CYSTIC DISEASES OF THE KIDNEY

MEDICAL GRAND ROUNDS

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The renal cystic diseases are a heterogenous group of disorders which are comprised of heritable, developmental, and acquired disorders. Internists and nephrologists have encountered these disorders with increasing frequency because of the widespread use of sensitive diagnostic tools such as computerized tomography (CT) and magnetic resonance imaging (MRI). Despite the relatively high frequency of these disorders, many physicians are confused by the nomenclature and are unclear about the natural history of renal cystic disease. The purpose of this presentation is to provide a simple clinical classification of the renal cystic diseases and to provide useful guidelines for diagnosis and management. A majority of the discussion focuses on autosomal dominant polycystic kidney disease (ADPKD).

I. Classification of Renal Cystic Kidney Diseases

Table 1 lists a simplified classification of the renal cystic diseases. This classification primarily includes those diseases that afflict adults. Each of these disorders will be discussed in order. A **renal cyst** refers to an enclosed sac or nephron segment lined by epithelium and dilated to more than 200 μm. A **cystic kidney** is one with 3 or more cysts; cystic kidney disease is the illness caused by cystic kidneys (1). **Polycystic kidneys** are those that have many cysts whereas the term "**multicystic kidney**" refers to a kidney with many cysts often containing dysplastic elements. **Medullary cystic kidney** disease is often an autosomal dominant disorder that tends to occur in young adults and progress to end-stage renal failure. This disorder must be distinguished from **medullary sponge kidney** which is a benign disorder without a clear inheritance pattern.

Table 1. Classification of Renal Cystic Disease

1.	Polycystic Kidney Disease (PKD)
	A. Autosomal dominant PKD
	B. Autosomal recessive PKD
2.	Juvenile Nephronopthisis/Medullary Cystic Disease
3.	Acquired Cystic Disease
4.	Medullary Sponge Kidney
5.	Simple Renal Cysts
6.	Cysts Associated with Other Diseases: Tuberous sclerosis, von Hipple-Lindau, etc.

II. Polycystic Kidney Disease

Polycystic kidneys are composed of numerous epithelium-lined cysts that contain a urine-like fluid; these cysts are scattered throughout the renal cortex and medulla. There are two main types of polycystic kidney disease: ADPKD, which is the dominant inherited cystic disease occuring in patients 30 to 50 years old and autosomal recessive

PKD (ARPKD) which is usually present at birth and is frequently lethal in the neonatal period. ADPKD can be expressed in newborns and ARPKD can be observed in adults on rare occasions (2).

A. Autosomal Recessive PKD

ARPKD is caused by a DNA mutation, but the exact location of the defective alleles is unclear. The parents of affected children do not express the disease. ARPKD is unusual, arising in approximately 1 in 16,000 live births. Children with this disorder typically have a marked decrease in GFR and hypertension. Patients who develop this disease later in childhood may have an initially enlarged liver which becomes smaller and firmer as hepatic fibrosis increases. The kidneys of these patients are enlarged and may fill the entire abdominal cavity. Several of the clinical features of ARPKD are listed in **Table 2.** The prenatal diagnosis of ARPKD may be possible by week 30 of gestation. Survival depends to a large extent on the age of the patient at presentation: 10 of 18 neonates died if they were less than one week of age at presentation, but 11 of 12 lived if the condition developed after one week (3). Survival depends on dialytic support followed by renal transplantation.

Table 2. Sonographic features of recessive polycystic kidney disease (2)

Age group	Sonographic feature
Neonates	Massive kidney enlargement
	Increased echogenicity of entire parenchyma
	Loss of corticomedullary differentiation
	Loss of central echo complex
	Small macrocysts, less than 2 cm in diameter
	Increased hepatic echogenicity caused by fibrosis
Children	Massive kidney enlargement
	Increased echogenicity, mainly in medulla
	Macrocysts less than 2 cm in diameter
	Enlarged echogenic liver
	Hepatic cysts
	Pancreatic cysts
	Splenomegaly secondary to portal hypertension

B. Autosomal Dominant Polycystic Kidney Disease

In recent years the general interest in ADPKD has grown dramatically. In part this growth and interest can be attributed to the discovery in 1985 of the location of the gene for ADPKD on the short arm of chromosome 16; this introduced the new technology of

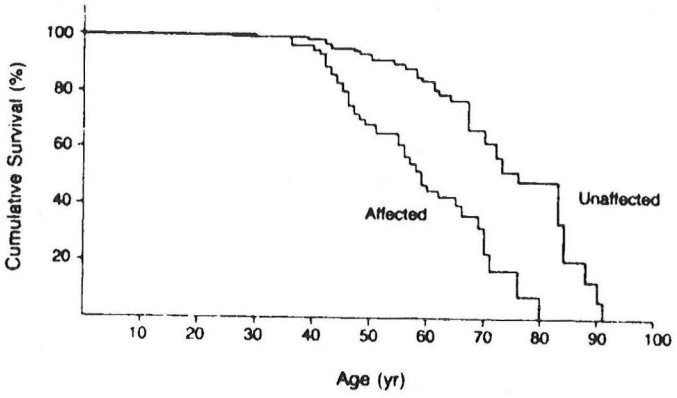
genotyping for presymptomatic diagnosis (4). ADPKD is the most common hereditary disease in the U.S.., affecting about 500,000 citizens and accounting for 8 to 10% of all end-stage renal disease (5). Interest in the disease has also been promoted by a new understanding of the mechanism of renal cystogenesis, as chemically-induced, transgenic, and naturally occurring models renal cystic disease and cell cultures of epithelium have yielded important observations about the characteristics of cell growth, cyst secretion, and extracellular matrix componetry. Finally, there have been advances in the clinical management of ADPKD, as our understanding of the importance of intracranial aneurysms, hepatic cysts and cardiovascular disease have all been improved.

