Immunohistochemical studies of type IV collagen show the absence of α3(IV), α4(IV), and α5(IV) chains from the GBM and distal tubular basement membrane. This abnormality occurs only in patients with Alport syndrome and is diagnostic. In families with an unquestionable diagnosis, evaluation of patients with newly diagnosed hematuria can be limited to kidney ultrasound and urinary tract examination in most cases. If a defined mutation has been previously identified, molecular diagnosis of affected men or gene-carrying women is possible. In other cases, confirmation of the diagnosis can be obtained by examination of skin biopsy by immunofluorescence for the expression of the α5(IV) chain. Absence of the α5(IV) chain from epidermal basement membrane is diagnostic of X-linked Alport syndrome and may avoid a renal biopsy. Direct sequencing of the *COL4A5* gene can help to diagnosis patients in whom a clear diagnosis cannot be made based on clinical findings and histologic methods or to identify the carrier state in asymptomatic female members of X-linked Alport syndrome families.

No specific treatment is available for Alport syndrome. Tight control of blood pressure and moderate protein restriction are recommended to retard the progression of renal disease, but the benefit is unproved. Patients with Alport syndrome are phenotypic knockouts for the α3(IV) chain. Consequently, kidney transplantation carries a 5% to 10% risk of subsequent Goodpasture's disease due to the α3(IV) chain (i.e., the Goodpasture antigen) in the transplanted kidney.

Thin Glomerular Basement Membrane Nephropathy

Thin glomerular basement membrane nephropathy, also known as benign familial hematuria, is a relatively common condition characterized by isolated glomerular hematuria and associated with the renal biopsy finding of an excessively thin GBM. It is usually transmitted as an autosomal dominant disease. Heterozygous mutations in the *COL4A3* or *COL4A4* genes have been described in numerous patients with thin glomerular basement membrane nephropathy, indicating a genetically heterogeneous condition.

The usual clinical presentation is isolated, persistent hematuria that is first detected in childhood. In some patients, hematuria is intermittent and may not manifest until adulthood. On light microscopy, glomeruli appear normal, and immunofluorescence microscopy shows no immunoglobulin or complement deposition. Electron microscopy shows diffuse thinning of the GBM (Fig. 28-16). In adults, a GBM thickness less than 250 nm strongly suggests thin GBM disease.

The condition is usually benign and requires no specific treatment. However, a few patients have progressive renal disease that leads to ESRD.

FABRY DISEASE

Fabry disease is an X-linked recessive inborn error of glycosphingolipid metabolism caused by deficient activity of the lysosomal enzyme α-galactosidase A, which results in the progressive accumulation of neutral glycosphingolipids (predominately globotriaosylceramide, particularly in the vascular endothelial cells of the kidney and heart.

Early manifestations of the disease include angiokeratoma, episodic pain crises, and hypohidrosis. With time, progressive globotriaosylceramide accumulation in the microvasculature in the kidney, heart, and brain leads to clinical manifestations such as proteinuria, renal failure, cardiac arrhythmias, and strokes, resulting in early death during the fourth and fifth decades of life of affected men.

Light microscopy reveals vacuolated glomerular cells, especially podocytes. Electron microscopy shows enlarged podocytes lysosomes filled with osmiophilic, granular to lamellated membrane structures (i.e., zebra bodies) (Fig. 28-17). Enzyme replacement therapy can lead to significant improvement of neuropathic

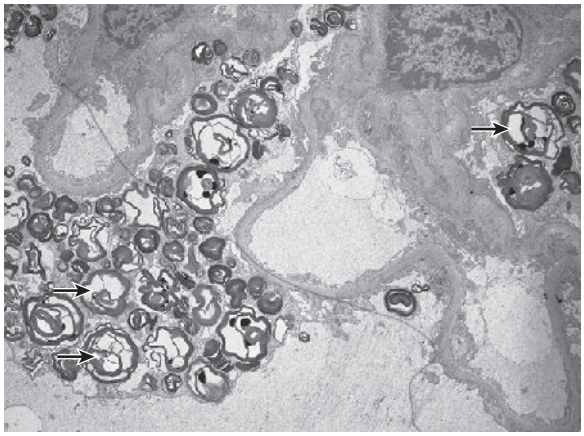

FIGURE 28-17 Fabry's disease. Electron microscopy shows visceral epithelial cells (i.e., podocytes) with numerous multilamellated structures called *myelin bodies* or *zebra bodies (arrows)* that are made of glycosphingolipids (×4800).

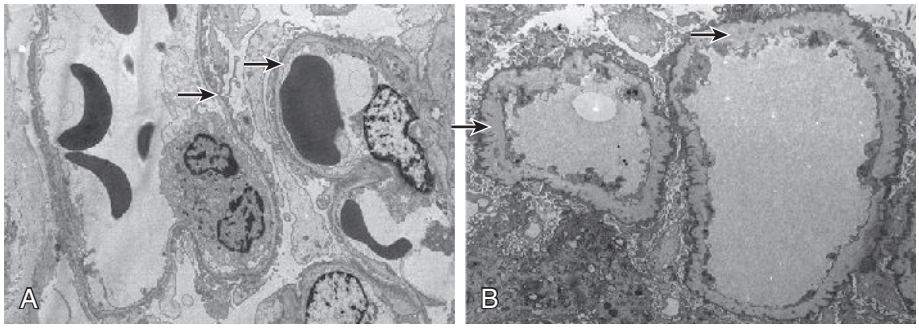

FIGURE 28-16 **A,** In thin glomerular basement membrane nephropathy, electron microscopy shows glomerular basement membranes *(arrows)* that are 198 nm thick (×5800). **B,** In Alport syndrome, electron microscopy shows thickened glomerular capillary walls with lamellations and disorganization of the glomerular basement membranes *(arrows)* and extensive foot process effacement of the visceral epithelial cells (×6000).