(focal proliferative glomerulonephritis), or rarely, overt crescentic glomerulonephritis. The presence of leukocytes within glomerular capillaries is a variable feature. The mesangial widening may be the result of cell proliferation, accumulation of matrix, immune deposits, or some combination of these abnormalities. Healing of the focal proliferative lesion may lead to secondary focal segmental sclerosis. The characteristic immunofluorescent picture is of **mesangial deposition of IgA** (Fig. 20-19*B*), often with C3 and properdin and lesser amounts of IgG or IgM. Early complement components are usually absent. Electron microscopy confirms the presence of electron-dense deposits predominantly in the mesangium; capillary wall deposits, if present, are usually sparse.

Clinical Features. The disease affects people of any age, most commonly older children and young adults. Many patients present with gross hematuria after an infection of the respiratory or, less commonly, gastrointestinal or urinary tract; 30% to 40% have only microscopic hematuria, with or without proteinuria; and 5% to 10% develop acute nephritic syndrome, including some with rapidly progressive glomerulonephritis. The hematuria typically lasts for several days and then subsides, only to return every few months. The subsequent course is highly variable. Many patients maintain normal renal function for decades. Slow progression to chronic renal failure occurs in 15% to 40% of cases over a period of 20 years. Onset in old age, heavy proteinuria, hypertension, and the extent of glomerulosclerosis on biopsy are clues to an increased risk of progression. Recurrence of IgA deposits in transplanted kidneys is frequent, and in approximately 15% of those with recurrent IgA deposits, the disease runs the same slowly progressive course as that of primary IgA nephropathy.

Hereditary Nephritis

Hereditary nephritis refers to a group of heterogeneous familial renal diseases associated with mutations in collagen genes that manifest primarily with glomerular injury. Two deserve discussion: *Alport syndrome*, because the lesions and genetic defects have been well studied, and *thin basement membrane lesion*, the most common cause of *benign familial hematuria*.

Alport Syndrome

Alport syndrome, when fully developed, is manifest by hematuria with progression to chronic renal failure, accompanied by nerve deafness and various eye disorders, including lens dislocation, posterior cataracts, and corneal dystrophy. The disease is inherited as an X-linked trait in approximately 85% of cases. In the X-linked form, males express the full syndrome, while female heterozygotes typically present with hematuria. Approximately 90% of affected males progress to ESRD before 40 years of age. Autosomal recessive and autosomal dominant pedigrees also exist, in which males and females are equally susceptible to the full syndrome.

Pathogenesis. The disease manifestations are due to mutations in one of several genes coding for subunits of the collagen IV molecule. More than 500 mutations resulting in disease have been identified, resulting in defective assembly of type IV collagen, which is crucial for function of the GBM, the lens of the eye, and the cochlea. Because the GBM consists of networks of trimeric collagen IV molecules composed of α_3, α_4, and α_5 chains, mutations affecting any one chain result in defective assembly of the collagen network. Since type IV collagen chains are encoded on autosomes (chromosomes 2 and 13) and the X-chromosome, the inheritance pattern can be autosomal or X-linked. Mutations of missense, splice site, insertions, and deletion types have all been identified. Genetic analysis has shown that in patients with X-linked disease, large deletions in the collagen IV α5 chain (COL4A5) are associated with end stage renal disease at an earlier age.

MORPHOLOGY

Fully developed Alport syndrome has characteristic electron microscopic findings. The GBM shows irregular foci of thickening alternating with attenuation (thinning), and pronounced splitting and lamination of the lamina densa, often producing a distinctive basket-weave appearance (Fig. 20-20). Similar alterations can be found in the tubular basement membranes.

Immunohistochemistry can be helpful in cases with absent or borderline basement membrane lesions, because antibodies to α_3, α_4, and α_5 collagen fail to stain both glomerular and tubular basement membranes in the classic X-linked form. There is also absence of α_5 staining in skin biopsy specimens from these patients. As the disease progresses there is development of focal segmental and global glomerulosclerosis and other changes of progressive renal injury, including vascular sclerosis, tubular atrophy, and interstitial fibrosis.

Clinical Features. The most common presenting sign is gross or microscopic hematuria, frequently accompanied by red cell casts. Proteinuria may develop later, and rarely, the nephrotic syndrome develops. Symptoms appear at ages 5 to 20 years, and the onset of overt renal failure is between ages 20 and 50 years in men. The auditory defects may be subtle, requiring sensitive testing.

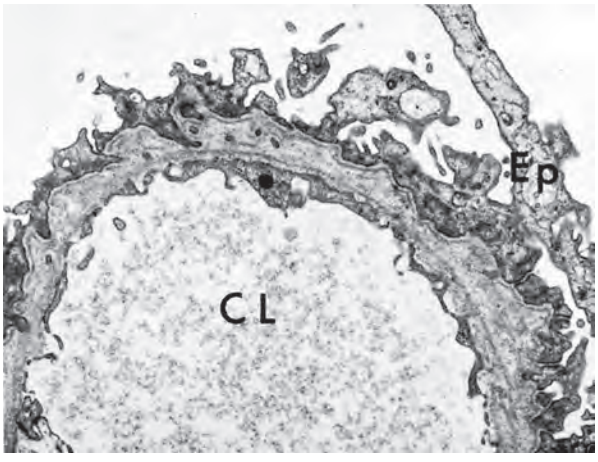

Figure 20-20 Hereditary nephritis (Alport syndrome). Electron micrograph of glomerulus with irregular thickening of the basement membrane, lamination of the lamina densa, and foci of rarefaction. Such changes may be present in other diseases but are most pronounced and widespread in hereditary nephritis. *CL*, Capillary lumen; *Ep*, epithelium.