1. Background

As mentioned above, breakthroughs in the field of molecular genetics have localized the genetic mutation in ADPKD to the short arm of chromosome 16 (4).
By linkage analysis more than 95% of informative families have a similar mutation identified by DNA probes to chromosome 16; this site has been named the ADPKD-1 site. Recently, it has been demonstrated that there are also families which do not demonstrate this linkage (6,7). There are at least two implications from this finding by Kimberling et al: first, the apparent heterogeneity of the inheritance of ADPKD means that prenatal and presymptomatic diagnosis must be approached with extreme caution until a method is found to distinguished between the two forms of the disease; second, there appears to be a different clinical course for the families with a mutation designated as ADPKD-2 (the non-chromosome 16 site). These patients have a clinically more benign course as shown by a recent study by Parfrey et al (8). These investigators studied 17 families with ADPKD to compare presymptomatic diagnosis by ultrasonography with the diagnosis by genetic linkage studies and to relate the clinical variation of the disease to whether the PKD-1 mutation site was implicated. Ten of the 17 families were determined to have the PKD-1 mutation, and 46% of the members of these families who were less than 30 years old had renal cysts, as compared to 11% of the members of the two families who did not have linkage. In PKD-1 families, all 67 diagnoses made by ultrasonography were confirmed by determination of the genotype as inferred from linkage. 83% of those persons less than 30 years old who inherited the PKD-1 had renal cysts and all 27 members who were over 30 years old who inherited the mutation had renal cysts, suggesting that the probability of a false negative diagnosis did not exceed 0.13 in this age group. The mean age at the onset of end-stage renal disease among members of the PKD-1 families was 56.7 ± 1.9 years as compared to 69.4 ± 1.7 years among members with cysts in the families without linkage. Cumulative survival to end-stage renal disease or deaths are depicted in **Figures 1 and 2**. The conclusion from this study was that in most persons with a 50% risk of inheriting ADPKD, imaging techniques were the only mode of reaching a diagnosis before symptoms appear. In such persons a negative ultrasound study

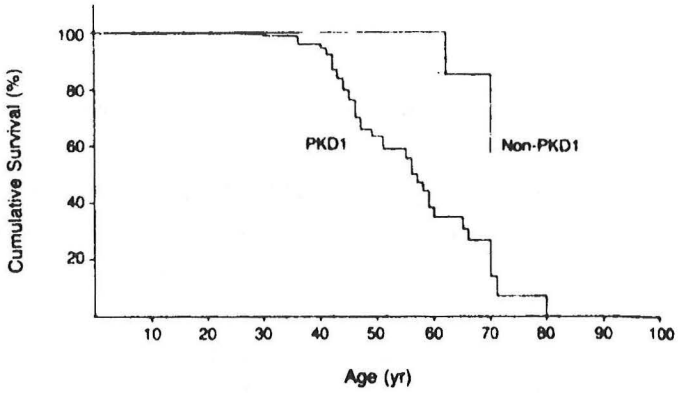
during early adult life indicated that the likelihood of inheriting the PKD-1 mutation is small. In the few who inherit a non-PKD-1 mutation (less than 5% of all ADPKD), renal failure is likely to occur relatively late in life.

Figure 1. Cumulative Survival to ESRD or Death in 166 ADPKD Pts and 340 Unaffected Relatives



From Ref. 8

Figure 2. Cumulative Survival to ESRD or Death in 134 Pts with PKD1 vs 18 Pts with Non-PKD1



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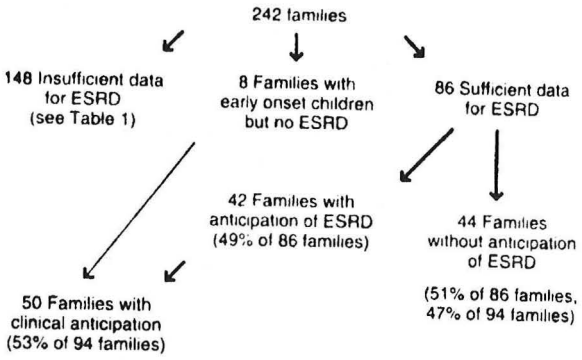
Another interesting feature of ADPKD has been the recent report that there is genetic anticipation in this disease. Until recent years many genetic diseases were considered stable disorders with a constant phenotype over several generations. However, there have been clinical examples which have shown anticipation, that is, the earlier onset and increased disease severity in successive generations. Such phenotypic alterations have been described in myotonic dystrophy, Huntington's disease, spinocerebellar ataxia type I, all autosomal dominant disease, fragile X syndrome, and X-linked disease (9-12). Recently, Fick et al (13), examined the possibility of anticipation in ADPKD in 242 pedigrees obtained during a prospective study on the natural history of ADPKD. Anticipation was defined in this study as a ten year difference in the onset of ESRD in offspring as compared to the affected parent or a child diagnosed in the first year of life. Anticipation of ESRD was found in 49% of informative families in at least one parent offspring pair, and when early onset children were included, 53% of informative families had at least 1 parent offspring pair with anticipation (13). Interestingly, the transmitting parent in the pairs with anticipation was more often the mother than the father, a finding similar to myotonic dystrophy in which the most dramatic form of

anticipation occurs almost exclusively with maternal transmission. The authors conclude that ADPKD may be another genetic disorder characterized by heritable unstable DNA (see **Figure 3**).

Figure 3. Anticipation in ADPKD



From Ref. 13

The issue of when to perform genetic linkage in order to diagnose ADPKD has been addressed in a number of recent publications (14-16). The diagnosis is very easy to establish in overt disease. There is a positive family history in about 75% of cases in addition to the typical findings in ultrasonography. Approximately 25-40% of new cases who have a negative family history are first diagnosed by either ultrasonography or have hematuria which heralds the onset of the disease. In a few patients, the development of renal failure late in life signals ADPKD due to the non-PKD-1 abnormality. The diagnosis of ADPKD is more difficult to establish when children of an affected parent are screened for ADPKD with genetic counseling or possible early therapy. Cysts as small as 1 to 1.5 cm can be detected by ultrasonography and as small as 0.5 cm by CT scanning (8). A single cyst or unilateral cyst should be considered suggestive in a child or young adult with a positive family history, and a clearly positive test will show bilateral involvement with a total of 3 to 5 cysts per kidney. With the PKD-1 abnormality the probability of a positive ultrasonogram in the children that have this disease is estimated to be about 8% below the age of 10, 60-65% by the age 20 and 85% by age 30; all patients above the age of 30 will have cysts on ultrasonography (8). Thus, a negative ultrasound does not exclude the presence of ADPKD until the patient is greater than 30 years old. Obviously families with the non-PKD-1 abnormality will form cysts later in life and therefore the above discussion does not apply to these individuals. However, since the disease has a later onset in these patients means that the fact that the diagnosis is initially missed is less critical because the onset of renal failure will be very late in life. The probes that are currently used to diagnose the PKD-1 gene locus on chromosome 16 have about 99% accuracy in screening. At present, the major indication at present for genetic screening is in the at-risk young adult with a negative ultrasound test who is a potential renal transplant donor (8). In no cases should genetic testing be done without extensive

counseling. The cost of doing these tests is about $2,000 per family in commercial laboratories. In addition, since several families have to be tested for the linkage analysis to be performed, the expense can exceed resources relatively quickly. **Table 3** lists

