36 Polycystic Kidney Disease

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Introduction

Polycystic kidney disease (PKD) is a heritable disorder with diffuse cystic involvement of both kidneys without dysplasia (1). All forms of PKD can have clinical manifestations in infants and children. The major clinical entities of autosomal-recessive polycystic kidney disease (ARPKD) and autosomal-dominant polycystic kidney disease (ADPKD) have considerable overlap in clinical presentation and radiographic features. Glomerulocystic kidney disease (GCKD) can be a feature of several inherited, sporadic, and syndromal conditions, as well as an expression of ADPKD.

Differential Diagnosis of Polycystic Kidneys in Childhood

The clinical presentation of polycystic kidneys and/or enlarged echogenic kidneys can be associated with a number of kidney disorders. Not all of these represent the classic genetic disorders of polycystic kidney *disease* (i.e., ARPKD and ADPKD). Additional diagnoses to consider include bilateral cystic dysplasia, which is often associated with congenital syndromes, and multicystic dysplastic kidney (MCDK). Both of these diseases generally occur sporadically and are reviewed in detail in Chapter 5. The inherited disorder of juvenile nephronophthisis (JN) is associated with cystic kidneys, but these are usually small or normal in size. JN is reviewed in Chapter 35. Other rarer causes of polycystic and/or enlarged echogenic kidneys are outlined in *Table 36-1*.

In most clinical settings, the major challenge in the differential diagnosis of polycystic kidneys in the pediatric patient is clearly delineating ARPKD from ADPKD. In fact, ADPKD presenting in the neonatal period may be indistinguishable clinically from ARPKD (2, 3). In such instances, a staged evaluation including careful history, physical examination, imaging, and histologic examination is recommended. As shown in *Table 36-2*, certain clinical features can help differentiate between ARPKD and ADPKD, although no single finding is diagnostic. A complete family history is often the most important element in difficult cases. Parents should have standard, or if available, high resolution renal ultrasonography. If the parents of a child with undiagnosed PKD are under 30, the grandparents should also be evaluated because 4–5% of patients with ADPKD may not have visible renal cysts before age 30. The absence of any cystic disease in family members makes the diagnosis of ARPKD more likely. It does not, however, exclude the diagnosis of ADPKD, since approximately 8–10% of all ADPKD cases are the result of new gene mutations (4). Radiographic studies, particular MRI imaging if the kidneys and liver, may clearly distinguish ARPKD and ADPKD in some cases (*Table 36-2*). However, in clinical practice, up to 20% of all cases will show certain features of both diseases on radiographic studies of the kidneys, making definitive diagnosis difficult unless extra-renal features of either disease are present (see below). Tissue diagnosis (biopsy of kidney and liver) is generally deferred given the availability of molecular diagnostics. Molecular genetic testing for ARPKD and ADPKD is available and is increasingly utilized given mutation detection rates of 85–90% in high quality laboratories (5). Such testing is indicated for the subset of patients in whom the clinical and/or tissue diagnosis is equivocal, and/or additional information is needed for genetic counseling. In the United States, passage of recent legislation (2008) preventing discrimination by employers or insurers against any individual with a genetic disorder (Genetic Information Non-Discrimination Act or GINA) will remove a major obstacle to diagnostic testing of asymptomatic, at risk PKD patients. Early diagnosis of asymptomatic individuals with ADPKD and ARPKD affords the current opportunity for maximal anticipatory care (i.e., BP control), and the future opportunity to benefit from new therapies (i.e., early treatment with therapies that will limit cyst development and enlargement) (6).

Pathophysiology of Cyst Formation in PKD

In the last decade, major advances have been made in understanding the molecular genetics of PKD. Through

Table 36-1
Differential Diagnosis of Polycystic and/or Echogenic Kidneys in the Pediatric Patient

Polycystic Kidney Diseases (PKD)
Autosomal-recessive polycystic kidney disease (ARPKD)
Autosomal-dominant polycystic kidney disease (ADPRD)
Glomerulocystic kidney disease (GCKD)
Inherited Disorders Associated with Polycystic Kidneys
Tuberous sclerosis complex
Meckel–Gruber syndrome
Jeune syndrome and other chondrodysplasia syndromes
Ivemark syndrome
Bardet–Biedl syndrome
Oro-facial-digital syndrome Type I
Zellweger cerebrohepatorenal syndrome
Beckwith–Wiedemann syndrome
Trisomy 9 and 13
Juvenile nephronophthisis (JN)/medullary cystic disease (MCD) complex
Von Hippel-Lindau Syndrome
Hajdu-Cheney Syndrome
Sporadic Disorders Associated with Cystic Kidneys
Isolated cystic dysplasia
Multicystic dysplastic kidney (MCDK)
Unilateral/localized cystic kidney disease
Caliceal diverticula
Miscellaneous Causes of Cystic and/or Enlarged Echogenic Kidneys
Nephroblastomatosis
Bilateral Wilms' tumor
Leukemia or lymphoma
Pyelonephritis
Glomerulonephritis
Radiocontrast nephropathy
Bilateral renal vein thrombosis
Transient nephromegaly
Congenital nephrotic syndrome
Glycogen storage disease
Acquired cystic kidney disease

Table 36-2
Differential Clinical Features of Childhood PKD

Major clinical features of *both* ARPKD and ADPKD
Enlarged kidneys
Hypertension
Concentrating defect
Sterile pyuria
Clinical features suggesting ARPKD rather than ADPKD
Neonatal presentation
Progression to end-stage renal disease as a child
Hepatosplenomegaly
Portal hypertension and esophageal varices
Bacterial cholangitis
Negative family history
Clinical features suggesting ADPKD rather than ARPKD
Positive family history
Extrarenal cysts
Cerebral aneurysms
Asymptomatic presentation
Unilateral renal presentation
Hematuria
Urinary tract infection

Adapted from Avner ED. Polycystic kidney disease. In Pediatric Nephrology. Drukker A, Grushkin A (eds.). In Pediatric and Adolescent Medicine. Branski D (series ed.). Basel, AG Karger, 1993

a combination of positional cloning, direct sequencing and utilization of the rapidly expanding genome databases, the major causative genes for both ADPKD (*PKD1* and *PKD2*) as well as ARPKD (*PKHD1*) have been identified (7–10) (*Table 36-3*). Details specific to the molecular genetics of ARPKD and ADPKD are addressed in the respective sections that follow. Numerous studies have demonstrated that the protein products of the ADPKD and ARPKD genes are membrane-bound proteins which interact and generally exist in multimeric protein complexes at various sites in cells. The primary sites of "cystoprotein complex" localization have been reported to be apical cell membranes (particularly on or adjacent to the primary cilium), adherins junctions, desmosomes, and focal adhesions (11–15). Multimeric cystoprotein complexes thus interact with a number of distinct signal transduction pathways which appear to be critical in normal tubular growth and differentiation. Mutations in PKD genes result in abnormal cystoprotein structure and function, with subsequent aberrant integration of complex signaling events resulting in the unique phenotype of the cystic epithelial cell. Although the precise mechanisms by which specific PKD gene mutations result in cyst formation have not yet been fully elucidated, considerable progress has been made in understanding the pathophysiology of cyst formation. Key pathogenic

Table 36-3
Human Polycystic Kidney Disease Genes and Proteins

Disease	Gene	Mode of inheritance	Chromosome location	Protein	Function/Role
ADPKD	*PKD1*	AD	16p13.3-p13.12	Polycystin 1	?Receptor
ADPKD	*PKD2*	AD	4q21-q23	Polycystin 2	Cation channel
ARPKD	*PKHD1*	AR	6p21	Fibrocystin (polyductin)	?Receptor
GCKD (hypoplastic variant)	*HNF-1β*	AD	17cen-q21.3	Hepatocyte nuclear factor – 1beta	Transcription factor

AD, Autosomal Dominant, *AR*, Autosomal Recessive

features of the cystic phenotype have been identified (6, 15, 16). Such features are critical as targets for the development of future therapies, and include:

- Abnormalities of expression and function of the epidermal growth factor (EGFR) – axis
- Decreased intracellular calcium with aberrant intracellular cAMP signaling
- Abnormal structure and/or function of the primary cilia
- Alterations in cell-cell, and cell-matrix interactions

Each of these pathogenic processes likely contributes to some extent to one or more of the fundamental features of renal cyst formation and progressive enlargement, namely: (1) tubular cell hyperplasia; (2) tubular fluid secretion; and (3) abnormalities in tubular extracellular matrix, structure, and/or function (*Fig. 36-1*) (16–20). As the following sections will illustrate, key insights into the pathogenesis of cyst formation in PKD have been provided by rodent models of ARPKD and ADPKD (*Table 36-4*). This Table does not include the increasing number of reported genetically-manipulated "knockout" or conditionally targeted genetic models, many of which have not been fully characterized as of this writing. The interested reader is referred to the following readings which review the most significant of these models produced to date (21–24). Several of these models have been used to test the efficacy of novel therapies.

Renal Tubular Cell Hyperplasia

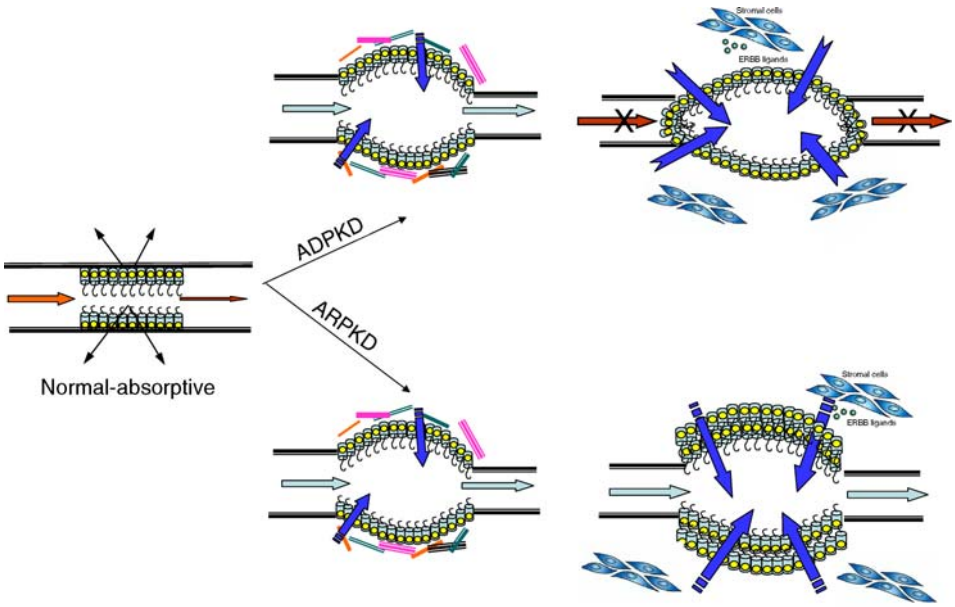
Renal tubular hyperplasia is a central morphologic feature of all described human renal cystic diseases (25, 26). On the basis of mathematic modeling of cyst growth, it has been shown that tubular cell hyperplasia, with expansion of tubular wall segments to accommodate an increased cellular mass, is an essential factor in cyst formation and enlargement (27). Multiple studies in vivo and *in vitro* have demonstrated abnormal renal tubule epithelial proliferation. Increased renal tubular epithelial cell proliferation is a feature of both cystic and non-cystic tubular epithelium from ADPKD and ARPKD kidneys (28). Cyst-derived epithelial cells from ADPKD and ARPKD demonstrate increased cell growth potential compared with controls (29, 30).

The EGFR-Axis

Dysregulation of growth factors/receptors have a primary role in tubular cell hyperplasia. A growing body of evidence implicates one or more members of the ErbB receptor family, including the epidermal growth factor receptor (EGFR), as well as the related receptors, ErbB2 and ErbB4. In both human ADPKD and ARPKD and in every rodent models of PKD published to date, cystic kidneys display characteristic alterations in EGFR expression. Both quantitative abnormalities, including increased mRNA and protein, and qualitative differences, in particular, the appearance of "mislocalized" EGFR expressed on the apical surface of tubular epithelium, are seen (31–33). Apical EGFR is functional and capable of transmitting mitogenic signals *in vitro* (34). Inhibition of EGFR function *in vitro* by treatment with either an inhibitor of tyrosine kinase function or a blocking antibody inhibits formation of proximal tubule cysts and significantly decreased explant growth and distal nephron differentiation in metanephric organ culture models (35, 36). Additional support for a central role for EGFR in the pathogenesis of cyst formation is provided by *in vivo* data. Inhibition or reduction of EGFR function, either by treatment with a novel tyrosine kinase inhibitor (37), or genetic manipulation (38), leads to a marked reduction in cyst formation and progressive enlargement in animal models.

Figure 36-1

Pathophysiology of renal cyst formation. Studies in a variety of experimental models, in addition to human ADPKD and ARPKD tissue, implicate three major factors in renal cyst formation and progressive enlargement. Normal renal tubular absorptive epithelium can become cystic if (a) hyperplasia, localized to a distinct nephron segment, requires accommodation of increased renal mass; (b) secretion, as opposed to absorption, leads to the accumulation of intratubular fluid; and (c) extracellular matrix (ECM) abnormalities alter the epithelial microenvironment to further stimulate proliferation and secretion. The figure depicts the difference between ADPKD epithelia, where proliferation leads to isolated cysts which are not connected to intratubular flow and can grow only through transtubular fluid movement; and ARPKD epithelia, where proliferation leads to thickened tubular ectasia and where fluid secreted across tubular walls remains part of urinary flow. These processes are not mutually exclusive, may reflect characteristics of undifferentiated epithelium, and operate in concert during tubular cysr formation and progressive enlargement.



The central role of EGFR-family members in the pathogenesis of ARPKD has been recently confirmed by the demonstration that ErbB2, rather than EGFR (or ErbB1) is predominantly overexpressed and apically mislocated in the PCK rat, an orthologous ARPKD rodent model. This model, which does not respond to ErbB1 inhibition (39) responds dramatically in-vivo to therapies which decrease active phosphorylated ErbB2 (40, 41) This response includes a dramatic reduction in renal cyst formation and progressive enlargement, an improvement in biliary tract ectasia and periportal fibrosis, and dramatic improvements in renal function and renal concentrating ability. Given the importance of G-protein coupled receptors in cystogenesis previously noted, it is significant that activation of such receptors leads to significant transactivation of the EGFR family (42).

ErbB2 (HER-2) overexpression is seen in some cysts of ADPKD kidneys but not seen in late-stage ARPKD kidneys (43). Late-gestation/early post-natal human ARPKD kidneys samples, however, show increased ErbB2 expression compared with normal human fetal and postnatal kidneys (44). Wilson et al. (45) demonstrated that apical localized EGFR complexes in normal fetal and ADPKD epithelia are heterodimers of EGFR (ErbB1) and ErbB2, while basal membrane localized EGFR in normal adult renal epithelia are comprised of EGFR (ErbB1) homodimers. They further showed that inhibition of ErbB2 corrected the migratory phenotype seen in ADPKD cells. Overexpression and mislocalization of another ErbB family member, ErbB4, has been demonstrated in cystic collecting tubule epithelia of two ARPKD rodent models (46).

