteral obstruction (UUO) also stimulates the selective proximal tubular expression of TGF-β1, a cytokine that promotes apoptosis and epithelial-to-mesenchymal transition. Available data therefore suggest that renal hypoxic or oxidant injury most likely targets the proximal tubule, eliciting a response mediated by limited resistance to inflammation, apoptosis, or epithelial-to-mesenchymal transition. These factors contribute to the preferential site for glomerulotubular disconnection being within the proximal tubule.

GLOMERULAR DISORDERS

Glomerulotubular junction stenosis has been reported in patients with IgA nephropathy and is associated with the generation of atubular glomeruli and the progression of periglomerular fibrosis. Infants with congenital nephrotic syndrome develop increasing numbers of atubular glomeruli with age, as a result of progressive and massive glomerulotubular disconnection. It is likely that the heavy proteinuria beginning in fetal life acts to accelerate the process, compared with disconnection occurring in mature glomeruli. The formation of atubular glomeruli also has been reported in diabetes, with a marked increase in glomerulotubular junction abnormalities in patients with proteinuric. Abnor-

Figure 5. Kidneys from eNOS knockout mice. (A) Sagittal section through the renal cortex of a 14-d-old mouse stained with the Apoptag (terminal deoxynucleotidyl transferase-mediated digoxigenin-deoxyuridine nick-end labeling) technique. A discrete wedge of selectively stained tissue is present. (B) Apoptosis in a degenerating zone. Although the glomerulus lacks any staining, an adjacent proximal tubule (shown in serial sections to be continuous with the glomerulus) contains several apoptotic epithelial nuclei (arrows). (C) Adult mouse kidney showing a scar on the left side. (D) Semithin plastic section through scar, showing clustered small atubular glomeruli embedded in a complex of microvessels, interstitial cells, and fragmented tubule remnants. (E and F) Adult mouse kidney tissue stained with platelet-endothelial cell adhesion molecule-1 to identify vascular endothelium. (E) Section from atubular scar showing blood vessel profiles concentrated as glomerular capillaries (GC) and interstitial vessels (V). (F) Section from adjacent normal renal parenchyma showing spacing of glomeruli among tubules. Bar = 500 μm in A; 25 μm in B; 2 μm in C; 100 μm in D; 100 μm in E and F.
malities of the glomerulotubular junction have been described in patients with membranous nephropathy, with glomerular “tip lesions.” These lesions of the glomerular tuft opposite the glomerulotubular junction are associated with a variety of proteinuric conditions, including FSGS. The tip lesion has been induced in a rat model of anti–glomerular basement membrane (anti-GBM) nephritis, associated with localized inflammatory infiltrate, prolapse of swollen podocytes into the origin of the proximal tubule, and formation of adhesions between the GBM and Bowman’s capsule. In rats with anti-GBM nephritis or renal ablation, glomerular cells undergo epithelial-to-myofibroblast transition in the evolution of glomerular crescents; these are associated with the localized development of columnar epithelium at the glomerular tip. Kriz and co-workers emphasized the importance of the extension of proteinaceous crescents onto the outer aspect of the proximal tubule at the glomerulotubular junction, leading to its constriction and to the formation of atubular glomeruli.

TUBULAR DISORDERS

In rats with renal ablation, tubular injury leading to glomerulotubular disconnection causes loss of remnant nephron function before glomerulosclerosis has progressed. Six months after renal ablation, atubular glomeruli with open capillary loops are more numerous than globally sclerotic glomeruli, thus suggesting that tubular injury precedes glomerular loss.

PYELONEPHRITIS

In a microdissection study of human renal disease, Fetterman described diverticula along tubules from patients with pyelonephritis and with congenital renal disorders. Proximal tubules are affected in 88% of cases, proximal tubules alone in 55%, and distal tubules alone in only 9%. Atubular glomeruli are common in pyelonephritic kidneys, which are characterized by reduced glomerular and proximal tubular volume. Selective destruction of the proximal tubule has also been demonstrated in experimental pyelonephritis.

Obstructive Nephropathy

The presence of atubular glomeruli in obstructive nephropathy was first described in dogs subjected to UUO; these glomeruli are perfused but nonfiltering. In children with obstructive ne...