Table 3. Methods of Diagnosis in ADPKD

Method	Limitation
Renal concentrating ability in algorithm	Untested in children No anatomic information
Ultrasonography	May miss 2% to 6% of patients with cysts Operator - and reader - dependent Will not identify precystic gene carriers
CT Scan	May miss rare patient with small cysts Radiation and contrast exposure Difficult to perform in chidren Expense Will not identify precystic gene carriers
Gene linkage analysis	Requires other family members' participation Requires physician understand interpretation of results Expense Provides no anatomic information of organs involved

From Ref. 14

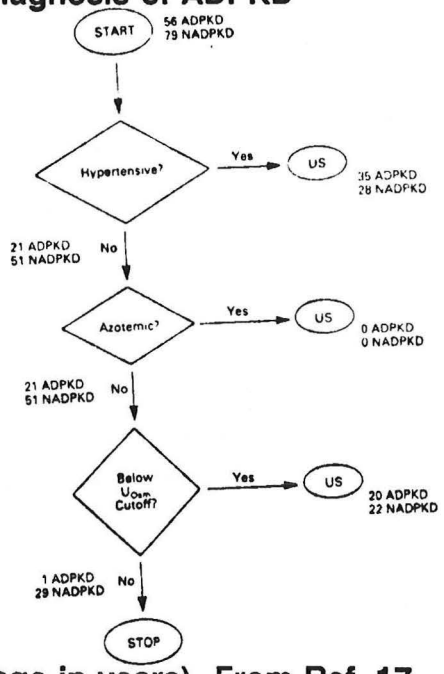
several of the methods of the diagnosis of ADPKD and there limitations. In addition to the use of ultrasonography and other studies to make the diagnosis of ADPKD, Gabow et al (17) have published an algorithm that uses an overnight renal concentrating capacity to make the diagnosis of ADPKD. They found that the overnight urinary osmolality was 812±13 mOsm/kg in controls as compared to 680±14 in patients with ADPKD. This concentrating defect was present in the youngest ADPKD subjects and the test was useful when applied prospectively to a group of 165 adults. This algorithm would have saved the cost of ultrasound in about 20% of subjects and failed to detect less than 2% of the affected subjects. This simple test therefore is a rapid and inexpensive way to screen for ADPKD. (see **Figure 4 and Table 4**).

Table 4. Characteristics of NADPKD and ADPKD Subjects

Group	N	Age yrs	Serum creatinine mg/dl	Creatinine clearance ml/min/1.73m^2	Solute excretion	U_{osm} mOsm/24 hr mOsm/kg
NADPKD	106	38±1	0.98±0.02	102±3	850±21	812±13
ADPKD	87	35±1	1.00±0.02	100±3	833±24	680±14

From Ref. 17

Figure 4. Algorithm for Diagnosis of ADPKD

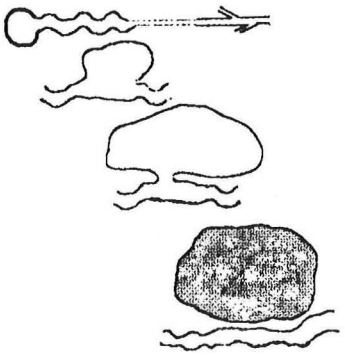


***U_{osm} cutoff 1086 - (8.3) (age in years) From Ref. 17**

2. Pathogenesis of Renal Cysts

It is interesting to note that only about 5% of nephrons develop cystic structures in ADPKD. However, the progressive growth of these cysts leads to massive structures that compromise normal renal tissue. Although ADPKD is a systemic disorder, it is the kidney that typically manifests the most pathology. As shown in **Figure 5**, cysts may develop in any portion of the nephron in ADPKD; moreover, cysts typically expand into an autonomous sac of fluid in most cases that becomes disconnected from the parent tubule (18). The study of cystogenesis has been dependent upon several models that lead to cyst formation. For example, some chemicals including adrenocorticoids in the rabbit, cisplatin in the rat, diphenylamine in the rat and nordihydroguiaretic acid in the rat are all known to produce cystic structures. Given this model, investigators can then study

Figure 5. Development of Renal Cysts

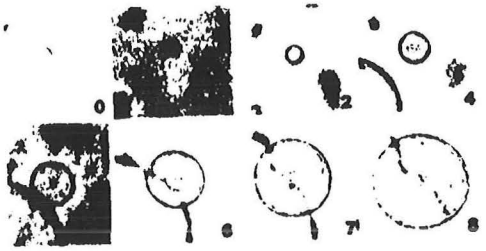


From Ref. 18

the factors that lead to further expansion of these cysts. In addition, there are three laboratory models of renal cysts that have become available that should allow for a more rigorous inquiry into the nature of biogenesis. These include the C57bl/6JCPK/CPK mutant strain of mice that develops an aggressive form of renal cystic disease that resembles PKD in humans (19). Second the DPA/2FGpcy (Nakahashi) mutant strain of DBA mice develops an insidious form of renal cystic disease that morphologically

