cell surface receptor with a role in collecting duct and biliary differentiation.

Analysis of autosomal recessive polycystic disease patients has revealed a wide range of different mutations. The vast majority of cases are compound heterozygotes (i.e., inherit a different mutant allele from each of the two parents). This complicates molecular diagnosis of the disorder.

MORPHOLOGY

The kidneys are enlarged and have a smooth external appearance. On cut section, numerous small cysts in the cortex and medulla give the kidney a spongelike appearance. Dilated elongated channels are present at right angles to the cortical surface, completely replacing the medulla and cortex (Fig. 20-44*C*). On microscopic examination, there is cylindrical or, less commonly, saccular dilation of all collecting tubules. The cysts have a uniform lining of cuboidal cells, reflecting their origin from the collecting ducts. In almost all cases the liver has cysts associated with portal fibrosis (Fig. 20-44*D*) and proliferation of portal bile ducts.

Patients who survive infancy (infantile and juvenile forms) may develop a peculiar hepatic injury characterized by bland periportal fibrosis and proliferation of well-differentiated biliary ductules, now termed *congenital hepatic fibrosis*. In older children, hepatic disease is the predominant clinical concern. Such patients may develop portal hypertension with splenomegaly. Curiously, congenital hepatic fibrosis sometimes occurs in the absence of polycystic kidneys or has been reported in the presence of adult polycystic kidney disease.

Cystic Diseases of Renal Medulla

The three major types of medullary cystic disease are *medullary sponge kidney*, a relatively common and usually innocuous structural change, *nephronophthisis* and *adult-onset medullary cystic disease*, which are almost always associated with renal dysfunction.

Medullary Sponge Kidney

The term *medullary sponge kidney* is restricted to multiple cystic dilations of the collecting ducts in the medulla. The condition occurs in adults and is usually discovered radiographically. Renal function is usually normal. On gross inspection the papillary ducts in the medulla are dilated, and small cysts may be present. The cysts are lined by cuboidal epithelium or occasionally by transitional epithelium. Unless there is superimposed pyelonephritis, cortical scarring is absent. The pathogenesis is unknown.

Nephronophthisis and Adult-Onset Medullary Cystic Disease

This group of progressive renal disorders is characterized by variable number of cysts in the medulla, usually concentrated at the corticomedullary junction. Initial injury probably involves the distal tubules with tubular basement membrane disruption, followed by chronic and progressive tubular atrophy involving both medulla and cortex and interstitial fibrosis. Although the medullary cysts are important, the **cortical tubulointerstitial damage is the cause of the eventual renal insufficiency.**

Three variants of the nephronophthisis disease complex are recognized: (1) sporadic, nonfamilial; (2) familial juvenile nephronophthisis (most common); and (3) renal-retinal dysplasia (15%) in which the kidney disease is accompanied by ocular lesions. The familial forms are inherited as autosomal recessive traits and usually become manifest in childhood or adolescence. As a group, the nephronophthisis complex is now the most common genetic cause of end-stage renal disease in children and young adults.

Children affected with nephronophthisis present first with polyuria and polydipsia, which reflect a marked defect in the concentrating ability of renal tubules. Sodium wasting and tubular acidosis are also prominent. Some syndromic variants of nephronophthisis (e.g., Senior-Loken syndrome, Joubert syndrome, Bardet Biedl syndrome, Jeune syndrome, Meckel Gruber syndrome, Mainzer-Saldino syndrome, Sensenbrenner syndrome) can have extrarenal associations, including ocular motor abnormalities, retinal dystrophy, liver fibrosis, and cerebellar abnormalities. The expected course is progression to ESRD in 5 to 10 years.

Genetics and Pathogenesis. Sixteen responsible gene loci, *NPHP1* to *NPHP11* (that encode proteins called nephrocystins, *JBTS2, JBTS3, JBTS9,* and *JBTS11,* are mutated in the juvenile forms of nephronophthisis and the list continually expands as additional loci that contribute to this ciliopathy are identified. These proteins are present in the primary cilia, basal bodies attached to these cilia, or the centrosome organelle from which the basal bodies originate.

The NPHP2 gene product has been identified as *inversin*, which mediates left-right patterning during embryogenesis. Adult-onset medullary cystic disease has an autosomal dominant pattern of transmission. At one time it was considered to be part of the nephronophthisis spectrum, but based on its distinctive genetics it is now considered a separate entity. Mutations in two genes (*MCKD1* and *MCKD2*) have been identified as causing medullary cystic disease, which is characterized by progression to end-stage kidney disease in adult life.

MORPHOLOGY

In nephronopthisis, the kidneys are small, have contracted granular surfaces, and show cysts in the medulla, most prominently at the corticomedullary junction (Fig. 20-45). Small cysts are also seen in the cortex. The cysts are lined by flattened or cuboidal epithelium and are usually surrounded by either inflammatory cells or fibrous tissue. In the cortex there is widespread atrophy and thickening of the tubular basement membranes, together with interstitial fibrosis. In general, glomerular structure is preserved.

There are few specific clues to diagnosis, because the medullary cysts might be too small to be visualized radiographically. The disease should be strongly considered in children or adolescents with otherwise unexplained chronic