Overexpression of several EGF related growth factors/ErbB ligands, is also a prominent feature of both ARPKD and ADPKD cystic epithelia. Renal cyst fluid contains EGF or EGF-like peptides in mitogenic concentrations, despite apparent reductions in EGF tissue expression

Table 36-4
Rodent Models of PKD[a]

Mouse model	Mode of inheritance	Chromosome location	Gene	Protein product	Function/Role/Comments
bpk	AR	10	*Bicc1*	bicaudal C	RNA-binding protein
cpk	AR	12	*Cys1*	cystin	Cilia-associated protein
inv	AR	4	*Inv*	inversin	Role in left-right axis development
jck	AR	11	*Nek8*	nek8	Function unknown
kat	AR	8	*Nek1*	nek1	Function unknown
jcpk	AR	10	*Bicc1*	bicaudal C	Allelic with *bpk*
orpk	AR	14	*Ift88 (TgN737)*	IFT88 (polaris)	Role in left-right axis development; Cilia-associated protein
pcy	AR	9	*Nphp3*	Nephrocystin3	Model of JN
Rat model	**Mode of inheritance**	**Chromosome location**	**Gene**	**Protein product**	**Function/Role/Comments**
Han-SPRD	AD	5	*PKDR (Cy)*	SamCystin	Function unknown
LPK	AR	?	?	?	Function unknown
PCK	AR	9	*PKHD1*	fibrocystin (polyductin)	Orthologous model of human ARPKD, with some clinical features of ADPKD
WPK	AR	5	*MKS3*	Meckelin	Function unknown

AD Autosomal Dominant, *AR* Autosomal Recessive
[a]"Knockout" models for PKD are not included in this listing

(29, 47–50). Treatment with EGF transiently improves renal function in murine models (51), but has no effect on histopathologic abnormalities and continued EGF treatment worsens disease and shortens survival (52). TGF-α and EGF are cystogenic in both murine embryonic organ cultures (53) and normal human kidney cells grown in a unique collagen gel system in vitro (54). ADPKD kidneys and cells derived from ADPKD have increased mRNA or protein levels of TGF-α (31, 55), and transgenic mice that overexpress TGF-α develop cystic kidneys (56). Loss of TGF-α, however, does not modify cystic kidney disease in an ARPKD mouse model, suggesting that there is significant redundancy in EGFR ligands which can promote cyst formation or growth in ARPKD (57).

Additional data suggest that inhibiting EGFR-ligand function may also partially ameliorate cystic disease. Treatment with an inhibitor of TACE, a metalloproteinase implicated in the processing of several EGF-related growth factors, decreased cystic kidney disease in a murine model, less effectively than EGFR inhibition (58). Combining inhibition of EGFR ligand release with EGFR inhibition maximized therapeutic effectiveness while minimizing toxicity (59). Additional EGFR ligands, including amphiregulin and heparin-binding EGF, are abnormally expressed in PKD and may prove to also have a role in proliferation of cystic epithelium (50).

c-Src is an important intermediate in several key cystogenic signaling pathways. Src is a critical intermediate which integrates proliferation from both G-coupled protein receptors and the EGFR-axis (6, 16). Increased Src activity (pY418) was found to be associated with a more severe renal cystic disease in two ARPKD rodent models. Furthermore, treatment of these models with an inhibitor of Src ameliorated both the renal and hepatic disease through inhibition of G-protein coupled receptor and EGFR-axis triggered phosphorylation cascades (41).

cAMP and Intracellular Calcium Ion

Another major contributor to cellular proliferation in both ADPKD and ARPKD is intracellular cyclic AMP (cAMP). Unlike normal renal epithelia, ADPKD and ARPKD cystic epithelia respond to increased intracellular cyclic AMP (cAMP) with an increase, rather than decrease, in proliferation due to phosphorylation of B-Raf (60–62).

Normal and polycystic kidney epithelia from an ARPKD rodent model also demonstrate differences in regulation of cAMP-dependent protein kinase (PKA), which is associated with increased proliferation *in vitro* (63).

Intracellular calcium concentrations have been identified as a critical component of the pro-mitogenic cAMP response of cystic epithelia. Several studies have demonstrated that calcium restriction induces a switch to this cAMP dependent growth phenotype, whereas addition of calcium to PKD cells in culture restores the normal anti-mitogenic response to cAMP (64, 65). In addition, cells that do not express *PKHD1*, the mutated gene in ARPKD, have decreased intracellular calcium and increased epidermal growth factor (EGF)-induced proliferation, suggesting that loss of one or more PKD proteins may lead to abnormal proliferation by modulation of intracellular calcium (66). In addition, Leuenroth et al. (67) recently showed that triptolide (a Chinese herb) induces calcium release in a polycystin-2 dependent manner. Further, triptolide treatment of a mouse model of ADPKD resulted in attenuated cyst formation and decreased tubular cellular proliferation.

The cAMP pro-mitogenic response in PKD cells is associated with phosphorylated B-Raf activation of the mitogen-activated protein kinase (MAPK) pathway, which can mediate a variety of cellular processes, most notably cell proliferation. There is considerable "cross talk" between the cAMP and MAPK signaling pathways in both normal and disease states (68). Increased phosphorylation of several MAPK pathway members is a prominent feature of rodent and human ADPKD and ARPKD kidneys and tubular epithelial cells (23, 69, 70). There are conflicting animal data, however, as to whether inhibition of ERK 1/2 impacts progression of cystic kidney disease (23, 71).

Apoptosis

Dysregulation of apoptosis, or the balance between apoptosis and proliferation, may also contribute to the progression of ARPKD and ADPKD (72–74). Increased rates of apoptosis and increased caspase 3 and 4 activity have been demonstrated in kidneys from ARPKD rodent models (75, 76). A marked increase in caspase 3 and 7 activity has also been reported in an ADPKD rodent model (77, 78). Furthermore, caspase inhibition reduced tubular apoptosis and proliferation and slowed cystic kidney disease progression in that same model (79).

Mice deficient in the anti-apoptotic molecule, bcl-2, develop severe multicystic hypoplasia characterized by proximal and distal tubular cysts and hyperproliferation of epithelium and interstitium (80). Alternatively, increased bcl-2 expression has been demonstrated in animal models of both ARPKD and ADPKD (73, 76, 77). These finding suggest that the balance of pro- and anti-apoptotic mediators, rather than the absolute expression levels, may be a critical factor in the development of cystic kidney disease (77).

Proto-oncogenes

Abnormal expression of proto-oncogenes, in particular, c-Myc may also contribute to abnormalities in proliferation and apoptosis, leading to cyst development. In both murine ARPKD and human ADPKD kidneys, c-Myc is overexpressed in cystic tissue (73, 81, 82) and is associated with a marked increase in both tubular cellular proliferation and apoptosis (83–85). In addition, c-Myc antisense oligonucleotides have been used to ameliorated cystic kidney disease in a murine ARPKD model (85).

mTOR

The target of rapamycin (mTOR) pathway is currently a growing area of interest in the pathophysiology PKD because it integrates signals from growth factors (including EGFR), G-protein coupled receptors (which generate cAMP), cellular energy levels, nutrient status and stress conditions to stimulate protein synthesis and cell growth through activation through phosphorylation of S6K1 and eIF4E (86, 87). The *TSC1* and *TSC2* genes, when mutated, cause tuberous sclerosis, a disease in which renal cystic lesions may accompany the more classical angiomyolipomas. *TSC1/2* mutations upregulate mTOR signaling. The fact that the *TSC2* and *PKD1* genes lie adjacent to each other on human chromosome 16p13.3, as well as the fact that the cytoplasmic tail of polycystin-1 interacts with mTOR led to an evaluation of mTOR activity in polycystic kidney disease. In a variety of animal models, as well as in human ADPKD and ARPKD cyst-lining epithelia, expression of phospho-mTOR and p70S6K is increased (88). The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal cystogenesis in polycystic kidney disease. These findings, combined with therapeutic efficacy of rapamycin (an mTOR inhibitor) in ameliorating cystic disease in the orpk, bpk and Han:SPRD rodent models has led to the development of pilot clinical trials for rapamycin in patients with ADPKD (87).

Arachidonic Acid Metabolites

20-hydroxyeicosatetratraenoic acid (20-HETE), is formed by the ω-hydroxylation of arachidonic acid by cytochrome P450 (CYP) 4A and 4F enzymes (89). Recent evidence has implicated 20 HETE as a mediator of cellular proliferation in normal and malignant renal cells (90–94). Further, norepinephrine, angiotensin II, and EGFR activity (all upregulated in PKD) stimulate the synthesis and release of 20-HETE and increase proliferation in both vascular smooth muscle cells and renal tubular epithelial cells (90–92, 95). With this rationale, recent studies have demonstrated a significant role of 20-HETE in mediating collecting tubular epithelial proliferation in the murine BPK and rodent orthologous PCK models of ARPKD (96); Further, in these studies, when 20-HETE synthesis was selectively decreased, or 20-HETE activity was specifically inhibited using genetic or pharmacological inhibition, both in vitro and in vivo, cystic epithelial proliferation, cyst formation, and progressive cystic enlargement were markedly inhibited (96). Notably, the decrease in proliferation and amelioration of cystic disease was associated with a dramatic decrease in EGFR-activity and downstream signaling. Clinical development of 20-HETE inhibitors as potential therapeutic agents in PKD is being actively pursued.

Fluid Secretion

In addition to epithelial hyperplasia, tubular fluid secretion is an important feature of renal cyst formation and progressive enlargement (25, 26, 29). Given the anatomical differences discussed below, it is likely that tubular fluid secretion is quantitatively and qualitatively different in the pathophysiology of cyst formation in ADPKD and ARPKD. On a theoretical basis, tubular fluid secretion in addition to hyperplasia, fulfills the requirements for cyst growth predicted by mathematic modeling (27). Cellular proliferation without tubular secretion would produce solid tumor nests of epithelial cells rather than cysts. In ADPKD more than 70% of cysts have no afferent or efferent tubular connections, and thus must fill by transepithelial secretion of solute and fluid (97, 98). In contrast, microdissection studies confirm that enlarged, ecstatic collecting tubules in ARPKD are in continuity with the urinary space (99). One would not expect transtubular secretion to be as critical in the pathogenesis of changes in ARPKD as in ADPKD, unless there is downstream obstruction (which is not a characteristic finding in ARPKD). Studies in a variety of model systems have evaluated possible mechanisms involved in PKD tubular fluid secretion. These include alterations in ciliary structure and function, intracellular calcium transport, cyclic-AMP activity, epithelial sodium channel function, and sodium potassium ATPase localization and activity.

Cilia

Studies in ARPKD and ADPKD animal models, and human kidneys and cells, (as well as studies in other renal cystic diseases, such as nephronophthisis), have demonstrated that many of the disease-associated proteins appear to be present as multimeric complexes on, or in close proximity to, the primary cilia that are present on the apical membranes of renal tubular epithelial cells (100). In tubular epithelial cells, cilia project into the lumen and are thought to have a mechanosensory role (101, 102). Abnormalities in ciliary structure and/or function have been demonstrated in many PKD animal models, as well as in epithelium isolated from human ADPKD and ARPKD kidneys (103–107).

Pkd1 −/− cells have normal-appearing cilia, but lack the flow-induced Ca^{++} response noted in normal cells (101, 108). This finding suggests that polycystin complexes in or near the cilia act as flow-sensors, and that Ca^{++} influx occurs via a functional polycystin channel (predominantly mediated by polycystin 2). The Ca^{++} influx consequently induces release of Ca^{++} from intracellular stores. As previously noted, the polycystin complex is also found at desmosomes, adherens junctions, and focal adhesions (11–15). Primary cilia can sense changes in shear stress and fluid flow at the apical cell surface, whereas focal adhesions can sense tensile strength of cell-matrix attachments, and cell-cell junctional complexes sense forces between cells. Therefore, polycystin complex localization to these sites suggests a complex integration of mechanosensation with multiple signal transduction pathways.

It should be noted that data localizing a large number of cystoproteins to apical cilia have recently been called into question. To co-localize proteins of interest to cilia, tagged-antibodies have often been mixed with an anti-acetylated alpha tubulin antibody prior to tissue staining. It now appears that this procedure gives many false positives through non-specific protein-protein interactions of the antibodies prior to tissue staining (personal communication, Joel Rosenbaum PhD; Yale University, August 2008).

At the time of this writing, a primary role for isolated ciliary abnormalities in cystogenesis remains controversial in ADPKD and ARPKD. One cannot ignore the findings

that ciliary structural and functional abnormalities appear to be present in cystic tissue. However, in addition to the methodological problems noted above in protein co-localization studies, recent data suggest that polycystin-fibrocystin complexes may be found in subapical endosomes adjacent to, but not superimposed upon, ciliary basal bodies (centrosomes) in electron micrographs of human ADPKD and ARPKD kidneys. These endosomes bud around cilial axonema and appear in cyst fluid and urine. (Chris Ward, PhD, Mayo Research Foundation, personal communication, August 2008). Current data suggest that ciliary abnormalities may have a more primary role in syndromic renal cysts and other organ abnormalities seen in so called "ciliopathies" such as Meckel-Gruber syndrome, Bardet-Biedl syndrome, Oral-facial-Digital syndrome and perhaps nephronophthisis (see chapter 6 on Syndromes in Section One of this Textbook and Chapter 36 on Nephronophthisis in this Textbook). However, as suggested above, in ADPKD and ARPKD, it appears that cilia are part of a complex pathophysiological process linking mechanosensation to integration of multiple cell-signaling pathways emanating from multiple sites within the cell.

cAMP and Transport

Several studies support a major role for cyclic adenosine monophosphate (cAMP)-mediated chloride secretion during *in vitro* cyst formation (60, 109–111). A putative lipid "secretagogue" isolated from cyst fluid of human ADPKD kidneys was found to stimulate intracellular cAMP and stimulate fluid secretion (112) and more recently was confirmed to be the cAMP agonist forskolin (113).