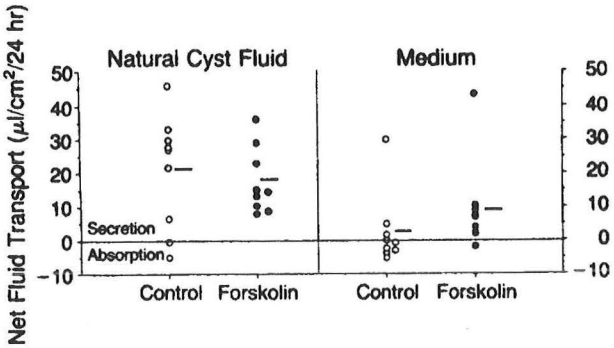
resembles the ADPKD in humans with the exception of this disease is rexcessively transmitted (20). Finally, Madin Darby K9 kidney (MDCK) cells forms cysts when planted in medium hydrated collagen gels (21). These single MCDK cells divide repeatedly to form a continuous vertical monolayer surrounding a cavity into which fluid is secreted; therefore, each cyst develops as a clonal outgrowth MCDK cell (see **Figure 6**). Normally, the growth of renal cysts is relatively slow since it takes between 30 and 40 years for a cyst to enlarge to an extent to cause renal damage. The current theory of cyst development is that initially cysts communicate with the urinary space; subsequently, an obstruction to the outflow of the cyst takes place leading to cyst enlargement. Eventually the cyst becomes detached in the urinary space (see **Figure 5**) becoming blind sacs. In these blind sacs, net fluid secretion is the only mechanism through which fluid enters the cyst cavity. The capacity of the tubular epithelium to transport fluid in a secretory direction has been described in several renal tubular epithelia including the MDCK cell. In addition, recent studies have shown that fluid secretion is accelerated by cyclic AMP agonists in MDCK cysts and cysts derived from normal and polycystic epithelium (22). A recent study on this subject by Ye and Grantham (23) examined the mechanism by which fluid accumulated in renal cyst of adults with ADPKD. In this study, in vitro intact cysts excised from 3 patients were examined. The cysts were loaded with natural cyst fluid or with a combination of Dulbecco's modified Eagle's medium and Ham's F12 medium; fluid secretion was assessed by the change of the weight of the cyst factored for surface area to correct for variation in cyst size. To determine the effect of endogenous cyst fluid on cyst fluid accumulation, cyst fluid was added to the cyst as well as to a confluent monolayer of cultures of K9 in human kidney cells. Results showed that there was a striking increase in the amount of cyst fluid secretion in 9 cysts containing natural cyst fluid (see **Figure 7**): natural cyst fluid produced about 21 μl/cm/24 hr as

Figure 6. MDCK Cells on Collagen: Development of a spherical monolayer



From Ref. 18

Figure 7. Secretion of Fluid by Cysts Containing Natural or Incubation Medium

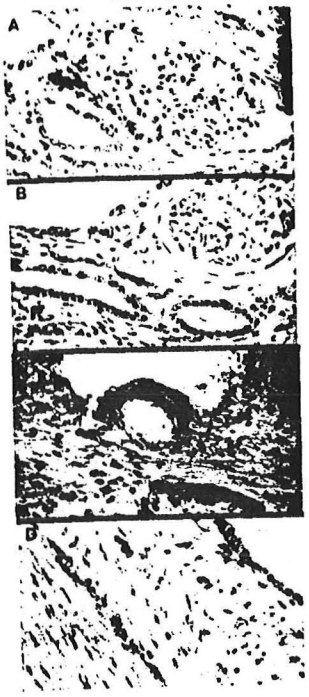


From Ref. 23

compared with 2.3 μl/cm/24 hrs. The addition of the nonspecific cyclic AMP stimulator forskolin did not change the accumulation of fluid in the experiments in which the natural cyst fluid was tested; however, in the experiments containing the physiologic media, forskolin did have a significant affect to increase cyst fluid accumulation. The authors

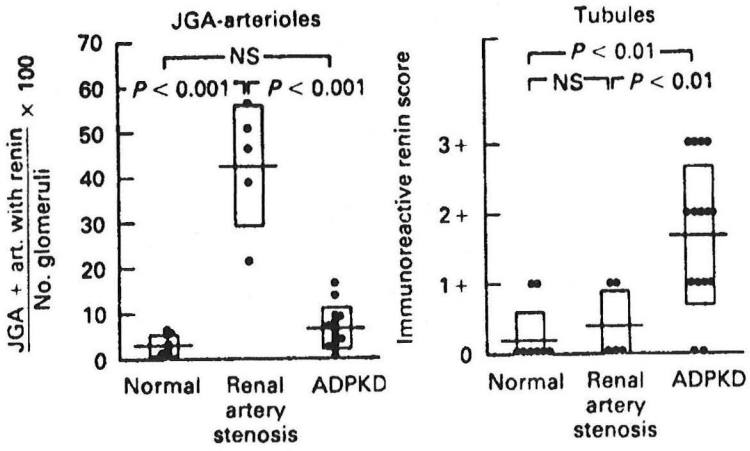
concluded from this study that renal cyst from patients with ADPKD can secrete fluid and that net fluid secretion can be increased by as yet unidentified secretagogues in the cyst fluid. The obvious implication from these studies is that it might be possible to find a pharmacologic intervention that would retard the growth of cysts in patients with ADPKD. Cyst fluid also produced net fluid secretion in human cortex cells and in MDCK cells in this and previous studies (24). In addition to the enhanced secretion of fluid that occurs in renal cysts, there is also a proliferation of epithelial cells that is known to occur (25). Epidermal growth factor (EGF) has been shown to retard development of cystic disease in the C57BL/cpk model of cystic renal disease (26). In addition, the presence of angiotensin II in the tubule cystic epithelium has been recently demonstrated by Torres et al (27). Renin was detected in the glomerulus, the arteriole, a small artery, in cells surrounding the cyst proper and in tissue excised from polycystic kidney disease (see **Figure 8**). **Figure 9** shows the vascular tubular renin score in normal kidney, kidneys with renal artery stenosis and ADPKD kidney. These findings of renin in the lining of the epithelium cyst walls raises the possibility that abnormal expression of the renin-angiotensin system may by a pericrine or autocrine mechanism regulate epithelial hyperplasia in growing renal cysts. With regard to the potential role of angiotensin and other peptides as simulators of cell proliferation, expression of protooncogenes c-phos, c-myc, c-ras, and EGR-1 are known to stimulate protein synthesis and secretion of type IV procollagen and induce hypertrophy in murine proximal tubule cells (28,29). Demonstration of one of these protonocogenes (c-myc) was recently shown in a transgenic mice model of ADPKD (30) (see **Figure 10**).

Figure 8. **Rabbit Anti-human Renin Stain: JGA, arteriole, small artery, cyst cells**



From Ref. 27

Figure 9. **Renin Scores in Normal Kidneys, RAS, PKD, JGA, and Tubules**



From Ref. 27

Figure 10. Detection of c-myc MRNA by in situ hybridization in transgenic SBM kidney tissue. Intense signal is present over the epithelial cells lining the tubular cysts.

