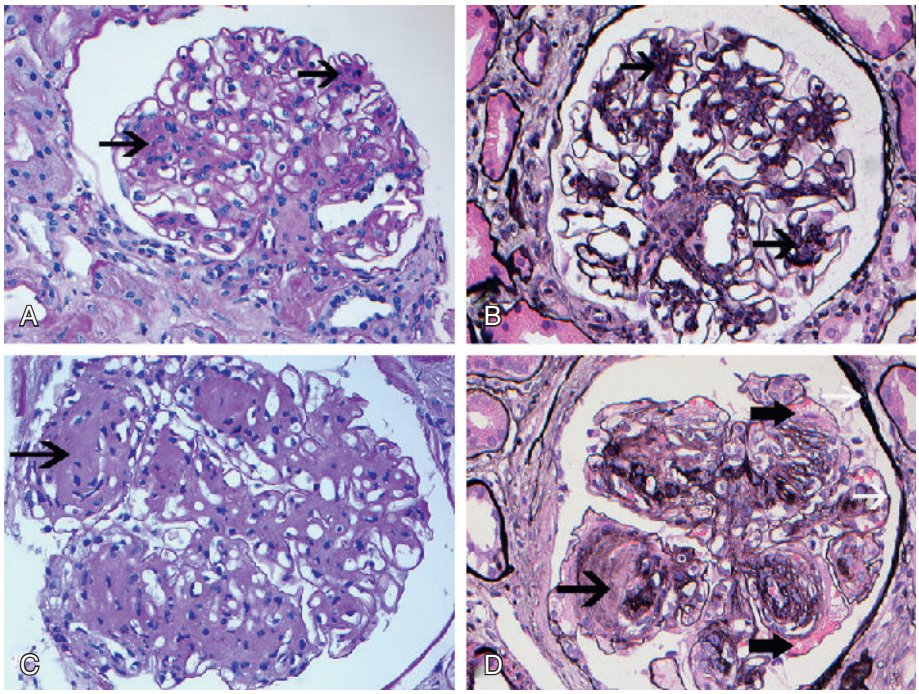

FIGURE 28-18 Light microscopy shows diabetic glomerulosclerosis. **A** and **B,** Early diabetic nodule formation *(arrows)*. **C** and **D,** Well-formed Kimmelstiel-Wilson lesions result from mesangial expansion *(thin black arrows)*. The nodules are periodic acid–Schiff and silver methenamine positive. The glomerular capillary lumen is distended by formation of small microaneurysms *(thick black arrows)*. The glomerular basement membrane and Bowman's capsule *(white arrows)* are thickened (**A** and **C,** periodic acid–Schiff; **B** and **D,** silver methenamine; all ×40).

pain, but the beneficial effects on the severity or progression of other disease manifestations are less clear.

DIABETIC NEPHROPATHY

Diabetic nephropathy accounts for more than 50% of patients on dialysis in the United States. In type 1 diabetes mellitus, nephropathy usually manifests 10 to 15 years after the initial diagnosis; and a similar natural history is likely for patients with type 2 diabetes mellitus. The main risk factors include a positive family history of diabetic nephropathy, hypertension, and poor glycemic control. The risk may be greater in some racial groups (e.g., Pima Indians, African Americans).

The pathogenesis is complex. Increased glycosylation of proteins with accumulation of advanced glycosylation end products that cross-link with collagen and glomerular hyperfiltration with hypertension are important. High albuminuria (i.e., urinary albumin excretion >30 but <300 mg/24h) is the initial manifestation of diabetic nephropathy. With time, high albuminuria may evolve into overt proteinuria (>300 mg/24h), with the degree of proteinuria correlating roughly with the renal prognosis.

After overt proteinuria develops, progression to ESRD is relentless, although rates of decline vary among patients. For patients with type 1 diabetes, there is a strong correlation (95%) between the development of nephropathy and other signs of diabetic microvascular compromise (e.g., diabetic retinopathy), but the correlation is weaker for patients with type 2 diabetes. Hypertension is almost universal among patients with proteinuria. It is difficult to control and usually requires at least three antihypertensive agents.

On renal biopsy, early signs of diabetic nephropathy include glomerular hypertrophy and thickening of the GBM. As the disease progresses, arteriolar hyalinosis, arteriosclerosis, and progressive mesangial expansion (i.e., diffuse diabetic glomerulosclerosis) and nodular formations (i.e., Kimmelstiel-Wilson nodules) develop (Fig. 28-18). For patients with a history of diabetes longer than 10 years and retinopathy, a renal biopsy may not be necessary. However, renal biopsy is indicated for patients with an atypical course of the disease (e.g., nephrotic syndrome), those with less than 10 years of type 1 diabetes, or patients with rapid loss of renal function.

Treatment with ACEIs or ARBs slows progression of diabetic nephropathy and should be used in all patients with albuminuria, even if normotensive. Tight glycemic control (i.e., glycated hemoglobin <7.0%) may also retard progression of diabetic nephropathy. Target systolic blood pressure should be less than 125 mm Hg, but this may be difficult to achieve and may require multiple medications and a strict low-salt diet.