glomerulonephritis has been de-emphasized. ANCAs have proved to be invaluable as a highly sensitive diagnostic marker for pauci-immune crescentic glomerulonephritis, but proof of their role as a direct cause of this glomerulonephritis has been elusive. Recent evidence of their pathogenic potential has been obtained by studies in mice showing that transferring antibodies against myeloperoxidase (the target antigen of most p-ANCAs) induces a form of RPGN.

To summarize, about one fifth of patients with RPGN have anti-GBM antibody-mediated glomerulonephritis without lung involvement; another one fourth have immune complex-mediated crescentic glomerulonephritis; and the remainder are of the pauci-immune type.

MORPHOLOGY

The kidneys are enlarged and pale, often with petechial hemorrhages on the cortical surfaces. Depending on the underlying cause, the glomeruli often show focal and segmental necrosis, and variably show diffuse or focal endothelial proliferation, and mesangial proliferation. Segmental glomerular necrosis adjacent to glomerular segments uninvolved by inflammatory or proliferative changes is the feature most typical of pauci-immune RPGN. The histologic picture, however, is dominated by distinctive **crescents** (Fig. 20-10). Crescents are formed by proliferation of parietal cells and by migration of monocytes and macrophages into the urinary space. Neutrophils and lymphocytes may be present. The crescents may obliterate the urinary space and compress the glomerular tuft. **Fibrin strands are frequently prominent between the cellular layers in the crescents;** indeed, as discussed earlier, the escape of procoagulant factors, fibrin and cytokines into Bowman space may contribute to crescent formation. By immunofluorescence microscopy, immune complex-mediated cases show granular immune deposits; Goodpasture syndrome cases show linear GBM fluorescence for Ig and complement, and pauci-immune cases have little or no deposition of immune reactants. Electron microscopy discloses deposits in those cases due to immune complex deposition (type II). Regardless of type, electron microscopy may show **ruptures in the GBM,** a severe injury that allows leukocytes, plasma proteins such as coagulation factors and complement, and inflammatory mediators to reach the urinary space, where they trigger crescent formation (Fig. 20-11). In time, most crescents undergo organization and foci of segmental necrosis resolve as segmental scars (a type of segmental sclerosis), but restoration of normal glomerular architecture may be achieved with early aggressive therapy.

Clinical Course. The renal manifestations of all forms of crescentic glomerulonephritis include hematuria with red blood cell casts in the urine, moderate proteinuria occasionally reaching the nephrotic range, and variable hypertension and edema. In Goodpasture syndrome the course may be dominated by recurrent hemoptysis or even life-threatening pulmonary hemorrhage. Serum analyses for anti-GBM antibodies, antinuclear antibodies, and ANCAs are helpful in the diagnosis of specific subtypes. Although milder forms of glomerular injury may subside, the renal involvement is usually progressive over a matter of weeks and culminates in severe oliguria. Recovery of renal function may follow early intensive plasmapheresis (plasma exchange) combined with steroids and cytotoxic agents in Goodpasture syndrome. This therapy can reverse both pulmonary hemorrhage and renal failure. Other forms of RPGN also respond well to steroids and cytotoxic agents. However, despite therapy, many patients eventually require chronic dialysis or transplantation, particularly if the disease is discovered at a late stage.

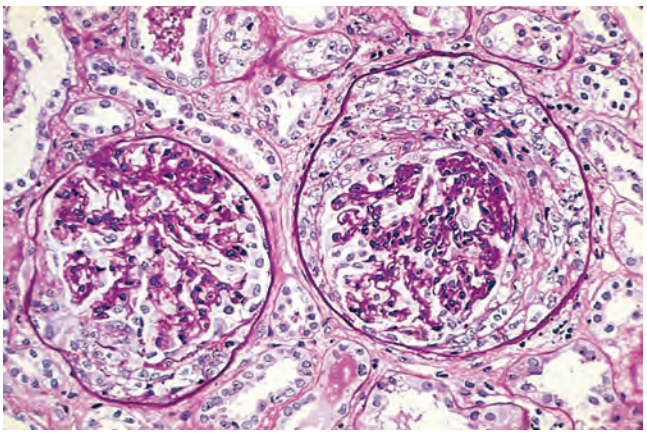

Figure 20-10 Crescentic glomerulonephritis (PAS stain). Note the collapsed glomerular tufts and the crescent-shaped mass of proliferating parietal epithelial cells and leukocytes internal to Bowman capsule. (Courtesy Dr. M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, Tex.)

KEY CONCEPTS

The Nephritic Syndrome

- The nephritic syndrome is characterized by hematuria, oliguria with azotemia, proteinuria, and hypertension.

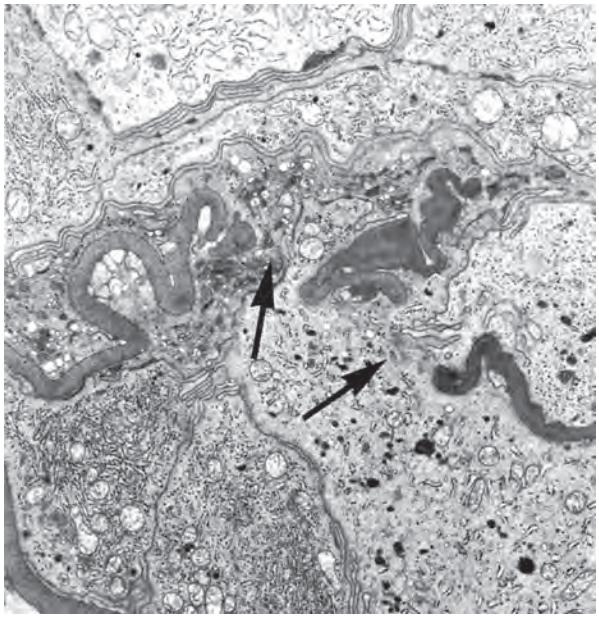

Figure 20-11 Crescentic glomerulonephritis. Electron micrograph showing characteristic wrinkling of glomerular basement membrane with focal disruptions *(arrows)*.