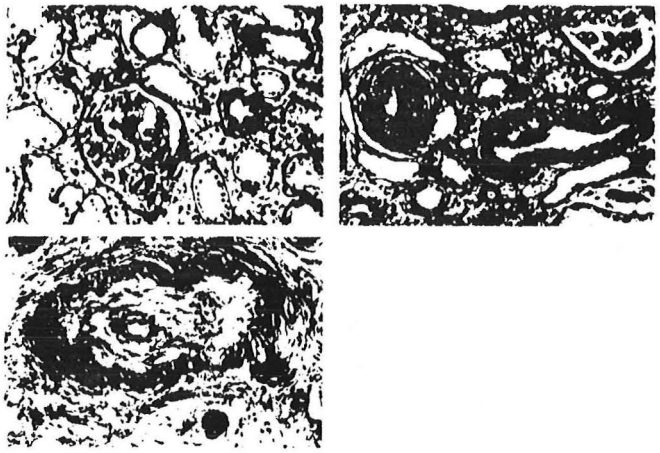
From Ref. 30

Other theories have been advanced to partially explain the formation of cysts in ADPKD. Wilson has pointed out that there may be some hypersensitivity of ADPKD to the mitogenic action of EGF (31). Roco and colleagues (32) have advanced the hypothesis that the attenuated expression of epithelial cell adhesion molecules (CAMS; E-cadherin, N-CAM, laminin receptor, and fibronectin receptor) is able to explain some of the disordered growth seen in cystic epithelia. A reduction in the transcripts for messenger RNA of N-CAM and E-cadherin was seen from kidneys of cystic mice (32). These findings suggest that it is possible that a maturation arrest occurs in tubule epithelial differentiation that may have as a cause the reduced expression of N-CAM followed by cadherin. Such a defect in cell adhesion receptors in cystic epithelium could play an important role in the pathogenesis of cyst formation and the altered function of cyst epithelium. In addition to this theory, there are also experiments showing that there is a strong increase in the abnormal deposition of extracellular matrix components such as undulin and tenascin that could play pathogenic roles in the development of cystogenesis (33).

Finally, it is obvious that the pathogenesis of cyst formation is multifactorial and it is therefore not surprising that the renal histology in polycystic kidney disease is variable. Zeier et al have shown that the primary region of damage in polycystic kidney disease is that of tubular interstitium and the vasculature with relative preservation of glomeruli (34). Several of these severe vascular lesions are shown in **Figure 11**. As might be anticipated from these heterogenous results, Gardner et al performed a study in which the fluid contents of cyst from several different patients were analyzed in order to determine whether the sodium concentration varied from kidney to kidney (35). A wide range of sodium concentrations were encountered in addition to a variable histology

pattern; hence, it would appear that based on the analysis of 156 fluids from 15 kidneys that different transporting mechanisms account for the variable sodium concentration in the fluid contents.

Figure 11. Severe Vascular Hyalinosis in PKD



From Ref. 34

3. Extrarenal Manifestations of ADPKD

The extrarenal manifestations of ADPKD are listed in **Table 5**. These are discussed in order below.

Table 5. Extrarenal Manifestations of ADPKD

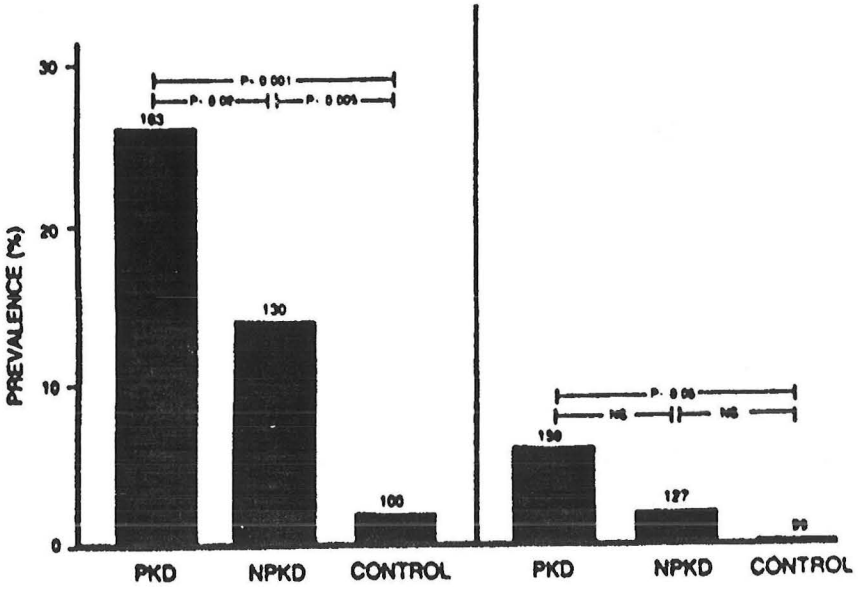
Cardiovascular abnormalities
Cardiac valvular abnormalities
Intracranial aneurysms
Gastrointestinal abnormalities
Hepatic cysts
Colonic diverticula
Genitourinary abnormalities
Ovarian cysts (?)
Musculoskeletal abnormalities
Gout
Hernias

From Ref. 14

a. Cardiovascular Manifestations of ADPKD

Cardiac valve abnormalities have been described in several previous reports in which echocardiographic data were obtained (36). The aortic valve is most often involved and in one series (36) 2 of 11 patients with aortic valve disease required aortic valve replacement. More recently Hossack et al (37) delineatated the frequency of cardiac symptoms, signs and valvular abnormalities as defined by echocardiographic and Doppler techniques in 100 control subjects and in 130 ADPKD family members without detectable renal cysts by ultrasonography and 163 affected individuals. 26% of the ADPKD subjects had mitral valve prolapse as compared with 14% of unaffected family members and 2% control subjects (see **Figure 12**). In addition to having mitral-valve prolapse, the ADPKD patients had a greater frequency of complaints of palpitations, atypical chest pain, a regurgitation murmur and clicks than did unaffected family members or control subjects. Interestingly, approximately 38% of individuals of ADPKD who had mitral-valve prolapse did not have either a murmur or a click on physical examination. It is currently recommended that ADPKD patients with mitral-valve prolapse receive antibiotic prophylaxis similar to others with prolapse.