Pharmacologic interventions directed towards down-regulating cAMP levels in cystic epithelia are therapeutic in both ARPKD and ADPKD animal models. Inhibitors of the vasopressin V2 receptor, a G-protein coupled, adenylate cyclase activating receptor present in the collecting duct, which modulates levels of intracellular cAMP, ameliorates renal cyst disease in the PCK rat model of ARPKD and the $Pkd2^{(-/WS25)}$ model of ADPKD (114–116). In both models, improvement in cystic kidney disease was associated with decreased levels of cAMP and aquaporin 2. Interestingly, increased water intake, which functionally down-regulates V2R activity, also improved cystic kidney disease and decreased kidney cAMP levels (117). In a related study, orthologous ARPKD (PCK) rats were bred to a Brattelboro rat strain (which lacks a functional renal vasopressin axis), and resultant double mutants demonstrated significant amelioration of renal cystic disease (118). Although background genetic modifiers may have influenced the results, such genetic complementation studies further support the primary role of G-protein mediated increases in renal epithelial cAMP in cystogenesis. Accordingly, controlled Phase 3 clinical trials with a VPV2R inhibitor (Tolvaptan) in patients with ADPKD have been initiated in both the United States and Japan. In addition, studies in animals and European pilot studies in ADPKD patients suggest that octreotide, a somatostatin analogue that decreases cAMP activity in both renal and biliary epithelium, may be effective in ameliorating cystic kidney and liver disease in ADPKD (119–121). However, recent data suggest that increased cAMP activity may not be the final "effector" for mediating cyst growth. The therapeutic effect of Src inhibition on renal and biliary disease in bpk and PCK rodent models, was not associated with significant changes in intracellular cAMP levels. These findings suggest that Src activity in PKD is downstream and independent from cAMP activation (41).

It has been hypothesized that cAMP-stimulated chloride and fluid secretion occurs in PKD through activity of the CFTR (cystic fibrosis transmembrane receptor), the chloride channel mutated in cystic fibrosis (122). CFTR Cl- channels exist in apical membranes of epithelial cells and are major mediators of forskolin-stimulated chloride and fluid secretion by epithelial cells of human polycystic kidneys *in vitro* (122, 123). CFTR is required for cAMP-dependant *in vitro* renal cyst formation (124). *In vivo* support for a role of CFTR in the pathogenesis of PKD was provided by a report of an ADPKD kindred in which cystic fibrosis was also present. Patients with ADPKD and CF (which results in a loss of functioning CFTR) were found to have less severe disease than those with ADPKD who did not have CF (125). However, a subsequent report failed to confirm such a protective effect (126). An *in vitro* study of CFTR inhibitors and cyst growth in 3D collagen gels demonstrated that cyst growth inhibition correlated with cAMP-stimulated chloride current inhibition, but not cell proliferation, suggesting that an effect, if present, is related to inhibition of fluid secretion only (127). Studies of ARPKD rodent models bred with a CFTR null mouse failed to show improvement in kidney disease in cystic animals lacking CFTR compared to those that expressed CFTR (128). Thus, these data demonstrate that CFTR does not have a significant impact on ARPKD cyst formation and expansion. The most attractive alternative hypothesis to date, supported by an increasing body of electophysiological data in normal and cystic tissue implicates abnormal EGFR-mediated down-regulation of the amiloride-sensitive Na^+ channel in tubular secretion in ARPKD (129–131). EGFR-expression

leads to decreased ENac subunit production at both the mRNA and protein level with consequent electrophysiological alterations. A block in active Na^+ transport at the luminal membrane results in intratubular Na^+ accumulation which obligates anion and fluid transport through active channels and perhaps, the paracellular pathway. With the availability of new reagents and technologies to perform definitive transport studies in human kidney epithelia, studies are underway in many laboratories to delineate both the similarities and differences underlying abnormal tubular secretion in ADPKD and ARPKD.

Additional *in vivo* and *in vitro* studies demonstrate a potential role for quantitative and qualitative alterations in Na^+-K^+-ATPase activity in mediating tubular fluid secretion in cystogenesis (132–137). In proximal tubules, it has been postulated that increases in Na^+-K^+-ATPase activity modulate tubular secretion and cyst formation through activation of a secondary active transport process (e.g., tubular organic anion secretion), which osmotically obligates intratubular fluid accumulation cystogenesis (132–134). In collecting tubules, apical, as opposed to normal basolateral cell surface Na^+-K^+-ATPase expression may mediate basal to apical vectorial sodium transport and thus directly drive fluid secretion in affected nephron segments in ADPKD and ARPKD (135–137). Apical Na^+-K^+-ATPase expression in murine ARPKD may reflect an exaggeration of the normal developmental profile of collecting tubule sodium pump expression (137). This, in association with the relatively undifferentiated ultrastructural and genetic profile of cystic tubular epithelium (18), suggests that abnormalities in the differentiation program of cystic tubular cells are fundamental to the process of cystogenesis.

Alternatively, apical misclocation of the Na^+-K^+-ATPase in many PKD specimens from end stage kidney (or those shipped under less than optimal conditions may), may reflect the results of ischemic injury. As ADPKD kidneys enlarge and vessels splay around enlarging tubular cysts, there are parenchymal areas which are underperfused and chronically ischemic. These changes not only result in mislocalization of the Na^+-K^+-ATPase and many additional changes, but contribute to the characteristic chronic fibrosis in ADPKD kidneys which leads to end stage renal disease. Similar alterations of the Na^+-K^+-ATPase and other polarized proteins can also artificially result from 24–48 h of cold ichemia time in ADPKD kidneys studied post-nephrectomy. These variables may explain, in part, conflicting reports demonstrating normal, basolateral Na^+-K^+-ATPase expression in freshly isolated PKD kidneys and some PKD models (138).

Extracellular Matrix

The third major mediator of tubular cyst formation and progressive enlargement is abnormalities involving the extracellular matrix (18, 25, 139, 140). Diffuse ultrastructural and biochemical abnormalities of tubular basement membranes have been demonstrated in human and animal models of PKD. Specific defects in the biosynthesis and transport of sulfated proteoglycans have also been identified (141–143). Renal tubular cells from patients with ADPKD grown *in vitro* produce increase amounts of extracellular matrix when compared with normal tubular epithelia (144).

It does not appear that matrix abnormalities mediate simple changes in the compliance or viscoelastic properties of tubular basement membranes leading to distension under normal intratubular pressures (145). Rather, it would appear that altered matrix composition modulates cyst formation through altered tubular epithelial cell–matrix interactions. These interactions regulate various aspects of cell growth, cell surface protein expression, cytodifferentiation, and gene expression (18, 19). Conceivably, altered epithelial cell-matrix interaction could modulate or amplify the processes of hyperplasia and fluid secretion discussed above. β-4 integrin and its ligand, laminin α-5, a component of the basement membrane, are aberrantly expressed in polycystic kidney disease and may have a role in cell adhesion and migration abnormalities seen in ADPKD cyst-lining epithelial cells (146). A recent study reported the development of PKD in a mouse harboring a hypomorphic mutation in the laminin α-5 gene (147). These and other findings suggest that a primary defect in one ECM component is sufficient to cause aberrant cell proliferation and development of renal cysts (148).

Experimental evidence suggests that matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) may also play a role in progression of disease in PKD (149–151). Elevated serum levels of MMPs, including MMP-1, TIMP-1 and MMP-9 have been demonstrated in a cohort of ADPKD patients when compared to normal controls (152). Although it is difficult to determine whether abnormal MMP expression is a reflection of a primary abnormality or a secondary effect, data suggest that inhibition of MMPs may have an impact on the severity of disease in animal models of ADPKD and ARPKD (58, 153). Overexpression of other basement membrane, extracellular matrix and cell adhesion components have also been demonstrated in PKD. Tenascin, an ECM glycoprotein, is abnormally expressed in human ARPKD and ADPKD fetal kidneys and in a

murine model of ARPKD (154, 155). Irregular expression of alpha-integrin subunits has also been demonstrated in fetal PKD kidneys (156).

Abnormal processes within the interstitium leading to interstitial inflammation and fibrosis contribute to progression in all cystic kidney diseases. For instance, MCP-1, a chemoattractant and mediator of interstitial inflammation, is upregulated in ADPKD rats (157). In addition, oxidant stress is increased and protective effects of antioxidants decreased in the kidneys of animal models of both ARPKD and ADPKD models (158). Abnormalities in steroid and lipid metabolism have also been demonstrated in murine ARPKD (159–161).

Angiogenesis may also have a role in the pathogenesis of cyst expansion in ADPKD. When cysts enlarge, their nutrient requirements may outstrip their blood supply, in a manner analogous to tumor progression in cancer. ADPKD kidneys show increased vascularity around cysts and evidence of ongoing angiogenesis (162). Endothelin levels are increased in human and rodent ADPKD kidneys (163). ET-1 overexpressing mice also develop polycystic kidneys and interstitial fibrosis, although they do not develop hypertension. Yet, interestingly, blockade of either endothelin A or B increased the severity of polycystic kidney disease in two ADPKD animal models (164, 165). The authors speculated that acceleration of cystic kidney disease was due to altered balance between ETA and ETB. Whether angiogenesis has a role in cyst expansion in ARPKD remains to be determined.

Theories of renal cyst formation generated in experimental models are not mutually exclusive and are largely complementary. A mutant gene or environmental factors can directly lead to alterations in tubular epithelial proliferation. In addition, there is increasing recognition that modifying genes can significantly alter the cystic kidney disease caused by the mutated PKD gene (161, 166–171). Environmental factors can also modulate the expression of a mutant gene or directly lead to tubular cell death. Resultant alteration of tubular cell metabolism may subsequently lead directly to the abnormal sorting of transport proteins, growth factor receptors, or cell adhesion molecules, with resultant abnormal extracellular matrix production, or production of growth factors mediating tubular hyperplasia. Induced changes in transtubular transport energetics may lead to hyperplasia secondary to increased transmembrane sodium flux, whereas programmed cell death may lead to further hyperplasia secondary to tubular regeneration. Alterations in sodium or chloride-mediated transtubular transport could lead to net intratubular fluid accumulation. Subsequent increases in tubular wall tension may further increase stimulation of epithelial proliferation, leading to tubular hyperplasia. The presence of a particular pattern of tubular hyperplasia, along with necrotic debris from cell death, may lead to partial tubular obstruction and further increases in tubular wall tension. Finally, abnormal extracellular matrix production could alter the epithelial microenvironment, further increasing hyperplasia and transtubular transport, thereby contributing to cyst formation and progressive cyst enlargement. Such an overall hypothetical schema of renal cyst formation appropriately focuses future investigations on the molecular mechanisms by which tubular epithelial hyperplasia is controlled and tubular metabolism are altered in both experimental and human cystic diseases.

The Cystic Phenotype and Targeted Future Therapy

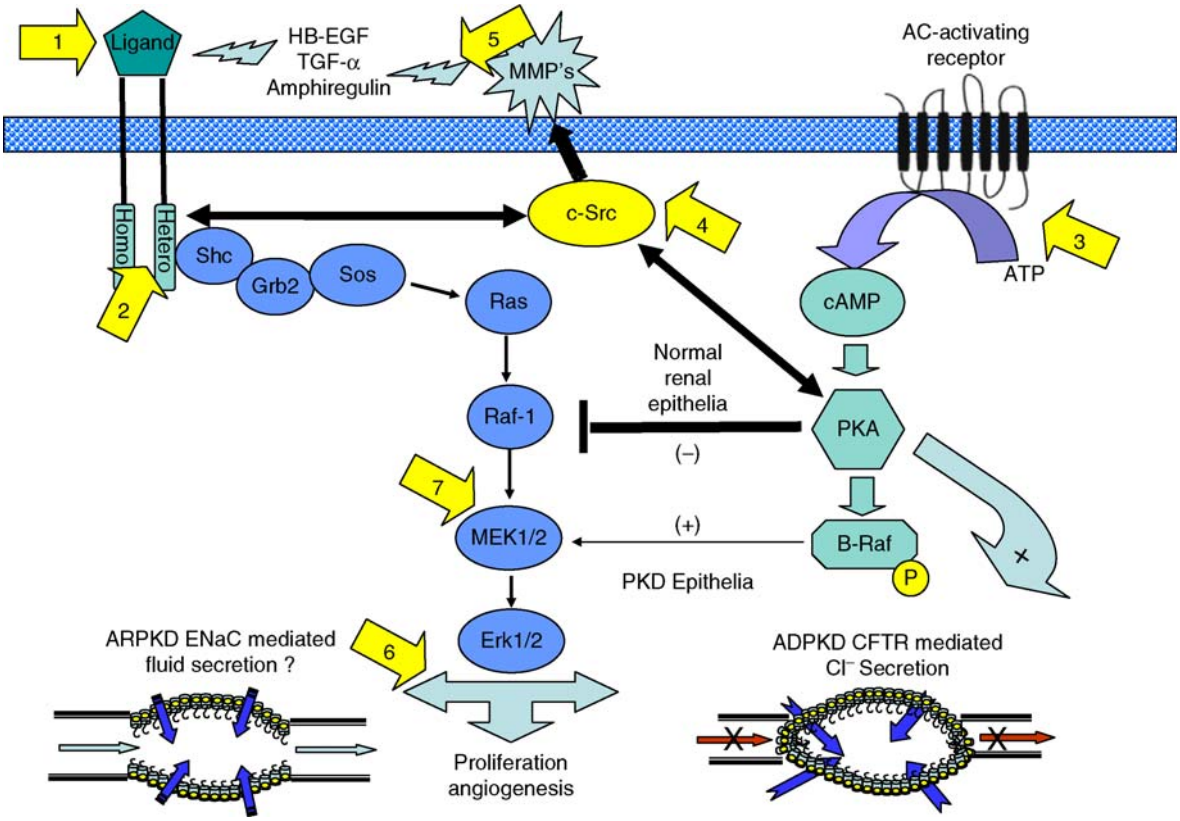
As discussed in the previous sections, the extensive studies delineating the molecular and cellular biology of ADPKD and ARPKD over the past decade have defined a unique "cystic phenotype", which provides a number of potential targets for future genetic and pharmacological therapy (*Fig. 36-2*). Relative to controls, the cystic ADPKD and ARPKD epithelial cell:

1. Demonstrates quantitative (increased amount) and qualitative (apical vs. basolateral) expression of various members of the EGFR-family of receptors and ligands. This initiates an autocrine-paracrine cycle of proliferation through activation of the Ras-Raf-MEK-ERK pathway and stimulates tubular fluid secretion by inhibiting amiloride sensitive sodium transport.
2. Demonstrates increased intracellular cAMP, which mediates proliferation through activation of PKA, phosphorylation and activation of the B-Raf/MEK-ERK pathway and stimulates tubular fluid secretion through activation of PKA and apical CFTR-mediated chloride transport.
3. Interacts with an abnormal microenvironment which includes poorly characterized abnormalities of ECM structure and function, increased cytokines, and angiogenesis that secondarily increases proliferation and tubular secretion.

