The principal characteristics of some of the more common heredofamilial and congenital glomerular disorders are described and illustrated. Diabetes mellitus, the most common heredofamilial glomerular disease, is illustrated in Volume IV, Chapter 1. These disorders are inherited in a variety of patterns (X-linked, autosomal dominant, or autosomal recessive). Many of these disorders appear to be caused by defective synthesis or assembly of critical glycoprotein (collagen) components of the glomerular basement membrane.
3.2 Glomerulonephritis and Vasculitis

**FIGURE 3-1**
Alport’s syndrome. Alport’s syndrome (hereditary nephritis) is a hereditary disorder in which glomerular and other basement membrane collagen is abnormal. This disorder is characterized clinically by hematuria with progressive renal insufficiency and proteinuria. Many patients have neurosensory hearing loss and abnormalities of the eyes. The disease is inherited as an X-linked trait; in some families, however, autosomal recessive and perhaps autosomal dominant forms exist. Clinically, the disease is more severe in males than in females. End-stage renal disease develops in persons 20 to 40 years of age. In some families, ocular manifestations, thrombocytopenia with giant platelets, esophageal leiomyomata, or all of these also occur. In the X-linked form of Alport’s syndrome, mutations occur in genes encoding the α-5 chain of type IV collagen (COL4A5). In the autosomal recessive form of this syndrome, mutations of either α-3 or α-4 chain genes have been described. On light microscopy, in the early stages of the disease the glomeruli appear normal. With progression of the disease, however, an increase in the mesangial matrix and segmental sclerosis develop. Interstitial foam cells are common but are not used to make a diagnosis. Results of immunofluorescence typically are negative, except in glomeruli with segmental sclerosis in which segmental immunoglobulin M and complement C3 are in the sclerotic lesions. Ultrastructural findings are diagnostic and consist of profound abnormalities of glomerular basement membranes. These abnormalities range from extremely thin and attenuated to considerably thickened membranes. The thickened glomerular basement membranes have multiple layers of alternating medium and pale staining strata of basement membrane material, often with incorporated dense granules. The subepithelial contour of the basement membrane typically is scalloped.

**FIGURE 3-2**
Schematic of basement membrane collagen type IV. The postulated arrangement of type IV collagen chains in a normal glomerular basement membrane is illustrated. The joining of noncollagen (NC-1) and 75 domains creates a lattice (chicken wire) arrangement (A). In the glomerular basement membrane, α1 and α2 chains predominate in the triple helix (B), but α3, 4, 5, and 6 chains are also found (not shown). Disruption of synthesis of any of these chains may lead to anatomic and pathologic alterations, such as those seen in Alport’s syndrome. Arrows indicate fibrils. (From Abrahamson and coworkers [1]; with permission.)

**FIGURE 3-3**
Neurosensory hearing defect in Alport’s syndrome. In patients with adult onset Alport’s syndrome, classic X-linked sensorineural hearing defects occur. These defects often begin with an auditory loss of high-frequency tone, as shown in this audiogram. The shaded area represents normal ranges. (Modified from Gregory and Atkin [2]; with permission.)
Thin basement membrane nephropathy. Glomeruli with abnormally thin basement membranes may be a manifestation of benign familial hematuria. Glomeruli with thin basement membranes may also occur in persons who do not have a family history of renal disease but who have hematuria, low-grade proteinuria, or both. Although the ultrastructural abnormalities have some similarities in common with the capillary basement membranes of Alport’s syndrome, these two glomerulopathies are not directly related. Clinically, persistent microscopic hematuria or occasional episodic gross hematuria are important features. Nonrenal abnormalities are absent. On light microscopy, the glomeruli are normal; no deposits are seen on immunofluorescence. Here, the electron microscopic abnormalities are diagnostic; all or virtually all glomerular basement membranes are markedly thin (<200 nm in adults) without other features such as splitting, layering, or abnormal subepithelial contours.

Fabry’s disease. Fabry’s disease, also known as angiokeratoma corporis diffusum or Anderson-Fabry’s disease, is the result of deficiency of the enzyme α-galactosidase with accumulation of sphingolipids in many cells. In the kidney, accumulation of sphingolipids especially affects glomerular visceral epithelial cells. Deposition of sphingolipids in the vascular tree may lead to premature coronary artery occlusion (angina or myocardial infarction) or cerebrovascular insufficiency (stroke). Involvement of nerves leads to painful acroparesthesias and decreased perspiration (anhidrosis). The most common renal manifestation is that of proteinuria with progressive renal insufficiency. On light microscopy, the morphologic abnormalities of the glomeruli primarily consist of enlargement of visceral epithelial cells and accumulation of multiple uniform small vacuoles in the cytoplasm (arrow in Panel A). Ultrastructurally, the inclusions are those of whorled concentric layers appearing as “zebra bodies” or myeloid bodies representing sphingolipids (B). These structures also may be observed in mesangial and endothelial cells and in arterial and arteriolar smooth muscle cells and tubular epithelia. At considerably higher magnification, the inclusions are observed to consist of multiple concentric alternating clear and dark layers, with a periodicity ranging from 3.9 to 9.8 nm. This fine structural appearance (best appreciated at the arrow) is characteristic of stored glycolipids (C).