Figure 12. Prevalence of Mitral-Valve Prolapse (left panel) and Tricuspid-Valve Prolapse (right panel) among the Patients with Polycystic Kidney Disease (PKD), the Unaffected Family Members (NPKD) and the Controls



From Ref. 37

Another recent study has demonstrated a significant increase in the left ventricular mass index of ADPKD patients in comparison to unaffected family members (38). Upon diagnosis of ADPKD, the prevalence of left ventricular hypertrophy was 24% in the affected members versus 14% in unaffected family members and 6% in age-matched

controls. After 10 years of ADPKD, the incidence of LVH increased to 35% in affected patients as opposed to 26% in unaffected family members and 13% in age-matched controls. The incidence of mitral incompetence in this study was 30% in ADPKD patients, and tricuspid valve prolapse was detected in 5% of the ADPKD patients. Regurgitant aortic lesions were present in higher prevalence in ADPKD patients at 19%, but this level of involvement was comparable to the unaffected family members who had an incidence of 17% of aortic valve lesions. Controls had an incidence of aortic valve disease of only 5%. Hence, there is a high prevalence of cardiovascular derangements of patients with ADPKD characterized by aortic valve disease, mitral valve prolapse and left ventricular hypertrophy. A recent longitudinal study of patients with ADPKD in mitral-valve prolapse showed that the prevalence of cardiac arrhythmia, sudden death, endocarditis, and the need for mitral-valve surgery was high (39).

b. Intracranial Aneurysms in ADPKD Patients

The rupture of an intracranial aneurysm is a rare but severe manifestation of ADPKD. There is a 50% mortality within 30 days of an intracranial rupture, and this devastating complication of ADPKD has lead to several recommendations regarding the workup and management of these patients. In one recent study, the natural history and prevalence of familial aggregation as well as the linkage to the PKD-1 locus were examined in 77 ADPKD patients from 64 families who presented with ruptured (n=71) or unruptured (n=6) aneurysms (40). The mean age at the time of rupture was 39.5 years (range 15 to 69 years), and renal function was normal in half of the patients whereas 11% were on dialysis. The location of ruptured aneurysms was usually the middle cerebral artery. One interesting finding was additional intact aneurysms were detected in 31% of the patients. Surgery or endovascular treatment was performed at 76% of the patients whereas 24% had medical management only. Rupture of the aneurysm was fatal in 10% of patients, and 38% were left with severe disability. Five of the patients bled from another aneurysm 2 days to 14 years after the initial rupture. No clinical marker associated with the aneurysms was found; a family history of aneurysm was demonstrated in 10 (18%) kindreds. Linkage to the PKD-1 locus was established in 2 of the 3 tested families. The data suggested that intracranial aneurysm rupture in ADPKD patients involves a very significant mortality and morbidity, comparable to the rates reported in non-ADPKD patients. Prophylactic screening for aneurysms was suggested for patients with a previous history of rupture, and possibly those with a family history of aneurysm.

Decision analysis has been applied to the subject of intracranial aneurysms by Levey et al who concluded that, based on certain assumptions, the benefit of cerebral arteriography and surgery exceeded 1 year of life only for patients younger than 25

years of age (41). Another recent report by Chapman et al who examined a very large kindred found that a 4% frequency of aneurysms was present in a young group of ADPKD patients (mean age 32 years), a frequency much higher that the general population (42). Moreover, the total number of aneurysms would have been under-estimated in their studies since small aneurysms can be difficult to detect with cross sectional imaging techniques. These non invasive imaging techniques have difficulty detecting aneurysms that are less than 5 mm in diameter. The advent of magnetic resonance angiography has been used to screen 71 patients with ADPKD (43). Using this technique, all but 1 of 39 aneurysms demonstrated by conventional arteriography were retrospectively detected in patients without ADPKD; the aneurysm missed was a 2 mm lesion. The Chapman et al report also details the high frequency of transient complications of angiography that occurred in patients with ADPKD - 9% of patients suffered a focal neurological defect (41). Clearly the probability of rupture after the discovery of unruptured intracranial aneurysms in patients with ADPKD is not known. The mean frequency of intracranial aneurysms in large autopsy studies (approximately 5%) and population-based incidence of aneurysm hemorrhage (approximately 10 per 100,000 per year) suggest that the vast majority of aneurysms never rupture. Among patients with unruptured aneurysms, those with no history of subarachnoidal hemorrhage should be distinguished from those with a history of hemorrhage from a different source. In one of the larger studies performed prospectively, 15 of 130 patients with unruptured intracranial aneurysms subsequently had intracranial hemorrhage during a mean follow-up of 8 years. Of the 102 aneurysms less that 10 mm in diameter, none ruptured during 824 patient years of follow-up, whereas of the 51 aneurysms that were 10 mm or more in size, 15 eventually ruptured, 5 of them within 3 months after they were detected (44). The size of the aneurysm, therefore, at the time of discovery was the only significant individual determinant of predicting if an aneurysm would rupture. Thus, it would appear that patients with no history of subarachnoidal hemorrhage who have an unruptured intracranial aneurysm that is 10 mm or more in diameter on angiography have a fairly high probability of subsequent rupture. For patients with aneurysms between 10 and 25 mm in diameter, surgical intervention seems justifiable for women under the age of 75 and men under the age of 69 years (45). For patients with no history of prior hemorrhage who have aneurysms less than 10 mm in diameter, the risk of rupture appears to be low - probably less than 0.5% per year (44). Another factor to consider in assessing patients with intracranial aneurysms in ADPKD is the morbidity and mortality among patients with unruptured aneurysms. In one recent study from North America, operative mortality was 0 and the rate of permanent neurologic defect 6.5% (46). Current recommendations based on the natural history studies in other studies besides ADPKD suggest that asymptomatic patients with ADPKD should be screened with non-invasive studies rather than cerebral arteriography. The low yield of screening procedures in the previous literature (42, 43) is reflective of the young age of the patients studied and the

fact that the lesions developed with increasing age, and possibly due to the fact that most aneurysms rupture soon after they are formed (44). Thus, routine non-invasive screening of all asymptomatic patients with ADPKD for intracranial aneurysms is unlikely to be cost effective. Non-invasive screening for asymptomatic patients therefore should be limited to certain subgroups of patients - specifically, those with a family history of intracranial aneurysms or subarachnoid hemorrhage, those who must undergo major elective surgery with anticipated hemodynamic instability, those who have symptoms that might suggest intracranial aneurysm, those in high risk occupations, and those who want the reassurance that screening can provide (47). A number of other relatively recent reports on this subject are available (48-52). One of the more interesting of these suggests that intracranial aneurysms can be detected by magnetic resonance angiography very reliably and that these aneurysms are present in 22% of patients with a positive family history aneurysm or hemorrhage as opposed to 5% of patients without a history (53). In addition, the presence of a positive family history of aneurysm was also found to be helpful in predicting which patients would have an aneurysms (see **Table 6**).

