penetrance. Although the susceptibility to develop this disease is inherited as an autosomal dominant trait, as with tumor suppressor genes, both alleles of the involved genes have to be nonfunctional for development of the disease. Thus, individuals prone to autosomal dominant polycystic kidney disease inherit one copy of a mutated APKD gene, and mutation of the other allele is acquired in the somatic cells of the kidney. The disease is bilateral; reported unilateral cases probably represent multicystic dysplasia. The cysts initially involve a minority of the nephrons, so renal function is retained until about the fourth or fifth decade of life.

Genetics and Pathogenesis. A wide range of different mutations in *PKD1* and *PKD2* has been described, and this allelic heterogeneity has complicated genetic diagnosis of this disorder.

- The *PKD1* gene is located on chromosome 16p13.3. It encodes a large (460-kD) integral membrane protein named *polycystin-1*, which has a large extracellular region, multiple transmembrane domains, and a short cytoplasmic tail. Polycystin-1 is expressed in tubular epithelial cells, particularly those of the distal nephron. At present its precise function is not known, but it contains domains that are usually involved in cell-cell and cell-matrix interactions. Mutations in *PKD1* account for about 85% of cases. In individuals with these mutations, the likelihood of developing renal failure is less than 5% by 40 years of age, rising to more than 35% by 50 years, more than 70% at 60 years of age, and more than 95% by 70 years of age.
- The *PKD2* gene, located on chromosome 4q21, accounts for most of the remaining cases of polycystic disease. Its product, *polycystin-2*, is an integral membrane protein that is expressed in all segments of the renal tubules and in many extrarenal tissues. Polycystin-2 functions as a Ca2+-permeable cation channel. Overall, the disease is less severe than that associated with *PKD1* mutations. Renal failure occurs in less than 5% of patients with *PKD2* mutations at 50 years of age, but this rises to 15% at 60 years of age, and 45% at 70 years of age.

The pathogenesis of polycystic disease is not established, but the currently favored hypothesis places the cilia-centrosome complex of tubular epithelial cells at the center of the disorder (Fig. 20-43). The tubular epithelial cells of the kidney contain a single nonmotile primary cilium, a 2- to 3-μm long hairlike organelle that projects into the tubular lumen from the apical surface of the cells. The cilium is made up of microtubules, and arises from and is attached to a basal body derived from the centriole. The cilia are part of a system of organelles and cellular structures that sense mechanical signals. The apical cilia function in the kidney tubule as a mechanosensor to monitor changes in fluid flow and shear stress, while intercellular junctional complexes monitor forces between cells, and focal adhesions sense attachment to extracellular matrices. In response to external signals, these sensors regulate ion flux (cilia can induce Ca2+ flux in cultured kidney epithelial cells) and cellular behavior, including cell polarity and proliferation. The idea that defects in mechanosensing, Ca2+ flux, and signal transduction underlie cyst formation is supported by several observations.

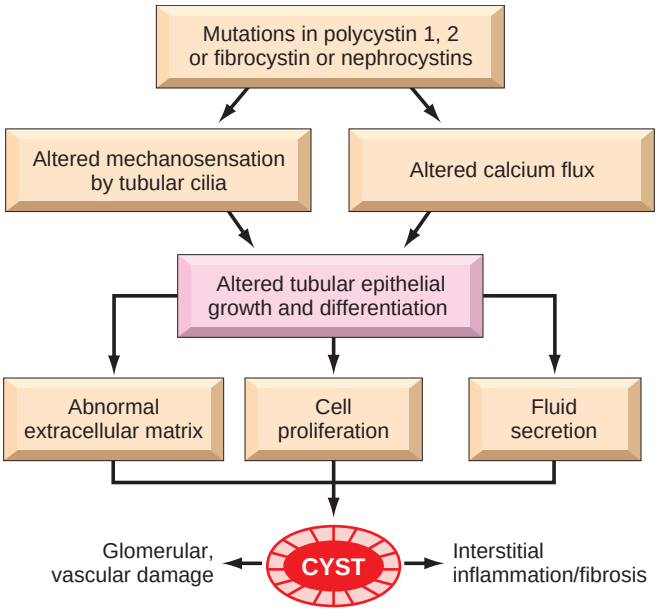

Figure 20-43 Possible mechanisms of cyst formation in cystic kidney diseases (see text).

- Both polycystin-1 and polycystin-2 are localized to the primary cilium.
- Other genes that are mutated in cystic diseases (e.g., the nephrocystin genes, described later) encode proteins that are also localized to cilia and/or basal bodies.
- Knockout of the *PKD1* gene in one model organism (the worm *Caenorhabditis elegans*) results in ciliary abnormalities and cyst formation.
- Tubular cells obtained from mice with a deletion of the *PKD1* gene (which causes embryonic lethality in this species) retain normal architecture of cilia but lack the flow-induced Ca2+ flux that occurs in normal tubular cells.

Polycystin-1 and polycystin-2 appear to form a protein complex that regulates intracellular Ca2+ in response to fluid flow, perhaps because fluid moving through the kidney tubules causes ciliary bending that opens Ca2+ channels. Mutation of either of the *PKD* genes leads to loss of the polycystin complex or formation of an aberrant complex. The consequent disruption of normal polycystin activity results in alterations of intracellular Ca2+, which (you will recall) regulates many downstream signaling events, including pathways that directly or indirectly impact cellular proliferation, apoptosis, and secretory functions. The increase in calcium is thought to stimulate proliferation and secretion from epithelial cells lining the cysts, which together result in progressive cyst formation and enlargement. In addition, cyst fluids have been shown to harbor mediators, derived from epithelial cells that enhance fluid secretion and induce inflammation. Finally, the calcium-induced signals also alter the interaction of epithelial cells with extracellular matrix, and this too is thought to contribute to the cyst formation and interstitial fibrosis that are characteristic of progressive polycystic kidney disease.