Delineation of the "cystic phenotype" identifies key targets for future therapeutic intervention. As noted in the text and *Fig. 36-2*, the most promising therapies for future development and clinical trial target the abnormal

Figure 36-2

The Cystic Phenotype and Therapeutic Interventions. The figure depicts the two primary signaling pathways which mediate progressive cyst formation and enlargement in ADPKD and ARPKD: Abnormal expression of the EGFR-axis and adenylate cyclase activating receptor activity leading to increased cAMP (see text for details). Superimposed on the figure are key sites of therapeutic targeting: 1. Monoclonal antibodies against the EFGR-family (e.g., cetuximab; transtuzumab; nimotuzumab); 2. Small molecule inhibitors of EGFR-family tyrosine kinase activity (e.g., erlotinib, lapatinib, HKI-272); 3. Inhibitors of adenylate cyclase activating receptors (e.g., tolvaptan; somatostatin analogues); 4. Inhibitors of c-Src kinase activity which decrease EGFR-family ligand availability and inhibit tyrosine kinase activity, as well as decrease B-Raf activity (e.g., bosutinib, SKI-758, SU-6656); 5. Matrix metalloproteinase inhibitors which inhibit release of bioavailable EGFR-ligands (e.g., XL-784); 6. mTOR inhibitors (e.g., rapamycin); 7. Inhibitors of MEK kinase activity (e.g., UO126, PD98059). Additional therapies described in the text and recent reviews (21, 173, 285) but not depicted include: 20-HETE inhibitors (96); CDK inhibitors (458), Reactive Oxygen Species inhibitors and TNF-alpha inhibitors (459).



EGFR-axis and adenylate cyclase activation at multiple sites. Perhaps the most promising therapies will target key signaling intermediates which appear to integrate these separate pathways, such as Src kinase (*Fig. 36-2*) (6, 16, 21, 41, 172, 173) and/or utilize multiple agents in combination. At this writing, a number of agents are in advanced states of pre-clinical development or Phase 2–3 pilot clinical trials. The interested reader is referred to regularly updated listings of ongoing clinical trials for ADPKD and ARPKD at (www.pkdcure.org; and http://clinicaltrials.gov/.).

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is an inherited disorder characterized by cystic dilations of renal collecting ducts and varying degrees of hepatic abnormalities consisting of biliary dysgenesis and periportal fibrosis (5). ARPKD has alternatively been referred to as "infantile" polycystic kidney disease. This term, however, is generally no longer used because of recognition that the disease can present any time from the prenatal period through adolescence, and rarely even

in adulthood. Furthermore, other forms of PKD, including ADPKD, can present in the neonatal period (2, 174).

Epidemiology and Genetics

Based on published reports, the incidence of ARPKD is 1:10,000–1:40,000 (175, 176). The frequency of the gene in the population is estimated to be approximately 1:70 (177). However, the exact incidence is unknown, since published reports vary in the populations studied (e.g., autopsied patients versus survivors), and affected children may die in the perinatal period without a definitive diagnosis. With improvements in neonatal management leading to improved survival rates, as well as formal reporting mechanisms (such as a newly developed ARPKD registry (178)), more accurate incidence rates may become established.

Consistent with autosomal recessive disease, heterozygotes (carriers) are unaffected. The recurrence risk for subsequent pregnancies is 25%, and unaffected siblings have a 66% risk of being a carrier for ARPKD (5). Males and females are affected equally and ARPKD affects all racial and ethnic groups.

ARPKD is caused by mutations in *PKHD1* (polycystic kidney and hepatic disease 1), a large, novel gene that localizes to chromosome 6p21 (179). To date, all kindreds with features typical of ARPKD have demonstrated linkage to this locus (177). Thus, there is no evidence for genetic heterogeneity in patients with the typical features of ARPKD. Of note, kindred with features of ARPKD as well as additional extrarenal abnormalities including skeletal and facial anomalies has been described and linkage to the 6q21 locus excluded (180). Intrafamilial variability in ARPKD disease phenotype was originally reported to be unusual (181) in contrast to the wide variability often seen in some ADPKD kindreds (see below). However recent data suggest that up to 20% of ARPKD multiplex pedigrees exhibit significant intrafamilial phenotypic variability (182). Among families with at least one neonatal survivor, the risk for perinatal demise of a subsequent affected child is 37%. These data are important for appropriate genetic counseling.

PKHD1 was cloned by two independent research groups in 2002 (9, 10). The gene spans a region of over 400-kb of genomic DNA and contains at least 66 and possibly over 86 exons. The mRNA for the gene is produced as multiple alternative transcripts. The primary transcript of approximately 14–16 kb in length encodes a novel protein termed fibrocystin (alternatively named polyductin). Several alternative transcripts have also been described, several of which lack the transmembrane domain, suggesting that (if translated) they may result in production of secreted forms of fibrocystin (10). Fibrocystin is a very large protein with a predicted molecular weight of 447 kD, similar in size to polycystin 1. The precise function of fibrocystin is unknown at present. However, protein modeling suggests that it is a membrane-bound protein with immunoglobulin-like properties including the presence of several TIG/IPT domains (immunoglobulin-like folds shared by plexins and transcription factors). These motifs suggest that fibrocystin may function as a receptor (9, 10). Recent studies have demonstrated that fibrocystin undergoes proteolytic cleavage and that the C-terminal fragment of fibrocystin translocates to the nucleus (183). In addition, further studies have shown that fibrocystin regulates the expression and function of polycystin-2 (184). The precise functional significances of these observations are as yet undefined but they again highlight the complexities of PKD protein and signal transduction biology.

Pathogenesis

With the cloning and identification of *PKHD1* as the causative gene in ARPKD, detailed observations about mutations and genotype-phenotype correlations have begun to emerge. Several published series of multiple ARPKD kindreds have demonstrated different *PKHD1* mutations throughout the gene, without a clear clustering at specific sites, and the majority of families have unique ("private") mutations (9, 185–187). In addition, most patients studied in an ethnically diverse population are compound heterozygotes (188), i.e., has a different mutation on each *PKHD1* allele. Mutations identified include both missense and truncating mutations.

Genotype-phenotype analyses have also been performed, although these studies are complicated by the large number of mutations and high rate of compound heterozygotes. The locus-specific database for *PKHD1* contains over 350 different mutations (www.humgen.rwth-aachen.de). Several studies have confirmed, however, that patients with more pathogenic mutations (those with two truncating mutations) displayed a very severe phenotype, associated with a high rate of perinatal/neonatal mortality (185, 188, 189). In contrast, amino acid substitutions (missense mutations) were found to be more commonly associated with a nonlethal presentation (190). The actual position of the mutation along the gene, however, did not appear to correlate overall with phenotype (188).

Despite recent advances in the understanding of the molecular genetics of ARPKD, the pathogenesis remains

poorly defined. Northern analyses and RT-PCR demonstrated that *PKHD1* is expressed in both fetal and adult kidney, and to a much lesser extent in liver, pancreas and lung. Expression in other organs was not seen (9, 10). With the development of antibodies to the fibrocystin protein, additional tissue and cellular localizations have been delineated. During development, fibrocystin is expressed in the branching ureteric bud/collecting ducts of the developing kidney and is also present in developing neural tube, gut, bronchi and vascular system (191, 192). In the postnatal kidney, fibrocystin is primarily expressed in the collecting duct, the site of cyst formation in ARPKD. It is also present in the bile ducts and pancreatic ducts and islets. This expression pattern persists into adulthood (191). On a cellular level, fibrocystin localizes to primary cilia of renal collecting tubule and loop of Henle epithelia as well as biliary and pancreatic ductal epithelia (191–193). On a subcellular level, fibrocystin colocalizes with polycystin 2 in the polycystin complex adjacent to the basal bodies of cilia on the apical cell surface, as well as at adherens junctions and focal adhesions (192, 194). Recent data suggest that fibrocystin can undergo a complex pattern of Notch-like processing in which a large extracellular domain is shed in a process mediated by ADAM family metalloproteinases. Concomitantly, an intracellular fragment is release by gamma secretase actions (195). A similar pattern of processing is also seen with polycystin 1, which appears to translocate to the nucleus where it presumably affects expression of multiple genes (196).

Studies of animals with *PKHD1* mutations (either spontaneous or genetically engineered) have provided important insights into the abnormalities that can develop when fibrocystin is not expressed normally. The PCK rat harbors a 157-bp deletion in exon 36 of the rat orthologue of the human ARPKD gene, and developed spontaneously in a colony of Sprague-Dawley rats (9, 197). Although it is a genetic model of ARPKD, this model has clinical features of both ARPKD and ADPKD kidney and liver disease (9, 197). Affected animals develop progressive cystic enlargement of the kidneys after the first week of life. Renal cysts develop predominantly in distal tubules and collecting ducts. The animals also develop features consistent with Caroli's disease/congenital hepatic fibrosis (198). Several *Pkhd1* "knockout" models have also been developed and harbor mutations at various points along the gene. Interestingly, the phenotypes are quite varied and quite dissimilar to human ARPKD (199, 200). Insights into the regulation of *PKHD1* expression, have been provided by the observation that mice with mutations in hepatocyte-nuclear factor 1(HNF-1β), the gene mutated in the human disease MODY5, develop renal cysts and show a decrease in *PKHD1* expression (201). Further data demonstrate that HNF-1β itself directly regulates the activity of the *PKHD1* promoter (202).

Recent studies have provided new information regarding the pathogenesis of congenital hepatic fibrosis in ARPKD. CHF is characterized primarily by fibrosis and bile duct proliferation although biliary cyst formation is not a prominent feature. Increased expression of pro-fibrotic molecules transforming growth factor-beta (TGF-β) and thrombospondin–1 have been demonstrated in human ARPKD livers (203). Livers from orthologous PCK rats show a pattern consistent with the ductal plate malformation of patients with CHF. Intrahepatic bile duct dilatation with cystic changes and marked portal fibrosis are particularly prominent (198, 204). Biliary epithelium in the PCK show abnormalities in proliferative activity, related to abnormal EGFR-axis expression as well as apoptosis (41, 198, 205). Cholangiocytes in this model have abnormal cilia, the length of which is related to the level of *PKDH1* expression (206).

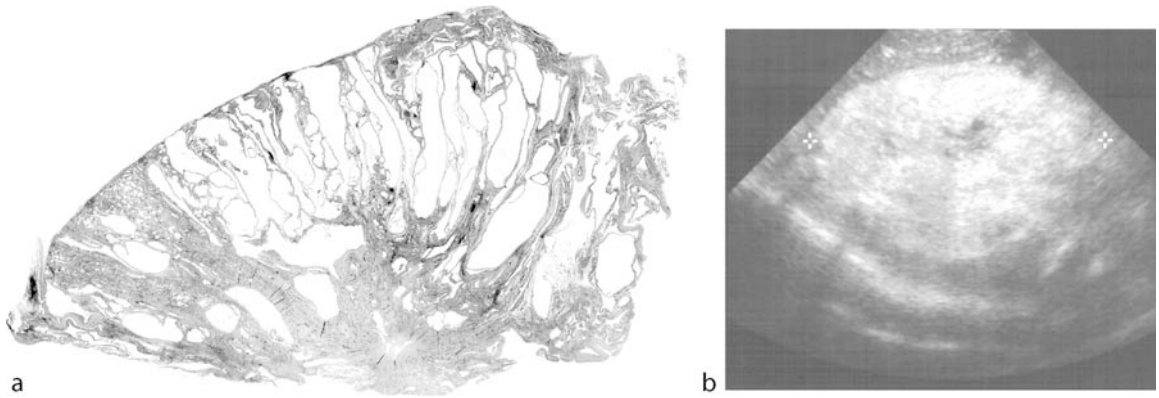
Liver disease is also evident in other ARPKD models, including the *bpk* and *cpk* mouse models. (170, 207–209). Biliary epithelial hyperplasia, like renal tubule hyperplasia appears to be mediated by a mitogenic cycle driven by abnormal EGFR-axis expression (205, 210).

Pathology

In infants and young children, the kidneys are reniform but grossly enlarged. Pinpoint opalescent dots are visible on the capsular surface and correspond to cystic cortical collecting ducts (211). Microscopically (see *Fig. 36-3a*), the cysts are usually less than 2 mm in size ("microcysts") and have been shown by microdissection, histochemical, and immunologic studies to be dilated collecting ducts lined by low columnar or cuboidal epithelium (212–215). The glomeruli and other tubular structures appear to be decreased in number because of marked collecting duct ectasia and interstitial edema. In fetal kidneys, proximal tubular cystic lesions have also been identified (216), but are largely absent by birth. The pelvicaliceal system and renal vessels appear normal. Unlike ADPKD, in which the cysts become discontinuous with the tubule, the cystic tubules in ARPKD are fusiform in shape and remain in contact with the urinary stream. Microdissection studies and scanning electron microscopy demonstrate that obstruction of urinary flow is not a component of ARPKD (211, 212). With increased patient survival, the development of larger renal cysts, interstitial fibrosis, and

Figure 36-3

Kidney histology and ultrasonography of autosomal recessive polycystic kidney disease (ARPKD). (a) Microscopic appearance of a kidney biopsy from a 7-month-old with ARPKD demonstrating multiple radially oriented collecting tubule cysts extending from the medulla to the peripheral cortex. A small amount of residual parenchyma contains glomeruli and noncystic tubules situated between the cysts. No glomerular cysts or signs of renal dysplasia are present. (Hematoxylin and eosin stain; original magnification x1.) (Specimen kindly provided by Dr. Steven Emancipator, Case Western Reserve University.). (b) Renal ultrasound (right kidney) of a newborn with ARPKD demonstrates the typical appearance of echogenic, enlarged kidneys (length = 6.5 cm; normal for age = 4.48 ± 0.62 cm) with poor corticomedullary differentiation.



hyperplasia produces a pattern more like ADPKD (see below) (217). Gang and Herrin (218) describe increasing fibrosis and inflammation in later specimens from patients who had typical collecting duct microcysts during infancy.

Some degree of biliary dysgenesis and hepatic fibrosis is always present in ARPKD. Although hepatic involvement is invariably present microscopically at birth, it is clinically evident in only 40–50% of neonates (219). The classic liver lesion shows a typical ductal plate abnormality consisting of portal fibrosis surrounding increased numbers of hyperplastic, ectatic biliary ducts with normal hepatocellular histology (217, 220, 221). With time, hepatomegaly and portal hypertension become evident in many patients. Intrahepatic biliary ectasia may result in macrocysts and dilation of extrahepatic bile ducts sometimes resulting in an enlarged gallbladder (222) or choledochal cysts (223). Although the combination of collecting tubule and biliary ectasia with periportal fibrosis is unique to ARPKD, portal fibrosis and bile duct proliferation may be associated with other types of renal disease, including ADPKD (224, 225).

Clinical and Radiographic Features

Historically, ARPKD was originally separated into four distinct clinical entities based on age at presentation and relative degrees of renal and hepatic involvement (226). Although such distinctions were useful as clinicopathological classifications, they are now recognized to be the result of different mutations within the same gene and are not used clinically (5, 227).