Figure 6. Kidneys from mice subjected to partial UUO. (A and B) Serial section arrays from 21-d-old mice stained with Lotus tetragonolobus lectin to identify proximal tubule epithelium. (A) Consecutive sections of a glomerulus from the intact contralateral kidney showing continuity of the lectin-stained cells of Bowman’s capsule with proximal tubule (lectin positivity is present within the glomerulus in all sections). (B) Sections of glomeruli from the kidney after relief of 5 d of ipsilateral partial ureteral obstruction. Although lectin-positive profiles appear in the region, none of them is connected to the glomeruli, which are smaller than their lectin-positive counterparts in A, indicating that such glomeruli are atubular. (C and D) Sections of a persistently obstructed kidney from a 42-d-old mouse. (C) An atrophic proximal tubule is distorted, with a tortuous lumen of varying bore and an atubular glomerulus (G). (D) Proximal tubular remnants are present near an atubular glomerulus (G), and densely staining material fills their luminal cavities, indicating that the tubules have shrunk and undergone fragmentation. (E) Proposed scheme of formation of atubular glomeruli. (1) In the mouse glomerulus, columnar epithelial cells extend from the proximal convoluted tubule (PCT) onto the parietal surface of Bowman’s capsule. (2) Consequent to partial UUO, apoptotic nuclei appear at the glomerulotubular junction, leading there to thickening of the basement membrane (between small arrows) and marked thinning of the tubule diameter. (3 through 5) The PCT becomes disconnected from the glomerulus and continues to degenerate. Bar = 100 μm in B and applies to all 10 panels in A and B; 25 μm in D and applies to both C and D.
phropathy or reflux nephropathy, atubular glomeruli were found to contain immunoreactive renin, which may contribute to hypertension in these patients. In a recent study of 61 children undergoing pyeloplasty for ureteropelvic junction obstruction, increased glomerular density and decreased proximal/distal size ratio emerged as correlates of severity of obstruction and postoperative functional decline. Similar to the case in human obstructive nephropathy, ureteral obstruction in the pig also leads to proximal tubular shortening and reduction in proximal tubular volume, and this is preceded by decreased mitochondria and surface area of basolateral membranes.

Apoptosis is present in human fetuses and infants with lower urinary tract obstruction. Tubular apoptosis and small crowded glomeruli are found also in kidneys of neonatal mice subjected to chronic partial UUO. In this model, atubular glomeruli were readily identified by the absence of lectin-staining columnar parietal epithelial cells that normally extend from the proximal tubule onto Bowman’s capsule in this species (Figure 6, A and B). Renal microdissection studies in children with obstructive uropathy reveal “beading” or segmentation and diverticula along the initial length of the proximal tubule (Figure 7). It is likely that progression of proximal tubular segmentation leads to fragmentation of the tubule, as shown in neonatal mice subjected to partial UUO (Figure 6, C through E). Obstruction of single nephrons causes loss of proximal tubule epithelial cell microvilli, with reductions in the cells’ mitochondria and basolateral interdigitations. It is notable that tubular obstruction plays a role in the progression of polycystic kidney disease in rats. Nephrons in these animals develop narrowing of the glomerulotubular junction, with 50% of glomeruli becoming atubular.

**Toxic Nephropathy**

In newborn rats subjected to long-term administration of lithium, the majority of glomeruli become atubular. There is a significant correlation between decrease in GFR and the fraction of atubular glomeruli. A similar correlation has been shown for experimental cisplatin and Adriamycin nephropathy. As discussed, increased susceptibility of the proximal tubule to oxidant injury may play a major role in this process.

**CONCLUSIONS**

In addition to describing the formation of atubular glomeruli in diseased human kidneys, Oliver was intrigued by his observation of apparently hypertrophied aglomerular tubules and their similarity to those in the daddy sculpin (*Myxocephalus scorpius*). This fish begins life with kidneys that contain glomeruli, but as it matures, there is progressive destruction of the glomerulotubular junction, with formation of atubular glomeruli and aglomerular tubules (Figure 8). In his monograph *From Fish to Philosopher*, Smith reviewed the evolutionary pressures for marine fish to curtail glomerular filtration, thereby explaining the

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**Figure 7.** Two microdissected glomeruli and proximal convoluted tubules from kidney of 17-yr-old patient with obstructive uropathy. There are multiple diverticula of the proximal tubule on the left and “beading” segmentation of the tubule on the right. Such segmentation is presumably the process by which isolated blind residual tubular segments form.

**Figure 8.** Microdissected nephrons from *Myxocephalus scorpius*, a fish with both glomerular and aglomerular tubules. On the left is a glomerulus with tapering proximal tubule ending blindly (atubular glomerulus). On the right is an aglomerular tubule from the same fish.
presence of aglomerular tubules in a number of species. Oliver postulated that hypertrophied aglomerular tubules in human renal disease may represent an attempt at adaptation to nephron loss by enhancing tubular secretion but one that is insufficient to maintain life: “That the transformation of the human kidney by the disease can never reach the state of completeness that characterizes the involutional process in the fish is readily understandable, since man has none of those auxiliary mechanisms of excretion that are peculiar to water-living forms. He dies, therefore, before his kidney is aglomerular, as perhaps would the fish if it had not gills to help in elimination.”

Regardless of whether glomerulotubular disconnection originated as an adaptation to renal injury, it ultimately seems to be a maladaptive response that contributes to the progression of renal insufficiency on land. The correlation of GFR with glomerulotubular integrity and improvement in renal function with preservation of glomerulotubular continuity in experimental renal disorders are consistent with this premise.

There is considerable evidence that the proximal tubule is especially vulnerable to a variety of forms of injury (Figure 9). The mediators and modulators of injury are those ascribed to most progressive renal damage, including inflammation, cell death, cellular phenotypic transition, and fibrosis. New approaches should be developed to study the mechanisms underlying glomerulotubular disconnection, and these should lead to novel therapies that will prevent this process from developing.

DISCLOSURES
None.

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