involvement, there is focal and segmental, sometimes necrotizing, glomerulonephritis, and most of these patients will have hematuria with mild decline in GFR. In the more severe cases, which may be associated with RPGN, there is more extensive necrosis, fibrin deposition, and extensive formation of epithelial (cellular) crescents, which can become organized to form fibrocellular and fibrous crescents if the glomerular injury evolves into segmental or global scarring (sclerosis).

Essential mixed cryoglobulinemia is another systemic condition in which deposits of cryoglobulins composed principally of IgG-IgM complexes induce cutaneous vasculitis, synovitis, and a proliferative glomerulonephritis, typically MPGN. Most cases of essential mixed cryoglobulinemia have been associated with infection with hepatitis C virus, and this condition in particular is associated with glomerulonephritis, usually MPGN type I.

Immunoglobulins secreted by plasma cell neoplasms may also induce glomerular lesions, including amyloidosis.

Tubular and Interstitial Diseases

Most forms of tubular injury involve the interstitium as well; therefore, diseases affecting these two components are discussed together. Under this heading we consider two major processes: (1) ischemic or toxic tubular injury, and (2) inflammatory reactions of the tubules and interstitium *(tubulointerstitial nephritis)*.

Acute Tubular Injury/Necrosis

Acute tubular injury (ATI) is a clinicopathologic entity characterized clinically by acute renal failure and often, but not invariably, morphologic evidence of tubular injury, in the form of necrosis of tubular epithelial cells. Since necrosis is not invariable, the term ATI is now preferred over the older term acute tubular necrosis (ATN). It is the most common cause of acute kidney injury (acute renal failure). ATI can be caused by a variety of conditions, including

- *Ischemia, due to decreased or interrupted blood flow*, examples of which include diffuse involvement of the intrarenal blood vessels such as in microscopic polyangiitis, malignant hypertension, microangiopathies and systemic conditions associated with thrombosis (e.g., hemolytic uremic syndrome [HUS], thrombotic thrombocytopenic purpura [TTP], and disseminated intravascular coagulation [DIC]), or decreased effective circulating blood volume, as occurs in hypovolemic shock (Chapter 4)
- *Direct toxic injury to the tubules by endogenous* (e.g., myoglobin, hemoglobin, monoclonal light chains, bile/bilirubin) *or exogenous agents* (e.g., drugs, radiocontrast dyes, heavy metals, organic solvents)

ATI accounts for some 50% of cases of acute kidney injury in hospitalized patients. Other causes of acute renal failure are discussed elsewhere in this chapter.

ATI is a reversible process that arises in a variety of clinical settings. Most of these, ranging from severe trauma to acute pancreatitis, have in common a period of inadequate blood flow to the peripheral organs, usually accompanied by marked hypotension and shock. This pattern is called *ischemic ATI*. The second pattern, called *nephrotoxic ATI*, is caused by a multitude of drugs, such as gentamicin; radiographic contrast agents; poisons, including heavy metals (e.g., mercury); and organic solvents (e.g., carbon tetrachloride). Combinations of ischemic and nephrotoxic ATI also can occur, exemplified by mismatched blood transfusions and other hemolytic crises causing *hemoglobinuria* and skeletal muscle injuries causing *myoglobinuria*. Such injuries result in characteristic intratubular hemoglobin or myoglobin casts, respectively; the toxic iron content of these globin molecules contributes to the ATI. In addition to its frequency, the potential reversibility of ATI adds to its clinical importance. Proper management can make the difference between recovery and death.

Pathogenesis. **The critical events in both ischemic and nephrotoxic ATI are believed to be (1) tubular injury and (2) persistent and severe disturbances in blood flow** (Fig. 20-22).

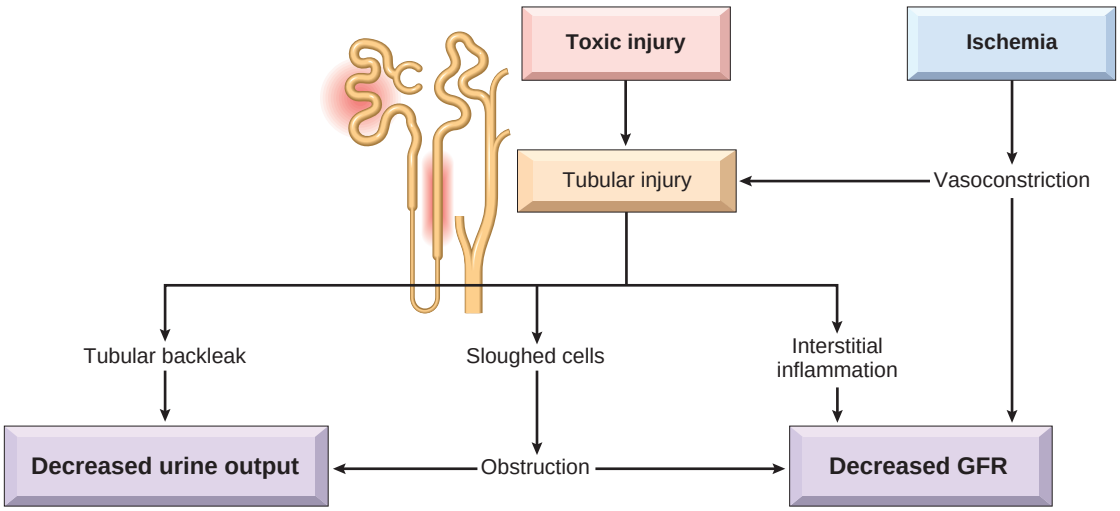

Figure 20-22 Postulated sequence in ischemic or toxic acute tubular injury.