The majority of patients with ARPKD present in infancy (178, 219, 228, 229). A subset of patients with ARPKD may present as older infants with abdominal enlargement secondary to enlarged kidneys or hepatosplenomegaly without the full spectrum of clinical symptoms outlined below (178, 229). A smaller, though increasingly recognized subset of patients with ARPKD are diagnosed as older children or adults (178, 230, 231). These patients typically present with signs and symptoms related to congenital hepatic fibrosis, including hepatosplenomegaly and portal hypertension (177, 232). A recent series showed that almost one-third of individuals with mutations in *PKHD1* and hepatic involvement were 20 years or older at the time of initial presentation, suggesting that the clinical spectrum of the disease is broader than previously appreciated (231).

With the widespread use of prenatal ultrasound, most patients with ARPKD are now detected *in utero*. Prenatal ultrasound may demonstrate the findings of oligohydramnios, large renal masses, or absence of fetal bladder filling (233). At birth, patients usually have large, palpable flank masses that may be large enough to complicate delivery. Urine output is usually normal; however,

oliguric acute renal failure may occur (175). In such patients, increased urine output and a corresponding improvement in renal function may be seen following improvement in respiratory status (234). Most patients (70–80%) have some evidence of impaired renal function in the newborn period (3, 219). However, death from renal insufficiency is uncommon (226). Transient hyponatremia related to a urinary dilution defect is often present, but usually resolves over time (219, 228). The treatment consists of water restriction. Metabolic acidosis has also been reported (3, 228). As might be predicted from a pathological process that affects the collecting tubule, most patients have a urinary concentrating defect and symptoms of polyuria and polydipsia (3, 217, 228, 229).

Hypertension, which may be severe, is common in both infants and children and may well be a presenting feature (175, 217). It can be present in patients with normal renal function and eventually affects almost all children with the disease (3, 178). However, the pathophysiology of hypertension in ARPKD is poorly understood (172). In ADPKD patients the renin-angiotensin aldosterone system (RAAS) is upregulated and thought to occur as the result of expanding cysts causing local ischemia (235). The role of the RAAS in mediating hypertension in ARPKD is less clear. Systemic renin levels are not usually elevated in hypertensive ARPKD patients or in an ARPKD rat model (228, 229, 236). In addition, kidney size in ARPKD stabilizes over time and does not show the progressive macrocystic enlargement classically seen in ADPKD. Thus, it is unknown whether the same mechanism accounts for hypertension in both ADPKD and ARPKD. Local (intrarenal) RAAS activation is suggested by a recent histologic study that demonstrated increased expression of several renin-angiotensin axis components in two kidneys of individuals with ARPKD (237). Similarly, intrarenal RAAS activation has also been demonstrated in the orthologous PCK rat (238).

Pulmonary insufficiency, as manifest by respiratory distress, is a major cause of morbidity and mortality in neonates with ARPKD. Oligohydramnios results in pulmonary hypoplasia, which may be complicated by restriction of diaphragmatic movement due to massively enlarged kidneys. Additional causes of respiratory distress in these patients include pneumothorax and atelectasis, or a variety of common neonatal pulmonary disorders such as surfactant deficiency, bacterial pneumonia, meconium aspiration, or persistent fetal circulation. Severely affected infants may demonstrate all features of the "oligohydramnios sequence", including pulmonary hypoplasia, abnormal extremities and characteristic Potter's facies (239). Infants with true pulmonary hypoplasia often die soon after birth secondary to pulmonary insufficiency.

The typical appearance of ARPKD by ultrasonography is one of large echogenic kidneys with poor corticomedullary differentiation (*Fig. 36-3b*). Macrocysts, a feature of ADPKD, are usually not present at birth, but are not uncommon with progression of disease (240). In a study of sonographic features of adult patients with ARPKD, Nicolau et al. (241) noted the presence of multiple small cysts in normal-sized kidneys, increased cortical echogenicity and loss of corticomedullary differentiation as common features. Stein-Wexler and Jain (242) proposed that the ultrasonographic findings of "focal rosettes," corresponding to the macroscopic appearance of radially-oriented collecting tubule cysts, are specific for ARPKD. In addition, although kidneys may be markedly enlarged at birth, over time, the majority show stable to decreased renal size (243, 244). In a preliminary report from a prospective, NIH-supported study of the natural history of ARPKD, kidney volumes of enlarged kidneys increased at approximately 1/3 of the normal rate for age over 2–4 years (245).

Findings on magnetic resonance imaging include enlarged kidneys with hyperintense T2-weighted signals (246). Kern et al. showed that ARPKD kidneys have a characteristic hyperintense, linear radial pattern in the cortex and medulla by RARE-MR urography that may reflect the microcystic dilatation seen histologically (246, 247).

ARPKD kidneys have also been reported to have characteristic features by nuclear medicine studies. DMSA scanning demonstrated loss of the normal kidney outline and internal structure and patchy tracer uptake with focal defects throughout the kidneys, particularly at the poles. In the majority of cases, these DMSA changes did not correlate with the ultrasonographic findings, in which the kidneys appeared more uniformly affected (248).

Ultrasonographic findings in the liver include hepatomegaly, increased echogenicity and poor visualization of the peripheral portal veins. Reversal of normal venous flow by Doppler study, suggestive of portal hypertension, may also be seen. Hypertrophy of the left lateral segment of the liver is also occasionally seen (249) and a subset of patients will have overt evidence of biliary ductal dilatation (Caroli's disease) (249). In a preliminary report of the NIH-supported natural history study, over 75% of ARPKD patients demonstrated intra and extra-hepatic biliary dilatations, with dilated common bile ducts and enlarged gall bladders (245). Macroscopic liver cysts are uncommon (250), although choledochal cysts have been reported (223), and MRCP demonstrates diffuse intrahepatic bile duct dilatation with periportal fibrosis (249).

Diagnosis

With the advent of modern obstetrical ultrasonography, many patients with ARPKD are identified in the prenatal period. Enlarged echogenic kidneys, oligohydramnios, and the absence of urine in the bladder, are very suggestive of ARPKD (251). Older literature suggests that sonographic features of ARPKD may present in the second trimester but usually are not apparent until after 30 weeks' gestation (252). Both false-positive and false-negative results have been reported (253). However, with newer high-resolution obstetrical ultrasonography it is probable that diagnostic sensitivity and detection rates will improve. Wisser et al. (254) reported a case of a fetus with pathologically-confirmed ARPKD who demonstrated echogenic, normal sized kidneys at 15 + 4 weeks gestation.

As noted previously, other cystic kidney diseases in infancy, including ADPKD and cystic dysplasia, may have antenatal sonographic appearances that are difficult to distinguish from ARPKD (2). It has been proposed that fetal MRI may be a useful additional diagnostic study in fetuses with inconclusive ultrasonography in the third trimester of pregnancy (255). However, its accuracy in confirming the diagnosis earlier in pregnancy has not been assessed. Increased maternal alpha fetoprotein and amniotic fluid trehalase activity have been identified as potential markers for ARPKD, but neither has been confirmed as specific or sensitive for disease detection *in utero* (256, 257).

Definitive diagnostic criteria for ARPKD have not been established. Those proposed by Zerres et al, with modifications (5, 219), are used by many pediatric nephrologists, and include:

1. Ultrasonographic features typical of ARPKD, including enlarged, echogenic kidneys, with poor corticomedullary differentiation; and
2. One or more of the following:
   a) Absence of renal cysts in both parents, particularly if they are at least 30 years old,
   b) Clinical, laboratory or radiographic evidence of hepatic fibrosis,
   c) Hepatic pathology demonstrating characteristic ductal plate abnormality,
   d) Previous affected sibling with pathologically confirmed disease,
   e) Parental consanguinity suggestive of autosomal recessive inheritance

As noted above, renal ultrasonography may be less diagnostic in children who present later in childhood. Furthermore, in the subset of patients who present as older children and adolescents, hepatic abnormalities are often the prominent presenting feature.

Although renal biopsies will clearly differentiate the isolated fusiform cortical collecting tubular cysts of ARPKD (*Fig. 36-3*) from the heterogeneous cystic nephron involvement of ADPKD (*Fig. 36-4*) (214, 258), they are generally not indicated for patients who fulfill the classic criteria for ARPKD and/or those for whom genetic testing is definitive (see below) (5). In certain instances, liver biopsy may provide additional information and reveal the characteristic biliary dysgenesis of ARPKD. However, hepatic portal fibrosis and bile duct ectasia have been associated with other types of renal cystic disease, including ADPKD.

Genetic testing is also typically not required for patients with classic ARPKD diagnostic criteria. Genetic testing is useful, however, for families who already have an affected child, in identifying sibling carriers and in instances in which the diagnosis is less clear. Prenatal diagnosis may be made in a family with at least one known affected child through the techniques of linkage analysis or mutation analysis. Linkage analysis uses analysis of polymorphic markers that flank the location of a known disease gene to "track" the disease. This technique can also be used to identify whether the unaffected sibling is a carrier of the disease. In informative families, the accuracy of prenatal diagnosis using linkage analysis was >95% (259). An accurate genetic diagnosis by linkage analysis, however, is critically dependent on the diagnosis of ARPKD in the affected sibling (259).

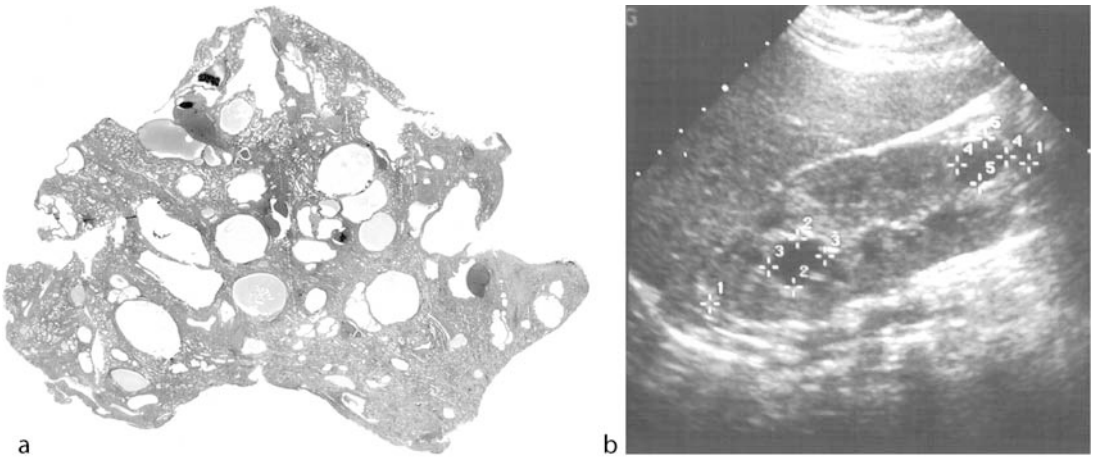
With the identification and cloning of *PKHD1*, molecular analysis is now available. Although initial studies reported a relatively low mutation detection rate (40–60%) by sequencing methods, newer studies using mutation screening by DHPLC demonstrate an overall mutation detection rate of 82–87% in individuals (including fetuses) with ARPKD (188, 260–263). In addition, pre-implantation genetic diagnosis (PGD) is now offered by a limited number of genetic laboratories (264). A complete list of laboratories offering clinical and research testing for ARPKD is available at www.geneclinics.org.

Treatment and Complications

Survival of neonates with ARPKD has improved in concert with overall medical advances in neonatal artificial ventilation and intensive care. It is currently impossible to predict which neonates with ARPKD who require immediate artificial ventilation have critical degrees of pulmonary hypoplasia incompatible with survival (3, 5). In some

Figure 36-4

Kidney histology and ultrasonography of autosomal dominant polycystic kidney disease (ADPKD). (a) Microscopic appearance of a kidney biopsy from an adult with ADPKD demonstrating multiple thin-walled cysts of varying sizes involving different nephron segments. Focal hemorrhage is noted within some cysts. (Hematoxylin and eosin stain; original magnification x1.) (Specimen kindly provided by Dr. Steven Emancipator, Case Western Reserve University.). (b) Renal ultrasound (right kidney) of a 13- year-old with ADPKD demonstrates several cysts (the largest measuring 1.5 cm × 1.6 cm). The left kidney also had several cysts not present on an ultrasound 2 years before this study. Kidneys are 11.4 cm (*right*) and 11.7 cm (*left*) (normal for age = 9.79 cm ± 1.5 cm).



instances, severe pulmonary distress may be secondary to potentially reversible fluid overload, neonatal lung disease, or restricted diaphragmatic motion secondary to massively enlarged kidneys. In selected cases, some authors have advocated continuous venovenous hemofiltration, unilateral or bilateral nephrectomy coupled with peritoneal dialysis to allow optimal ventilation and thereby assess the long-term pulmonary prognosis of the patient (265–268).

Infants and young children with ARPKD, including those without significant renal insufficiency must be followed closely. Because most children with ARPKD have urinary concentrating defects, significant dehydration is a particular risk during intercurrent illnesses, which may increase insensible water loss (fever), limit free water intake (nausea), or increase extrarenal water loss (vomiting, diarrhea). In patients with severe polyuria, thiazide diuretics may be of benefit to decrease distal nephron solute and water delivery. Supplemental bicarbonate therapy is required for those with metabolic acidosis.

Hypertension can be difficult to manage and may require multiple medications (175). Despite the fact that peripheral renin values are not usually elevated in hypertensive ARPKD patients, most patients respond well to angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, which are considered by many to be the treatments of choice. It should be noted, however, that the safety of ACEi or ARBs in neonates has been called into question by recent studies in neonatal rats that demonstrated adverse effects on tubular maturation and exacerbation of injury associated with obstructive uropathy (269). In addition, ACEi can precipitate acute renal failure in PKD patients (270), as well as in infants in general (271), particularly with dehydration. If additional medications are required, second-line agents include calcium channel blockers, β-blockers (in those without chronic lung disease or signs of congestive heart failure), and diuretics. Recent studies on the pathophysiology of cyst formation (see above) raise the theoretical concern that Ca^{++} channel blockers may exacerbate low intracellular Ca^{++} in cystic renal epithelia and increase abnormal proliferation and disease progression.

Urinary abnormalities may be present or develop over the course of disease. Pyuria is a relatively common finding and can be seen in the absence of demonstrable bacteriuria or documented infection (217). Urinary tract infection has been reported as a common complication in at least one uncontrolled series (3), but it is unclear whether children with ARPKD truly have an increased incidence of upper or lower urinary tract infections (UTIs) when compared with appropriately age-matched controls. Thus, as in any child with an abnormal urinalysis, clinical features and

appropriately obtained urine cultures must guide antibiotic therapy. If a UTI is documented, a voiding cystourethrogram and renal ultrasound should be performed to determine the possible presence of vesicoureteral reflux and rule out obstruction or superimposed upper tract structural abnormalities (218). Microscopic or gross hematuria and proteinuria may also be seen (3, 175). In infants and children who develop chronic kidney disease, the consequences of progressive CKD (e.g. growth failure, anemia, and renal osteodystrophy) become apparent as renal function decreases.