Table 6. Clinical data on the patients with ADPKD with and without ICA at the time of MRA[a]

	With ICA (N=11)	Without ICA (N=76)	P Value
Age (yr)	48±11 (29-72)	45±12 (17-67)	NS
Sex (M:F)	3:8	31:45	NS
Family history of ICA[b]	6/11 (55%)	21/74 (28%)	0.08
Hypertension	10/11 (91%)	66/76 (87%)	NS
Serum creatinine (mg/dl)			
≤ 1.2	2 (18%)	28 (34%)	
1.3-3.0	5 (46%)	27 (32%)	
3.1-10	3 (27%)	13 (18%)	
ESRF	1 (9%)	8 (10%)	NS
Polycystic liver disease[c]			
None	1 (10%)	14 (20%)	
Mild (<10% SA)	2 (20%)	26 (38%)	
Moderate (10-40% SA)	2 (20%)	16 (23%)	
Severe (>40% SA)	5 (50%)	13 (19%)	0.05

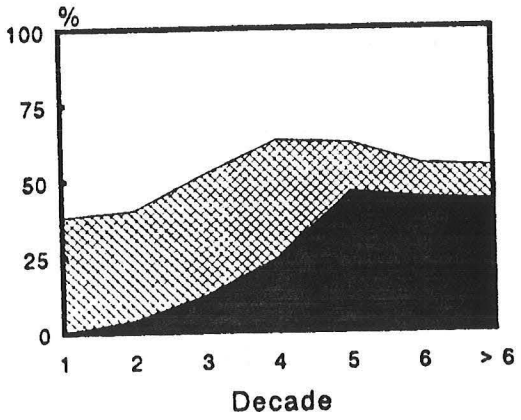
[a]ICA, intracranial aneurysm; ESRF, end-stage renal failure; SA, cross-sectional area on CT; NS, not significant,
[b]Information not available in two patients without ICA
[c]Information not available in seven patients without and one patient with ICA

From Ref. 53

c. Hepatic Cyst Formation in Polycystic Kidney Disease

There are number of common of gastrointestinal manifestations of ADPKD, the most common of which is the formation of hepatic cysts and the development of colonic diverticula (14). Hepatic cysts appear to be the result of dilatation of the biliary tract, although the exact location of the anatomical derangement is not clear. As shown in **Figure 13**, the development of hepatic cysts typically follows the appearance of renal cysts, as the mean age for the development of renal cysts alone is 32.5 years compared with an age of 42.3 years for the development of both hepatic and renal cysts (54,55). Large hepatic cysts appears to be a disorder of women, raising the possibility that female hormones play some role in hepatic cystogenesis in ADPKD. The massive hepatomegaly seen in some patients can be debilitating, and requires percutaneous cystic decompression, surgical decompression and partial hepatectomy in some instances (14, 56). Further, the presence of hepatic cysts can no longer be considered as benign as once held, since in one series 10% of ADPKD patients with end-stage renal disease died

Figure 13. Prevalence of Hepatic and Renal Cysts



Hatched area, renal cysts; solid area, liver cysts From Ref. 55

from complications with hepatic cysts including cyst infection and malignancy (57). Further support for the hypothesis that female hormone exposure may facilitate the development of hepatic cysts is provided by data that show among women with ADPKD there is both an increase in the number of cysts and in the size of cysts and women with prior pregnancies. The analysis of the composition of cyst fluids suggests that it is essentially an ultrafiltrate plasma, resembling fluid secreted by biliary epithelium. The intraluminal pressure in hepatic cysts ranges from 18 to 42 cm H_2O. The effect of hepatic cysts on liver function has been assessed in several ways. These studies have shown that the parenchymal volume of patients with either minimal or massive hepatic cystic disease is similar to that of control. This explains why patients with hepatic cystic disease have preserved hepatic function and rarely, if ever, manifest symptoms or signs of liver failure (55). Levels of liver enzymes with an ADPKD patients are typically normal. The main complication arising from the development of hepatic cystic disease is that of infection or cancer. Patients with hepatic cyst infection exhibit a triad of fever, pain over

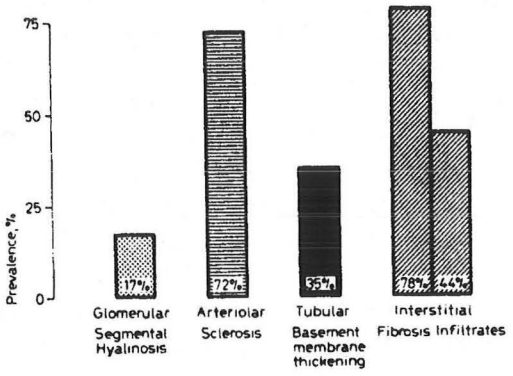
the hepatic bed, and leukocytosis. The use of antibiotics and percutaneous drainage of the infected cyst aids the resolution of this problem in most cases; surgery is not usually required to treat hepatic cyst infection. The main problem with hepatic cysts is typically their size, and there are many women who have developed debilitating symptoms from massive hepatic cystic disease. Since the presence of a hepatic cyst is inherently benign, aggressive surgical therapy should be limited to highly selected cases. Aspiration of cyst fluid and alcohol sclerotherapy is useful in patients who have very large cysts that are amenable to a percutaneous puncture. The surgical experience with 14 patients who required hepatic resection from massive hepatic cystic disease has been recently reported (58). Surgical resection provided a 40% reduction in hepatic volume. However, a number of complications were described: transient pleural effusions, bleeding requiring reoperation in 3 cases and, transient biliary fistulae occurred in 3 cases. The wide spread use of hepatic resection for treating hepatic disease is not usually required and should be limited to patients with severe symptoms and performed in medical centers where there is a great deal of expertise with this kind of surgery (59).

Colonic diverticula occur at a frequency of about 83% in patients with ADPKD (14). Interestingly, many of the patients (in one study 4 out of 10) with colonic diverticula and ADPKD suffer a major complication of the diverticula including perforation (60). Stated another way, of the patients who developed a diverticular complication and were receiving renal replacement therapy, 28% of these patients had ADPKD. This problem is worth noting because of the high frequency of ADPKD among renal transplant patients and the risk for colonic perforation in this group of patients.

