immune complexes can precipitate along the subendothelial side of the GBM, while other immune deposits form in situ on the subepithelial side. These latter deposits accumulate when circulating autoantibodies find their antigen trapped along the subepithelial edge of the GBM. Immune deposits in the glomerular mesangium may result from the deposition of preformed circulating complexes or in situ antigen-antibody interactions. Immune deposits stimulate the release of local proteases and activate the complement cascade, producing C_{5-9} attack complexes. In addition, local oxidants damage glomerular structures, producing proteinuria and effacement of the podocytes. Overlapping etiologies or pathophysiologic mechanisms can produce similar glomerular lesions, suggesting that downstream molecular and cellular responses often converge toward common patterns of injury.

PROGRESSION OF GLOMERULAR DISEASE

Persistent glomerulonephritis that worsens renal function is always accompanied by interstitial nephritis, renal fibrosis, and tubular atrophy **(see Fig. 62e-27)**. What is not so obvious, however, is that renal failure in glomerulonephritis best correlates histologically with the appearance of tubulointerstitial nephritis rather than with the type of inciting glomerular injury.

Loss of renal function due to interstitial damage is explained hypothetically by several mechanisms. The simplest explanation is that urine flow is impeded by tubular obstruction as a result of interstitial inflammation and fibrosis. Thus, obstruction of the tubules with debris or by extrinsic compression results in aglomerular nephrons. A second mechanism suggests that interstitial changes, including interstitial edema or fibrosis, alter tubular and vascular architecture and thereby compromise the normal tubular transport of solutes and water from tubular lumen to vascular space. This failure increases the solute and water content of the tubule fluid, resulting in isosthenuria and polyuria. Adaptive mechanisms related to tubuloglomerular feedback also fail, resulting in a reduction of renin output from the juxtaglomerular apparatus trapped by interstitial inflammation. Consequently, the local vasoconstrictive influence of angiotensin II on the glomerular arterioles decreases, and filtration drops owing to a generalized decrease in arteriolar tone. A third mechanism involves changes in vascular resistance due to damage of peritubular capillaries. The cross-sectional volume of these capillaries is decreased by interstitial inflammation, edema, or fibrosis. These structural alterations in vascular resistance affect renal function through two mechanisms. First, tubular cells are very metabolically active, and, as a result, decreased perfusion leads to ischemic injury. Second, impairment of glomerular arteriolar outflow leads to increased intraglomerular hypertension in less-involved glomeruli; this selective intraglomerular hypertension aggravates and extends *mesangial sclerosis* and *glomerulosclerosis* to less-involved glomeruli. Regardless of the exact mechanism, early *acute tubulointerstitial nephritis* **(see Fig. 62e-27)** suggests potentially recoverable renal function, whereas the development of *chronic interstitial fibrosis* prognosticates permanent loss **(see Fig. 62e-30)**.

Persistent damage to glomerular capillaries spreads to the tubulointerstitium in association with proteinuria. There is a hypothesis that efferent arterioles leading from inflamed glomeruli carry forward inflammatory mediators, which induces downstream interstitial nephritis, resulting in fibrosis. Glomerular filtrate from injured glomerular capillaries adherent to Bowman's capsule may also be misdirected to the periglomerular interstitium. Most nephrologists believe, however, that proteinuric glomerular filtrate forming tubular fluid is the primary route to downstream tubulointerstitial injury, although none of these hypotheses are mutually exclusive.

The simplest explanation for the effect of proteinuria on the development of interstitial nephritis is that increasingly severe proteinuria, carrying activated cytokines and lipoproteins producing reactive oxygen species, triggers a downstream inflammatory cascade in and around epithelial cells lining the tubular nephron. These effects induce T lymphocyte and macrophage infiltrates in the interstitial spaces along with fibrosis and tubular atrophy.

Tubules disaggregate following direct damage to their basement membranes, leading to epithelial-mesenchymal transitions forming more interstitial fibroblasts at the site of injury. Transforming growth factor β (TGF-β), fibroblast growth factor 2 (FGF-2), hypoxemia-inducible factor 1α (HIF-1α), and platelet-derived growth factor (PDGF) are particularly active in this transition. With persistent nephritis, fibroblasts multiply and lay down tenascin and a fibronectin scaffold for the polymerization of new interstitial collagen types I/III. These events form scar tissue through a process called fibrogenesis. In experimental studies, bone morphogenetic protein 7 and hepatocyte growth factor can reverse early fibrogenesis and preserve tubular architecture. When fibroblasts outdistance their survival factors, apoptoses occurs, and the permanent renal scar becomes acellular, leading to irreversible renal failure.

APPROACH TO THE PATIENT: Glomerular Disease

HEMATURIA, PROTEINURIA, AND PYURIA

Patients with glomerular disease usually have some hematuria with varying degrees of proteinuria. Hematuria is typically asymptomatic. As few as three to five red blood cells in the spun sediment from first-voided morning urine is suspicious. The diagnosis of glomerular injury can be delayed because patients will not realize they have *microscopic hematuria,* and only rarely with the exception of IgA nephropathy and sickle cell disease is *gross hematuria* present. When working up microscopic hematuria, perhaps accompanied by minimal proteinuria (<500 mg/24 h), it is important to exclude anatomic lesions, such as malignancy of the urinary tract, particularly in older men. Microscopic hematuria may also appear with the onset of benign prostatic hypertrophy, interstitial nephritis, papillary necrosis, hypercalciuria, renal stones, cystic kidney diseases, or renal vascular injury. However, when red blood cell casts **(see Fig. 62e-34)** or dysmorphic red blood cells are found in the sediment, glomerulonephritis is likely.

Sustained proteinuria >1–2 g/24 h is also commonly associated with glomerular disease. Patients often will not know they have proteinuria unless they become edematous or notice foaming urine on voiding. *Sustained proteinuria* has to be distinguished from lesser amounts of so-called *benign proteinuria* in the normal population **(Table 338-1)**. This latter class of proteinuria is nonsustained, generally <1 g/24 h, and is sometimes called *functional* or *transient proteinuria*. Fever, exercise, obesity, sleep apnea, emotional stress, and congestive heart failure can explain transient proteinuria. Proteinuria only seen with upright posture is called *orthostatic proteinuria* and has a benign prognosis. Isolated proteinuria sustained over multiple clinic visits is found in many glomerular lesions. Proteinuria in most adults with glomerular disease is *nonselective,* containing albumin and a mixture of other serum proteins, whereas in children with *minimal change disease,* the proteinuria is *selective* and composed largely of albumin.

TABLE 338-1 URINE ASSAYS FOR ALBUMINURIA/PROTEINURIA

	24-Hour Albumin[a] (mg/24 h)	Albumin[a] /Creatinine Ratio (mg/g)	Dipstick Proteinuria	24-Hour Urine Protein[b] (mg/24 h)
Normal	8–10	<30	–	<150
Microalbuminuria	30–300	30–300	–/Trace/1+	–
Proteinuria	>300	>300	Trace–3+	>150

[a]Albumin detected by radioimmunoassay. [b] Albumin represents 20–60% of the total protein excreted in the urine.