Dialysis and/or transplantation are indicated when children with ARPKD reach symptomatic end-stage renal failure or if progressive uremia results in growth failure or developmental delay. Peritoneal dialysis is often the preferred method of dialysis and may be the only practical long-term option in the young child. Peritoneal dialysis in ARPKD is usually successful even in the face of large kidneys and hepatosplenomegaly. Kidney transplantation offers definitive renal replacement therapy in children with ARPKD. Successful kidney transplantation prolongs survival and often accelerates growth and development in young uremic children. Nephrectomies may be indicated prior to, or at the time of, transplantation to control hypertension and/or to permit room for transplant placement in patients with massively enlarged kidneys.

Difficulties in feeding, even in patients without renal insufficiency, are often noted. This is presumably due to the presence of enlarged kidneys and or liver, interfering with normal gastrointestinal function. Supplemental feeding via nasogastric or gastrostomy tubes is often required to optimize weight gain and growth. Although growth failure in ARPKD may also occur as the result of chronic kidney disease, a study by Lilova et al. (272) suggests that growth failure in this population is common, may be attributable to factors other than CKD alone, and responds well to growth hormone treatment. In contrast, the preliminary report from the NIH-supported Natural History Study of ARPKD suggests that completely normal growth curves may not be uncommon (245).

With improved patient survival and advances in renal replacement therapy, hepatic complications progressively dominate the clinical picture of many patients with ARPKD (178, 219, 221, 232, 273). These include hepatosplenomegaly, bleeding esophageal varices, portal vein thrombosis, and hypersplenism causing thrombocytopenia, anemia, and leucopenia. Data from two recent series showed that portal hypertension occurred in 37–44% of neonatal survivors and was age-related (178, 274). Although significant complications related to portal hypertension develop, liver synthetic function is usually intact.

One serious and potentially lethal complication in ARPKD patients with significant hepatic involvement is bacterial cholangitis, which has been reported as early as a few weeks of age (3). Fever or elevation of liver function tests at any time should lead to the suspicion of cholangitis and result in complete evaluation and appropriate antimicrobial therapy. However, patients may not present with the classic clinical findings of cholangitis and the diagnosis should be strongly considered in ARPKD patients with unexplained recurrent sepsis with gram negative organisms (275). Caroli's disease (dilated intrahepatic bile ducts) has been identified as a potential risk factor for bacterial cholangitis (276, 277). Cholangiocarcinoma has also been reported in patients with CHF/Caroli's (278).

In infants and children with hepatic involvement, close monitoring for complications of portal hypertension is mandated, particularly since typical "liver function" tests (such as serum albumin and transaminases) may be normal. Yearly ultrasonography to determine changes in liver or spleen size to identify portal hypertension by reversal of venous flow is non-invasive and may be of value. Endoscopy is necessary to evaluate suspected esophageal varices that can be treated by sclerotherapy or banding prior to life-threatening hemorrhage. Periodic monitoring should reveal the hematologic profile of hypersplenism. Sudden worsening of anemia should raise the possibility of occult gastrointestinal blood loss secondary to splenic sequestration or variceal bleeding. Porto-systemic shunting may be indicated in some cases (228, 279), but concerns have been raised about reported cases of ultimately fatal recurrent hepatic encephalopathy in children with porto-caval shunts who progressed to ESRD (280). It has been hypothesized that the loss of kidney function results in impaired clearance of toxins that are shunted from the liver. This finding has raised concerns about whether liver transplantation should be considered as an alternative therapy for ARPKD patients with portal hypertension being evaluated for possible shunts or those with recurrent episodes of cholangitis (281). The increased use and successful outcome of living-related partial liver transplants makes this a more realistic option. In fact, successful sequential liver and kidney living-related transplants have been reported (282).

In addition to the significant medical problems, the psychosocial stresses of ARPKD on the patient and family can be overwhelming. Social support measures and periods of respite care are often necessary. A team approach using the skills of pediatric nephrologists in concert with

other pediatric medical subspecialists, specialized nurses, dietitians, social workers, psychiatrists, and other support staff is required to provide optimal comprehensive care for children with ARPKD.

Prognosis

Prognosis is difficult to assess, although it is now clear that survival of all but the most severely affected neonates who demonstrate pulmonary hypoplasia is possible (1, 217). Published reports vary with respect to neonatal survival rates, but suggest that approximately 70–80% of patients survive the newborn period with aggressive neonatal intensive care (3, 228, 232). Actuarial survival rates calculated from birth for 55 patients with ARPKD referred to a pediatric tertiary care center revealed that 86% were alive at 3 months, 79% at 1 year, 51% at 10 years, and 46% at 15 years (228). Calculations based on patients who survived to 1 year of age showed that 82% were alive at 10 years and 79% at 15 years (228). Similar findings were reported in a more recent study of 164 neonatal survivors with confirmed *PKHD1* mutations. Patients in that cohort had a 1 year survival rate of 85% and a 10 year survival rate of 82% (274). In a cohort of 166 ARPKD patients born after 1990, 75% were alive at a median age of 5.4 years (178).

Patients who survive the neonatal period usually have a decreased glomerular filtration rate (GFR), but studies have demonstrated subsequent improvement in renal function consistent with some degree of continued renal maturation (175). However, a significant number of patients with ARPKD will progress to end-stage kidney disease. In a cohort of patients surviving the first month of life, Roy et al. (232) reported renal survival of 86% at 1 year and 67% at 15 years. A more recent study of patient with confirmed *PKHD1* mutations showed actuarial renal survival rates of 86% at 5 years, 71% at 10 years, and 42% at 20 years (274).

With the success of renal transplantation and improved survival of patients with ARPKD, morbidity and mortality of complications related to congenital hepatic fibrosis are more common and clinically relevant. Whether these complications result in significant mortality post-kidney transplant is a subject of some debate. Khan et al. reported the outcome of 14 patients with ARPKD after renal transplantation (283). With a mean follow-up of 14 years, the study showed 1 and 5 year patient survival rates of 93% and 86% respectively. Overall 36% of patients died and, in 4 of 5 of those patients, death was directly related to complications of hepatic disease. In those who survived, 63% had portal hypertension. Thus, complications of CHF developed in almost 80% of patients following renal transplantation for ARPKD. In contrast, in a retrospective study of patients included in the North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS) registry, Davis et al. (284) reported similar patient and graft survival rates in kidney transplant patients with ARPKD compared to those without. It is interesting to note, however, that among those patients who died, sepsis was the cause in 64% of those with PKD versus 32% in those without PKD, suggesting that ARPKD patients may be at increased risk of infection compared to the general pediatric transplant population.

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is a systemic inherited disease characterized by progressive renal cystic enlargement of all nephron segments coupled with variable extrarenal manifestations involving the gastrointestinal tract, cardiovascular system, reproductive organs and the brain (4, 173, 285). ADPKD has alternatively been called "adult" polycystic kidney disease. However, this term is a misnomer because ADPKD has been diagnosed in the fetus, newborns, older children and adolescents (175, 229, 286, 287).

Epidemiology and Genetics

ADPKD is the most common inherited human kidney disease and occurs at an incidence of approximately 1:400 to 1:1000. It affects all races and males and females are both affected; however, the kidney phenotype may be more severe in males (288). ADPKD is a rare cause of ESRD in the pediatric population, but accounts for approximately 5–10% of ESRD in adults. The two major disease-causing genes are *PKD1* and *PKD2*. In the general population, *PKD1* accounts for approximately 85% of ADPKD and *PKD2* the remaining 15%. A third ADPKD locus has been suggested by a few case reports (289–291), but has not been substantiated (4). Mutations in *PKD1* and *PKD2* produce similar phenotypes, however, the age of onset of cystic disease, hypertension, and renal insufficiency is delayed in the latter (21, 292–294).

PKD1 has been mapped to chromosome 16p13.3 (295). Like *PKHD1*, *PKD1* is a very large gene, spanning 53 kb of genomic DNA with 46 exons encoding a 14.5 kb transcript (7). A portion of the gene is duplicated in the proximal portion of chromosome 16. The gene encodes a large, novel 4304 amino acid protein product,

polycystin-1 (PC-1), a 460 kD protein with a large extracellular domain that contains motifs likely to function as protein and carbohydrate binding sites. The PKD repeats in the extracellular domain may mediate homodimerization of PC-1. The extracellular domain of PC-1 also contains a physiologically important G-protein-coupled receptor proteolytic site (GPS). Taken together these motifs suggest that PC-1 may function as a receptor and/or have roles in cell-cell interactions. *PKD2* has been linked to chromosome 4q13-q23 (8, 296) and expresses a 5.4 kb mRNA, which encodes a 968 amino acid polypeptide, polycystin-2 (PC-2) (8). Polycystin-2, also called TRPP2, is a calcium permeable, non-selective cation channel (297, 298) whose NH2 and COOH termini are both cytoplasmic.

Pathogenesis

ADPKD is characterized by considerable intrafamilial and interfamilial phenotypic variation (189, 299). Several studies have supported a role for genetic background/genetic modifiers as a cause of this variability (300). A number of candidate genes have been examined as potential modifiers of the disease phenotype. These include members of the renin-angiotensin system, including the angiotensin converting enzyme (ACE) gene, the endothelin system and the cystic fibrosis gene, *CFTR*. However, positive results suggesting an effect have not been reproducible (189).

One gene that has been found to influence disease severity is the tuberous sclerosis 2 (*TSC2*) gene. Several kindred's were identified that had co-existent *TSC2* and *PKD1* mutations with severe childhood-onset ADPKD. These kindreds were subsequently found to have large deletions in an area containing both *PKD1* and *TSC2*, resulting in a contiguous gene syndrome (301).

One explanation for phenotypic variability may be related to the so-called "second hit" theory of ADPKD which result in heterozygous mutations at the level of individual cysts. By analyzing two closely linked polymorphic markers within the PKD1 gene, Qian et al. revealed that the renal epithelia from single cysts are monoclonal, containing only the mutant haplotype (302). A subsequent study by Brasier et al. (303) confirmed these findings. These two studies suggest that patients harboring a germline mutation in the one allele of a PKD gene undergo a somatic "second hit", which results in the loss of the remaining normal allele and genetic heterozygosity in those affected cells. These studies provide a possible molecular explanation for both the focal nature of cysts (<5% of tubules are cystic in ADPKD) as well as the phenotypic variability within families harboring the same germline mutation. The extent to which this two-hit phenomenon contributes to the overall phenotypic variability remains a subject of some debate (304).

Because of the significant intrafamilial variability in ADPKD, including kindreds with more severe disease noted in successive generations, the genetic phenomenon of anticipation has been postulated to be an explanation for this heterogeneity. However, a recent study of ADPKD patients with *PKD1* mutations failed to find evidence for anticipation in this disease (305).

PKD1

Numerous different mutations throughout the *PKD1* gene have been identified in patients with ADPKD with no specific mutational "hot spots" identified (306). The majority of mutations are predicted to result in truncation of the PC-1 protein. Substantial phenotypic variability has made genotype-phenotype correlations unachievable, but a number of recent studies have made significant observations about the nature of *PKD1* mutations and disease phenotype. Rosetti et al. (307) found that, even taking into consideration the significant inter- and intrafamilial phenotypic heterogeneity, patients with mutations in the 5′ region of *PKD1* had significantly more severe kidney disease than those with mutations in the 3′ portion of the gene. Thus, the location, rather than the type of *PKD1* mutation, was found to be the factor that correlated with the onset of ESRD. In addition, 5′ *PKD1* mutations have also been reported to be predictive for the development of cerebral aneurysms (308).

PC-1, the protein product of *PKD1*, is expressed in multiple tissues, including kidney, liver, pancreas, intestine and cerebral blood vessels (all sites of pathologic changes in ADPKD), as well as in the lung, testis, and other tissues (309–312). Localization studies demonstrated robust PC-1 expression in human fetal renal tubular epithelia that diminished with age, but persisted at low levels into adulthood (309, 313), suggesting a role in renal development and tubular maintenance.

PC-1 possesses a large extracellular domain, multiple transmembrane spanning regions, and an intracellular carboxy-terminus (314, 315). The extracellular domain is dominated by immunoglobulin-like repeats (the PKD domain) as well as a leucine-rich repeat, a LDL-A domain, a REJ domain, and a calcium-dependent lectin domain. These structural components, taken as a whole, suggest that the extracellular portion of PC-1 may be capable of

binding an as yet undefined ligand (315). PC-1 is anchored to the cell membrane by 7–11 putative transmembrane domains. These numerous features suggest that PC-1 is a large, multifunctional molecule involved in carbohydrate motif recognition, ligand binding, and Ca^{2+} regulation. It may engage in cell–cell and/or cell–matrix interactions, which regulate signal transduction pathways mediated by cell surface protein–protein interactions or directly participate in regulating transcriptional programs.

PC-1 has been localized to the plasma membrane of renal epithelial cells in a basal distribution at areas of cell-cell contact (adherens junctions), cell-matrix contacts (focal adhesions), and in the primary cilia. PC-1 has been shown to bind to polycystin 2 (316, 317) and regulate the channel activity of polycystin-2 (a non-selective cation channel) (318). The polycystin complex at the cilia appears to play a role in mechanosensation as previously discussed and loss of function of one of the complex members can result in loss of flow induced-calcium response (101). Interestingly, Chauvet et al. (319) showed that mechanical stimuli can induce proteolytic cleavage and nuclear translocation of the polycystin-1 carboxy terminus tail suggesting that polycystin-1 may have a role in regulating gene expression.

PC-1 co-localizes with and forms multimeric complexes with a wide variety of other proteins at other sites along the plasma membrane as previously discussed. These include those involved with cell-matrix interactions (such as $\alpha_2$beta 4 integrins and focal adhesion complexes) as well as cell-cell interactions (including E-cadherin-β-catenin complexes) (11, 13, 315, 320). PC-1 has also been shown to interact with intermediate filaments at the desmosomes (321) and cells lacking polycystin 1 show mislocalization of desmosomal proteins (14).

Additional data demonstrate that polycystin-1 induces resistance to apoptosis via the phosphatidylinositol 3-kinase/Akt signaling pathway and promotes spontaneous tubulogenesis in MDCK cells (322, 323). The carboxy terminal of polycystin-1 triggers branching morphogenesis and migration of inner medullary collecting duct (IMCD) cells, and supports *in vitro* tubule formation (324).

