severe hypertension, often malignant, in a patient with a disease flare. Urinalysis and urine microscopy may be bland or may show cellular activity. Fibrinoid necrosis with ischemic injury occurs in the kidney. ACE inhibitors effectively control BP and improve AKI.

Rarely, AKI may develop in the setting of renal vein thrombosis, a well-known complication of nephrotic syndrome. Imbalance of anticoagulant substances lost in the urine and procoagulant substances produced by the liver leads to a hypercoagulable state and renal vein thrombosis. AKI is thought to develop from raised intrarenal pressures and reduced kidney perfusion. Therapy includes acute thrombolysis and chronic anticoagulation as well as treatment of the underlying glomerular lesion (often membranous nephropathy) and reduction in proteinuria.

Glomerular Disease

A number of glomerular diseases can cause AKI, and the more common entities are reviewed here. Acute proliferative GN may be broadly classified as (1) immune complex disease, (2) pauci-immune disease, or (3) anti-GBM–related disease. They are all characterized by glomerular cell proliferation and necrosis, polymorphonuclear cell infiltration, and, with severe injury, epithelial crescent formation (E-Fig. 31-4). Acute proliferative GN manifests with hypertension and edema formation and with laboratory results pertinent for hematuria and proteinuria, described as *nephritic sediment*. Examination of the urine sediment classically reveals dysmorphic RBCs and RBC casts. Therapy is directed at the underlying cause, with supportive measures and RRT as necessary.

TTP and HUS are two of the more common causes of thrombotic microangiopathy, which is marked by platelet deposition and endothelial injury with thrombosis of arterioles and glomerular capillaries. AKI results from severe glomerular damage with profound ischemia and necrosis. The thrombotic microangiopathies may manifest with nephritic sediment. Patients with HUS may have severe AKI, or it may be mild, as in patients with TTP. Microangiopathic hemolytic anemia and thrombocytopenia are key features. Therapy often includes modulation of the immune system with plasma exchange or eculizumab, in addition to supportive measures.

The dysproteinemias, which deposit monoclonal immunoglobulin light or heavy chains (or both) in the kidney, may also promote glomerular lesions. The type, metabolism, and packaging of the immunoglobulin determine which type of glomerular lesion develops: light or heavy chain deposition disease, amyloidosis, or one of the fibrillary GNs. The immunoglobulin deposition diseases often manifest with nephrotic proteinuria and AKI, rarely with hematuria.

Light chain deposition disease, heavy chain deposition disease, and light/heavy chain deposition disease cause nodular glomerular lesions. Amyloidosis is also associated with the formation of acellular glomerular nodules. The fibrillary GNs (fibrillary and immunotactoid) may be associated with mesangial expansion or glomerular nodules. More commonly, they appear as a mesangial proliferative, mesangiocapillary, or membranous lesion, sometimes with formation of epithelial crescents. These diseases can be distinguished by electron microscopy. Light and heavy chain diseases produce granular deposits, whereas amyloidosis appears as haphazard fibrils in the 8- to 12-nm size range. Fibrillary GN has fibrils in 20- to 30-nm range, and immunotactoid GN shows fibrils in the 30- to 50-nm range with organized microtubular fibrils.

Tubular Disease

Acute Tubular Necrosis

ATN is the most common form of hospital-acquired intrinsic AKI, accounting for more than 80% of AKI episodes. It is classically divided into ischemic ATN, which makes up almost 50% of the cases, nephrotoxic ATN, and combinations of both. In many instances, ATN results from multiple insults acting together to injure the kidney. The end result of either ischemic or toxic insult is tubular cell injury and death. E-Table 31-4 outlines the important factors underlying the pathogenesis of ATN.

Ischemic ATN

Ischemic ATN is, for the most part, an extension of severe and uncorrected prerenal AKI. Prolonged renal hypoperfusion causes tubular cell injury, which persists even after the underlying hemodynamic insult resolves and may be associated with ischemia-reperfusion injury. Intraoperative and postoperative hypotension impairs renal perfusion and occurs relatively frequently after cardiac and vascular surgical procedures. Ischemic, nephrotoxic, and multifactorial ATN are common on the medical wards and in the ICU. Risk for ischemic ATN is increased by the comorbidities these patients possess. Sepsis and septic shock, severe intravascular volume depletion, cirrhotic physiology, and cardiogenic shock are examples of situations that confer high risk for development of ischemic ATN. Employment of vasopressors to restore BP may further reduce renal perfusion and exacerbate ischemia. In some cases, ischemic ATN is so profound that cortical necrosis (ischemic atrophy of the renal cortex) develops.

Nephrotoxic ATN

Nephrotoxic ATN occurs when exogenous substances injure the tubules, primarily through direct toxic effects but also through perturbations in intrarenal hemodynamics or a combination of these factors. In the past, organic solvents and heavy metals (e.g., mercury, cadmium, lead) were a frequent cause of ATN. Since then, many potentially toxic medications have been synthesized and observed to cause tubular injury by multiple mechanisms.

Aminoglycosides cause proximal tubular injury. AKI rarely develops within the first week of therapy, and injury initially manifests with subtle changes in urine concentrating ability and increased RTECs and granular casts in the urine sediment. The antifungal agent amphotericin B induces AKI through two distinct mechanisms: destruction of cellular membranes through sterol interactions and vasoconstriction-induced tubular ischemia. ATN develops in a dose-dependent fashion and manifests with increasing serum creatinine levels and RTECs and granular casts in the urine. Liposomal and lipid complex formulations are less nephrotoxic but can precipitate AKI in high-risk patients.

Radiocontrast material is a common cause of AKI because it is so widely used with imaging procedures. AKI develops in patients with underlying risk factors such as CKD, especially diabetic nephropathy, "true" or "effective" intravascular volume