Both under- and over-expression of polycystin-1 is associated with cyst formation and/or developmental abnormalities. In cystic epithelium of human ADPKD kidneys (309), polycystin 1 is overexpressed and data from animal studies suggest that *PKD1* overexpression is sufficient to induce cysts (325). "Knockout" mouse models, in which a variety of PKD1 mutations have been introduced that result in the loss of functional polycystin, have also provided important clues to its function, particularly during development. Animals lacking polycystin-1 die *in utero* or soon after birth and demonstrate abnormalities in multiple organs, including the heart, blood vessels kidneys and pancreas (326–328). To overcome this lethal phenotype, investigators have developed PKD1 mutant mice that either produce low levels of PC-1 (hypomorphs) or have a "conditional" mutation (floxed allele) that is controlled via breeding with a Cre-recombinase expressing mouse or by pharmacologically driven Cre-gene expression. These animals survive, but develop kidney, pancreatic and vascular disease of variability severity (22, 329). Interestingly, the timing of the loss of PC-1 post-natally has a significant impact on the disease phenotype. Neonatal mice that lose PC-1 develop massive cystic kidney enlargement within 4 weeks, whereas older mice who lose PC-1 expression develop only mild cystic kidney disease (330). These observations suggest that cyst formation requires not only loss of PC-1, but also concomitant cell proliferation, such as is seen during early post-natal kidney development.

PKD2

Multiple mutations in *PKD2* have been identified in affected families, and as with *PKD1*, most families have unique mutations (331, 332). These mutations truncate polycystin-2 (PC-2) and appear to be loss-of-function mutations. As with PKD1, considerable intrafamilial phenotypic variability is reported in families with PKD2 mutations (189, 332). Genotype-phenotype studies have suggested that, unlike *PKD1*, the location of *PKD2* mutations does not appear to influence the age of onset of ESRD.

Similar to PC-1, PC-2 is widely expressed. The highest levels of expression within the kidney are the thick ascending loop of Henle and the distal convoluted tubule, where PC-2 localizes to the basolateral plasma membrane of renal tubular epithelium (333). PC-2, like polycystin-1, is expressed in the vasculature, including porcine aorta and normal human elastic and intracranial arteries (334). On a subcellular level, PC-2 localizes to the plasma membrane as well as to the endoplasmic reticulum and Golgi apparatus (12, 333).

PC-2 contains six transmembrane regions and has intracellular domains at both its amino- and carboxy-termini. The transmembrane regions share significant homology with voltage-activated Ca^{2+}/Na^{+} channels, which suggested that polycystin-2 may be a channel protein. The carboxy-terminus contains an EF-hand domain

that binds Ca^{2+} in addition to several potential phosphorylation sites. Koulen et al. (297) confirmed by single channel studies that PC-2 (a member of the subfamily of the transient receptor potential (TRP) channel superfamily) functions as a calcium-activated intracellular ion release channel *in vivo* and hypothesized that polycystic kidney disease results from the loss of regulation of an intracellular calcium release signaling pathway.

As noted previously, PC-2 interacts with PC-1 to form a complex located at the cilia. Data suggest that PC-2 located on the endoplasmic reticulum also interacts with PC-1 present at the plasma membrane (173). Recent data also demonstrate that PC-2 has a role in regulating the cell cycle through direct interaction with Id2, a member of the helix-loop-helix (HLH) protein family known to regulate cell proliferation and differentiation. This interaction requires PC-1-dependent phosphorylation of PC-2 (335). PC-2 also interacts with the protein, kidney injury molecule-1 (KIM1), a chemosensor present on the cilia (336, 337). Finally, Li et al. (338) reported that intracellular portions of PC-2 associate with alpha-actinins, which are actin-binding and actin-bundling proteins. They hypothesized that the aberrant interactions between PC-2 and alpha-actinins could play a role in the cell proliferation, adhesion and migration abnormalities seen in PKD epithelia.

Animal models with reduced or absent *PKD2* expression have also provided important insights into the function of PC-2. Similar to *PKD1*, PKD2 knockout mice die *in utero* or soon after birth and demonstrate cardiac defects in septum formation as well as kidney and pancreatic cysts (339). Studies of two *PKD2* mutant models expressing variable levels of PC-2 demonstrate that increased cell proliferation is an early event associated with the loss of *PKD2* expression and precedes cyst formation (340). This *in vivo* finding was supported by *in vitro* studies of cell lines lacking PC-2. In those cell lines, the loss of *PKD2* was associated with increased proliferation rates, suggesting that PC-2 is a negative regulator of cell growth (341). In addition, loss of *PKD2* has been reported to induce changes in the localization of *PKD1*, suggesting it has a role in mediating *PKD1* subcellular localization (342).

Pathology

In ADPKD (see *Fig. 36-4a*), kidney cysts form in glomeruli and all tubular segments. Glomerular cysts may be seen as a component of ADPKD or as a separate disease entity. Unlike ARPKD, in which the cystic dilatations are fusiform in nature and remain in connection with the tubular lumen, in ADPKD the enlarging cysts eventually "pinch off" and become disconnected from the tubular lumen and urinary space.

Clinical and Radiographic Features

Patients with ADPKD are usually diagnosed and become symptomatic in adulthood (173). However, children affected with ADPKD may also become symptomatic or be diagnosed as an incidental finding. The clinical spectrum of pediatric ADPKD ranges from severe neonatal manifestations indistinguishable from ARPKD to renal cysts noted on ultrasound in asymptomatic adolescents (2, 175, 229, 286, 343, 344).

As with ARPKD, hypertension can present during the newborn or infant periods and is common in pediatric and young adult ADPKD patients, despite the presence of normal renal function (229, 286, 345, 346). The acceptance of ambulatory blood pressure monitoring (ABPM) as an important tool for blood pressure assessment has allowed for more in depth studies of blood pressure abnormalities in patients with ADPKD. A significant proportion of normotensive young adults with ADPKD have "prehypertension" by ambulatory blood pressure monitoring (347). Blunted "nocturnal dipping" on ambulatory blood pressure monitoring has also been reported to be associated with endothelial dysfunction in this population (348). It is also notable that in a study of adults with ADPKD, a history of hypertension in affected parents was associated with an earlier onset of hypertension in their affected offspring (349).

Hypertension in ADPKD has been hypothesized to be due to reduced renal blood flow due to cyst compression with subsequent activation of the renin?angiotensin system, and increased sodium retention (350, 351). Recent case–controlled studies that have specifically controlled for sodium intake have shown no differences in the systemic RAS activation in hypertensive ADPKD patients compared to patients with essential hypertension (352). It is still possible, however, that local (intrarenal) RAS activation could still play a role in the pathogenesis of both hypertension as well as progressive kidney damage associated with ADPKD (353, 354). In addition, increased ACE independent generation of angiotensin II (via mast cell production of chymase) has been reported (355).

Increased left ventricular mass been reported to occur in normotensive children and young adults with ADPKD (356) and is associated with impaired relaxation time during exercise testing (357). Doppler abnormalities

consistent with early diastolic dysfunction has been reported in some patients, although the data are conflicting (356, 358). In addition, Oflaz et al. (359) reported an increased rate of biventricular dysfunction in both hypertensive and normotensive ADPKD patients, suggesting early cardiac involvement prior to the development of overt hypertension. An intrinsic cardiac abnormality is not unexpected given the diffuse vascular localization of *PKD1* and *PKD2* and the severe vascular phenotypes associated with null mutations in these genes. On the other hand, in light of the data about prehypertension diagnosed by ABPM in apparently normotensive ADPKD patients, it is possible that patients who were reported to be "normotensive" may, in fact, have had subtle blood pressure abnormalities not recognized by standard casual blood pressure measurements.

The increased incidence of cardiac valvular abnormalities such as mitral valve prolapse, commonly seen in the adult ADPKD population (360, 361), has also been reported in children with ADPKD (362). There have also been several reports of endocardial fibroelastosis in children with ADPKD (363, 364). An increased risk of coronary aneurysms has been reported in adults, but no pediatric cases have been reported, to date (365). An increased risk of pericardial effusion has also been reported in adults with ADPKD (366). Although rarely detected before the age of 20, there are reports of clinically significant cerebral vessel aneurysms in pediatric ADPKD patients as well (367).

In addition to hypertension, other presenting symptoms can include abdominal pain, palpable abdominal masses, gross or microscopic hematuria, UTIs, abdominal or inguinal hernias. The occurrence of gross hematuria after seemingly minor trauma to the flank region should raise the possibility of ADPKD. Renal insufficiency is rare, but can occur in childhood (286, 344). A renal concentrating defect, which may be associated with clinical evidence of polyuria and polydipsia, may be present in up to 58% of children with ADPKD (3, 368) and its presence correlates with the presence of hypertension by ABPM as well as the number of renal cysts (369). These findings suggest that impaired renal concentrating ability may be another clinical indicator of cystic kidney disease severity in children with ADPKD. Renal infections are common in adult patients with ADPKD and can be a presenting feature in the affected infant and child (229). Pain can also result from urolithiasis, a common finding in adults with ADPKD, as well as cyst rupture.

The typical appearance of ADPKD in children by ultrasonography is one or more renal cyst. ADPKD renal involvement in children is commonly asymmetric and may be unilateral in a small minority (370). The Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP) is a longitudinal prospective study of adult ADPKD patients, which uses high-resolution magnetic resonance (MR) imaging (371). This series of studies has demonstrated that individual cysts, as well as total cyst and kidney volumes, are well-delineated by magnetic resonance imaging (MRI), which can also be used to monitor cyst and kidney growth and blood flow over time (372, 373). These insights have allowed the development of clinical trials with novel therapeutic agents by providing a non-invasive means of monitoring response to therapy over a relatively short (one to three) year period.

The extrarenal cysts seen commonly in adults with ADPKD (360, 374) are uncommon in pediatric patients. Although hepatic, pancreatic, or testicular cysts are rarely detected before puberty, they have been reported in affected children, even in the first year of life (375, 376). Although liver cysts (detected by ultrasonography) were thought to be uncommon in children, a recent MRI study suggested that liver cysts may be present in up to 55% of adolescents and young adults (377). The prevalence in that study was reported to be directly related to the kidney volume. Liver cysts in children, when present, are not generally associated with pain, infection, and hepatomegaly as noted in adult patients. Congenital hepatic fibrosis with severe portal hypertension in children and adults with ADPKD has been reported rarely (224, 225). The presence of pancreatic cysts has been found exclusively in *PKD1* patients and do not appear to contribute to morbidity or mortality (378).

Diagnosis

There are no specific clinical diagnostic criteria for children with suspected ADPKD. As noted previously, ADPKD can present in any age group, including fetuses and neonates. The diagnosis of ADPKD has been made *in utero* by ultrasound, and affected newborns can present with Potter's phenotype and die from pulmonary hypoplasia. Affected infants can be born with large hyperechoic kidneys with or without macrocysts and variable degrees of renal insufficiency. Prenatal diagnosis is suggested by antenatal ultrasound findings of moderately enlarged hyperechogenic kidneys with or without cysts, with increased corticomedullary differentiation (379). However, these findings may not be evident until the third trimester (380, 381).

In families with known ADPKD, asymptomatic children may be identified by ultrasonographic examination

or as an incidental finding during evaluation for an unrelated problem (*Fig. 36-4b*). In pediatric patients with a 50% risk of ADPKD, the finding of one cyst or enlarged echogenic kidneys without cysts may be considered diagnostic (4, 286).

Even in families not known to have ADPKD, the finding of one or more kidney cysts in a fetus or child should alert the clinician to the possibility of ADPKD, since approximately 8–10% of patients with ADPKD will have *de novo* (new) mutations (4). Although radiographic studies may report the presence of a "simple cyst" and note it as a normal finding, in fact, such cysts are extremely rare in childhood (382). If ADPKD is clinically suspected in a child, the parents (and/or grandparents if the parents are younger than 30) should be considered for radiographic evaluation (383). It is not uncommon that the diagnosis of ADPKD in a child can lead to the diagnosis of ADPKD in asymptomatic adults following parental radiographic studies. Additional rare causes of solitary or even grouped unilateral cysts in a patient without a family history should also be considered. These include caliceal diverticula or isolated renal cystic disease (384, 385). In such instances, additional diagnostic studies, including contrast enhanced CT or IVP can help to exclude these diagnoses (385).

Screening evaluations of asymptomatic children at risk for ADPKD is currently not recommended. Because cysts may not be evident until adulthood, the finding of a negative ultrasound may be falsely reassuring (386). Conversely, there may be significant psychosocial and financial implications of the diagnosis of ADPKD in an asymptomatic patient who may not develop clinical signs of disease for several decades (387, 388). Some adults with ADPKD choose not to be tested, and testing of asymptomatic children eliminates their ability to make that decision as an adult. Thus, it is currently recommended that for "adult onset" genetic diseases such as ADPKD, screening should not be done unless a there is anticipated benefit to the child (389). With the emergence of novel, potentially disease-modifying therapies for ADPKD, and the passage of legislation in the United States preventing discrimination against individuals with genetic disorders (Genetic Information Nondiscrimination Act, or GINA) recommendations regarding screening are being re-evaluated as previously noted.

Genetic testing (including prenatal testing) is available for ADPKD. Previously, genetic testing was via the technique of linkage analysis (229). However, because of the need for a relatively large number of family members willing to be tested, this technique may be appropriate for fewer than 50% of families (173). With improvement in mutation detection techniques, direct sequence analysis is now the more commonly used methodology. Current mutation detection rates are approximately 85% using this methodology (331, 390).

While prenatal genetic testing, including preimplantation genetic diagnosis (PGD) (391) is available, it is not widely used. In the majority of kindreds, fetuses harboring an ADPKD mutation will not show any obvious renal or other abnormalities and patients may be asymptomatic for 2–3 decades. Surveys of ADPKD families indicate that only 4% would consider pregnancy termination if the fetus were affected (392). An up-to-date listing of laboratory currently performing genetic testing of ADPKD patients for clinical or research purposes is available at www.geneclinics.org.

Treatment and Complications

Treatment of ADPKD is primarily focused on detecting and managing renal and extra-renal complications. Asymptomatic children at risk for ADPKD should be followed annually for the development of hypertension, hematuria (gross or microscopic), polyuria, proteinuria or palpable abdominal masses. Any of these findings is an indication for ultrasound examination and close clinical follow-up.

As with other forms of chronic kidney disease, identification and treatment of hypertension is essential in slowing progression to ESRD in ADPKD. In adults with ADPKD, more intensive blood pressure control (<120/80) has been reported to have a greater impact on LVH reduction than standard control (<140/90)(393). It has been suggested that ACE inhibitors and AII receptor antagonists (ARB), alone or in combination, may offer benefits in addition to anti-hypertensive effects (394–396); however, the data are not entirely conclusive (397). A longitudinal study of children with ADPKD treated with ACE inhibitors is currently underway. A larger-scale multicenter NIH trial (HALT/PKD) is underway to address the question of whether ACE inhibitor plus ARB is more beneficial than ACE alone in modifying disease progression. In addition, a smaller study of 49 hypertensive ADPKD patient: found that treatment with an ARB appeared to be more favorable than that of a calcium channel blocker (CCB) in terms of rates of decline in renal function and proteinuria. As previously noted, reports in rodent PKD models suggested that CCBs exacerbate cystic kidney disease because of depletion of intracellular calcium (398). Although the results of these animal studies are intriguing, avoidance of CCBs is not

currently recommended for ADPKD, or as previously noted, ARPKD (399). It is also notable that reversible acute renal failure may be precipitated by ACE inhibitors in ADPKD patients with diminished kidney function and massive cystic involvement (270). Although acute renal failure would be extremely unlikely in children (given the absence of massive cystic involvement and intact renal function during childhood), it is prudent to obtain follow-up serum chemistries after initiation of ACE and/or ARB therapy.

Urinary tract infection, in particular, cyst infection may occur in children and adults with ADPKD. It has been reported that the risk of pyuria and bacteriuria in ADPKD increases progressively from 2% in the second decade to 32% in the seventh decade. Most adult ADPKD patients have some degree of renal insufficiency when UTIs develop (213). Although no data are available regarding specific features of UTIs or renal cyst infections in pediatric ADPKD patients, it is reasonable to presume that their clinical course is similar to that described for adult ADPKD patients (400). Sterile pyuria is common, and appropriate cultures are needed to determine whether an infection is present. Most renal infections are caused by Gram-negative enteric organisms and can be complicated by cyst infection. Eradication of cyst infections is often difficult, despite *in vitro* sensitivity of responsible organisms; thus, the use of antibiotics that penetrate cyst walls is mandated (401). Antibiotics that generally penetrate cyst walls include ciprofloxacin (402) and sulfonamides. Penicillins and aminoglycosides (standard treatments for urinary tract infection) are generally ineffective in treating cyst infection (401, 403). Aggressive antibiotic treatment is critical because recurrent or ineffectively treated UTIs appear to be a definite risk factor in progression of renal disease (404). Occasionally, cyst drainage may be required to control infection, and MRI or PET scan may be a useful in identifying which cyst is infected (405, 406). In extreme cases, nephrectomy may be indicated (401). Prophylactic antibiotics should be considered before the introduction of any urinary tract instrumentation in children with ADPKD.

Episodes of flank pain are unusual in pediatric patients with few cysts. However, with progressive disease, particularly in adolescents, flank pain may become a more prominent feature. In the majority of instances, the painful episodes will resolve within a few days. Pain relief is accomplished with acetaminophen or brief courses of oral narcotics. Non-steroidal anti-inflammatory agents should be avoided. Long term narcotic use is discouraged, due to abuse potential. Non-pharmacologic interventions and referral to a chronic pain management center should be considered (407). In cases of severe pain, laparoscopic denervation and nephropexy has been reported to significantly relieve pain in adolescents (408, 409). Laparascopic cyst decortication is an addition therapeutic option, particularly in instances of recurrent pain and infection (410). Renal calculi, a common finding in adult patients with ADPKD (411), and a frequent cause of flank pain, are rare in childhood.

Hepatic cysts are relatively uncommon in the pediatric population, but have been recognized more frequently with the increased resolution of imaging studies. Patients with hepatic cysts may develop cyst infections, which typically present as right upper quadrant pain, fever, leukocytosis, and a rise in liver enzymes (412). Antibiotics alone may be ineffective, and the addition of surgical drainage is generally recommended (413). Intestinal diverticular disease (360) has not been reported in pediatric ADPKD patients, to date.

Cerebral aneurysms occur in approximately 10% of ADPKD patients. The risk of rupture of asymptomatic aneurysms in adults is related to the size, with the risk ranging from 0.05% per year for those less than 10 mm to 6% within one year for those greater than 25 mm (414). The risk of rupture for symptomatic aneurysms is about 4% per year (414). Although aneurysms are found in patients with negative family histories, intrafamilial clustering of aneurysms and aneurismal bleeding has been reported in ADPKD populations (415–417). Use of magnetic resonance angiography (MRA) may permit effective, noninvasive detection of significant aneurysms (418). However, routine screening of all ADPKD patients is not recommended, since many patients are asymptomatic and the incidence of rupture is low (419). Screening MRA may be recommended for patients with symptoms or a positive family history (415).

The incidence of clinically significant aneurysms and/or aneurismal rupture in children with ADPKD is thought to be very low, although data are limited. Ruptured aneurysms have been reported in children as young as 4 years old (420). Given the intrafamilial clustering of aneurysms, it is important to obtain a detailed family history. If such a history is present, and/or the patient complains of headache, further evaluation by MRA should be considered.

There are currently no disease-specific treatments available for ADPKD. Newer therapies, however, are being investigated in preclinical studies, and Phase II and III trials of adults with ADPKD. As previously noted (see *Fig. 36-2*) these include trials of inhibitors of the EGFR-axis, the vasopressin receptor antagonist, Tolvaptan, the mTOR inhibitor, Rapamycin, and the somatostatin analogue, octreotide (120, 421–423). A regularly

updated list of clinical trials in the US and around the world is available at www.clinicaltrials.gov, and www.pkdcure.org. A number of dietary interventions have been shown to slow progression of disease in animal models. These include dietary flaxseed, soy protein or protein restriction, sodium citrate, or caffeine restriction. To date, none has proven to significantly alter the clinical course of disease in humans (424).

Prognosis

The prognosis of ADPKD presenting in the fetus or neonate was once thought to be very poor. However, a number of recent studies of "very early onset" ADPKD suggest that it may be compatible with favorable long-term patient and renal survival (425, 426). Prognosis in the older child is also very favorable and progression to ESRD in childhood is rare in ADPKD (427). However, disease progression does occur in childhood, particularly in children with evidence of severe renal enlargement at a young age (427). Proteinuria has been identified as a potential early marker of severe cystic disease in children (428). The CRISP studies confirm that significant cyst growth, parenchymal damage and volume progression occurs in ADPKD well before changes in measured GFR are seen. Thus assessments of renal function, such as serum creatinine measurements are poor indicators of overall disease severity. Recent data, including that of the CRISP investigators, has shown that kidney volume and its rate of change are the most predictive factors for subsequent decline in renal function and clinical outcomes (288, 429) (430, 431). The CRISP study established that mean renal volume increases 5.3% per year in patients with ADPKD, providing a valuable non-invasive, short term parameter to monitor effectiveness of new therapies.

Approximately 50% of adult patients with ADPKD will progress to ESRD. On average, patients with PKD1 typically progress at an earlier age, with a mean age at ESRD of 53.0 years, whereas those with PKD2 progress to ESRD at a mean age at ESRD of 69.1 years (293). In light of the significant inter- and intrafamilial phenotypic heterogeneity, it is difficult to predict at what age a given patient with ADPKD will develop renal failure.

Glomerulocystic Kidney Disease

The term *glomerulocystic disease* (GCKD), coined by Taxy and Filmer in 1976, is used to describe the morphologic appearance of glomerular cysts, which occur in a variety of conditions (432). GCKD was first described clinically by Ross in 1941(433). Glomerulocystic kidney disease can be categorized into three major groups: *(a)* nonsyndromal inherited and sporadic forms of GCKD; *(b)* GCKD as the major component of congenital malformation syndromes; and *(c)* glomerular cysts as a minor component of abnormal or dysplastic kidney disease, some of which are syndromic.

Epidemiology and Genetics

Primary GCKD with isolated renal involvement can be an autosomal dominant disease, a familial hypoplastic disease, as well as a sporadic occurrence. Reports exist of infants with GCKD who have family members affected with ADPKD, which raises the question of whether these two entities are different expressions of the same genetic defect. Sporadic GCKD and GCKD occurring in the context of familial ADPKD are clinically, sonographically, and histopathologically indistinguishable. However, several recent studies of kindreds with autosomal dominant inheritance of GCKD excluded mutations in one or more of the PKD genes, including *PKD1*, *PKD2* and *HNF-1beta* (434, 435). Thus, with emerging molecular diagnostic techniques, the genetic basis for this rare and heterogenous disease may be more fully defined.

An apparently distinct entity is hypoplastic glomerulocystic kidney disease, a dominantly inherited disease reported in only a few families (436, 437). These kidneys, apart from being glomerulocystic, are small, and imaging studies show abnormal pyelocaliceal anatomy. Mutations in the hepatocyte nuclear factor-1beta (HNF-1β) gene were been identified in 4 kindreds with this hypoplastic GCKD variant (438).

GCKD can be associated with congenital syndromes such as orofaciodigital syndrome, type I (439); brachymesomelia–renal syndrome (440); trisomy 13 (441); Majewski-type short rib–polydactyly syndrome (441); and Jeune syndrome (442) and can be seen as a component of the renal abnormalities in nephronophthisis (443). Although tubular sclerosis generally includes tubular cysts, glomerular cysts can be present (443). Glomerular cysts also occur as a minor component in several other syndromes including Zellweger cerebrohepatorenal syndrome (441, 442) in which the cysts are typically present but rarely serious enough to affect renal function.

Other syndromes that may be associated with glomerular cysts as a component of renal dysplasia include Meckel syndrome, glutaric aciduria type II and renal–hepatic–pancreatic dysplasia (443). The glomerular cysts

are minor in comparison with the dysplastic components of the renal disease, although they may be present in sufficient numbers to create confusion with other glomerulocystic conditions.

Pathogenesis and Pathology

The pathogenesis of GCKD remains unknown. Clinically, GCKD can be difficult to distinguish from other cystic kidney diseases. The diagnosis can only be established by histologic examination of renal tissue. Sporadic GCKD in young infants is histopathologically indistinguishable from ADPKD-related GCKD. The kidneys in both the familial and sporadic forms are variably enlarged, with the degree of renal enlargement related to the degree of cyst formation (443). The cysts in both groups may be diffuse but can also be clustered, which may be responsible for asymmetric and asynchronous clinical presentations. Diffuse involvement is associated with interstitial edema, whereas patchy involvement is associated with better preservation of overall renal structure and function.

Characteristically, the cysts are dilated Bowman's spaces, comprising a sphere lined with cuboidal or columnar cells and containing abortive or primitive-appearing glomeruli (432), which occur as small scattered cysts separated by normal parenchyma. The cysts are located in the cortex, with preservation of the medulla. This lack of tubular involvement differentiates GCKD from other cystic diseases in which cysts generally arise from tubular dilation. In rare cases, they are more diffuse, surrounded by atrophic and fibrotic parenchyma. They may be found in association with tubular cysts and dysplasia (443).

The kidneys in sporadic GCKD and the GCKD form of ADPKD often contain abnormally differentiated pyramids, a type of medullary dysplasia. Both forms of GCKD are associated with biliary dysgenesis in approximately 10% of cases (443).

Clinical and Radiographic Features

Most GCKD patients described in the literature have some degree of renal failure and many have hypertension at presentation. The typical presentation is that of an infant with abdominal masses, renal insufficiency, and enlarged cystic kidneys on sonography. GCKD may manifest in adulthood with hypertension, flank pain, and hematuria. Variable degrees of renal dysfunction are seen. Later detection may be consistent with a milder course (286, 444). Clinically, hepatic cysts have also been described (443).

Patients with the familial hypoplastic glomerulocystic kidney disease variant have small kidneys with abnormal collecting systems and abnormal or absent papillae (436, 437). Family studies show a pattern compatible with autosomal-dominant inheritance. Most patients appear to have chronic kidney disease with some degree of renal impairment early in life but subsequently have stable courses without progression to ESRD.

Several reports of GCKD describe patients with no clear familial or syndromic association (441, 445, 446). Histologically and clinically, these patients resemble familial cases with large, hyperechoic kidneys. It remains unclear whether these sporadic cases are a distinct entity or are associated with unrecognized syndromal or familial cases. Reports on an infant with GCKD and multiple cardiac rhabdomyomas and an infant with severe GCKD who later developed skin findings consistent with tuberous sclerosis strongly suggest an association of GCKD with tuberous sclerosis (447, 448). This, together with the new information regarding the molecular basis of ADPKD and tuberous sclerosis and the reported familial association of GCKD and ADPKD, raises the possibility that autosomal dominant GCKD, ADPKD, and tuberous sclerosis are genetically linked in some kindreds. Single case studies have also reported GCKD in association with Henoch-Schoenlein purpura (449), hepatoblastoma (450), and as a sequelae of hemolytic-uremic syndrome (451, 452).

Ultrasonography demonstrates bilateral renal enlargement without distortion of the renal contour, increased echogenicity of the cortex and medulla, loss of corticomedullary junction differentiation, and small cortical cysts (445, 453). Radiographically, a feature that can help distinguish GCKD from ARPKD is abnormal medullary pyramids in the latter. In the future, CT and nuclear MRI may be of some value in differentiating between these two diseases (454). Reduced intensity of cortex on T1-weighted images and abnormalities of corticomedullary differentiation may help confirm the diagnosis.

In summary, GCKD represents a heterogeneous collection of heritable and nonheritable clinical entities. This clinical course and prognosis is quite variable and often dependent on the presence of associated disorders.

Polycystic Kidney Disease Associated with Congenital Syndromes

Many diseases can present with enlarged kidneys or cysts in the infant and young child and can initially be confused

with PKD (*Table 36-1*). Most syndromic and other inherited disorders can usually be differentiated from ARPKD and ADPKD by associated clinical features, with the exception of GCKD, occasionally tuberous sclerosis and von Hippel-Lindau disease (1, 5, 455). GCKD can be a feature of several inherited, sporadic, or syndromic conditions as discussed above. In addition, GCKD may be an early histopathologic expression of the ADPKD gene in young patients. Tuberous sclerosis is an autosomal-dominant neurocutaneous disorder, in which hyperplastic cystic lesions may affect any portion of the nephron (447). Genetic linkage of the chromosome 16 loci for tuberous sclerosis and ADPKD1 has been demonstrated (456). The tuberous sclerosis 2 (TSC2) gene has been identified and encodes a novel protein, tuberin. Uncommonly, patients show polycystic renal involvement without clinical neurocutaneous involvement or positive family history. Several kindreds have been identified with tuberous sclerosis and severe childhood-onset ADPKD; they have large deletions in the area containing *PKD1* and adjacent tuberous sclerosis 2 (TSC2) gene (301). Analysis of the deletions indicates that they inactivate *PKD1*, in contrast to mutations reported in ADPKD patients in which abnormal transcripts have been detected. Von Hippel-Lindau disease is a dominantly inherited cancer syndrome characterized by renal cell carcinoma, pheochromocytoma and hemangioblastomas of the eye, spine and cerebellum. Cystic kidneys and pancreas may be seen and, rarely, patients may present with "typical" features of ADPKD (457). To differentiate GCKD, tuberous sclerosis and von Hippel-Lindau from ARPKD and ADPKD, detailed family history, physical examination and close clinical follow-up are necessary.

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