d. Hypertension in ADPKD

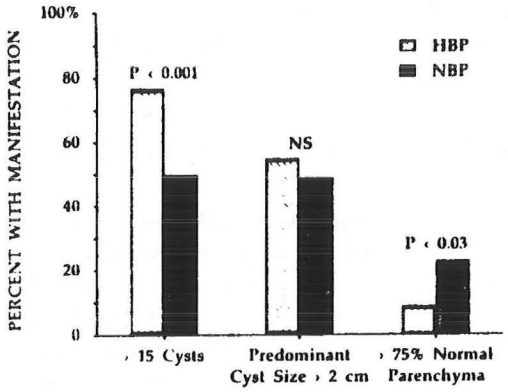
Hypertension is present in more than 60% of patients with ADPKD (61). The exact etiology of hypertension in ADPKD is unclear; hypertension correlates with renal volume even in the absence of renal insufficiency (62). There is some debate over the activity and role of the renin-angiotensin system in the pathogenesis in this hypertension in this disease, although there may be inappropriately high renin-angiotensin system activity for the degree of volume expansion in many of these subjects. Patients who are infused with hypertonic saline with ADPKD have an enhanced natriuresis when compared to healthy control subjects (63). In addition, there is compelling evidence that the activity of the renin-angiotensin system is greater when provoked as compared to age-matched patients with essential hypertension (64, 65) **(see Figures 14-16)**. Typically the response to treatment of hypertensive ADPKD patients with converting enzyme inhibitors is a fall in renal vascular resistance and a decline in filtration fraction (64) (see **Figure 17)**. Normally the renal hemodynamics in patients treated with ACE inhibition in ADPKD remain stable, but the activation of the renin-angiotensin system in the presence of large cysts has lead to the association of reversible renal failure associated with ACE inhibitor therapy (66). Several of the patients in this series had concomitant hemorrhage into a cyst at the time that they developed acute renal failure from ACE inhibitor therapy (**Figure 18**). These changes in the renin-angiotensin system have been confirmed by others (67). The approach to anti-hypertensive therapy is empirical since there are no studies that compare differing regimens in these patients. If ACE inhibition is selected for antihypertensive therapy in ADPKD patients, renal function should be closely monitored to be certain that sharp adverse changes in renal function do not occur. A reduction of cyst volume by percutaneous cyst aspiration or by surgical marsupialization can result in blood pressure improvements in some cases. However, the blood pressure improvement is of a variable duration and therefore the procedure cannot be justified in most cases (68).

Figure 14. Vascular Changes in ADPKD Kidneys



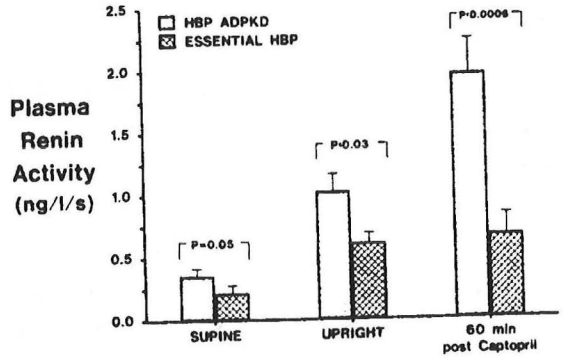
From Ref. 61

Figure 15. Cyst Prevalence and Hypertension



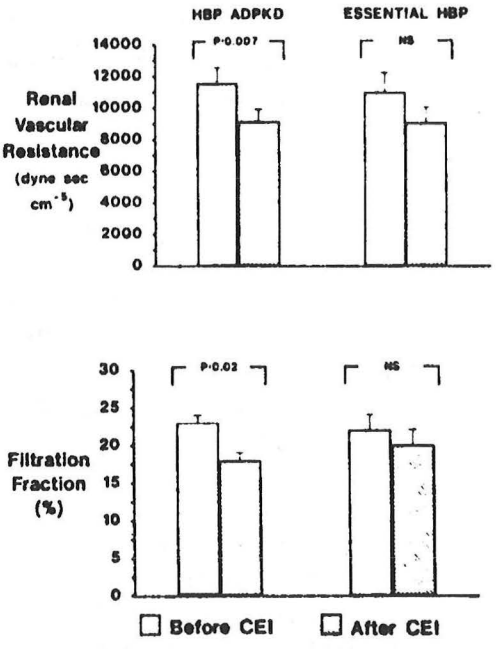
From Ref. 61

Figure 16. PRA Response in ADPKD



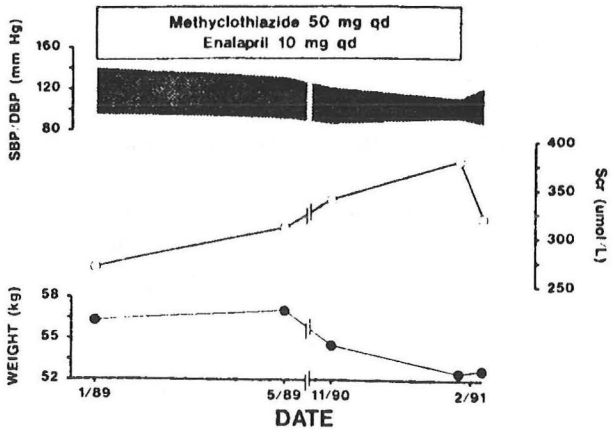
From Ref. 61

Figure 17. Changes in Renal Hemodynamics in ADPKD Therapy



From Ref. 61

Figure 18. Clinical Course of Acute Renal Failure in a 37 year old woman with autosomal-dominant polycystic kidney disease



From Ref. 66

e. Nephrolithiasis in ADPKD Patients

The frequency of stone disease with ADPKD ranges from between 10 and 40%. One recent estimate placed the incidence at about 20% of patients (69). Stone disease should always be considered in a differential diagnosis of flank pain in patients with ADPKD, and the diagnosis is often made more difficult by the distorted anatomy of the polycystic kidneys and the frequent occurrence of calcium in the parenchymal walls. Computed tomography is the most sensitive imaging technique for detecting stones. The composition of stones is most frequently uric acid and/or calcium oxalate. **Table 7** lists the composition of several stones found in patients with ADPKD as well as the metabolic derangements associated with stone formation in these patients. Calcification defects may be present in some patients although the presence of hypocitraturia is believed to be the most important pathogenic factor in the development of renal stone disease in these patients. Cyst calcifications are found in older patients with larger kidneys in worse renal function.

Table 7. Chemical Composition and Metabolic Derangements of Stone Forming in Patients with or without Autosomal Dominant Polycystic Kidney Disease

	With ADPKD* (%)	Without ADPKD (%)
Chemical composition		
Uric acid	57	10
Calcium oxalate	47	70
Calcium phosphate	20	20
Struvite	10	9
Metabolic derangement+		
Hypocitraturia	67	19
Hyperoxaluria	19	16
Hyperuricosuria	15	38
Hypercalciuria	11	39
Primary hyperparathryroidism	5	5

* The total number of observations ranged from 15 to 74 depending on the parameter studied
+ The normal ranges used in these studies were slightly different

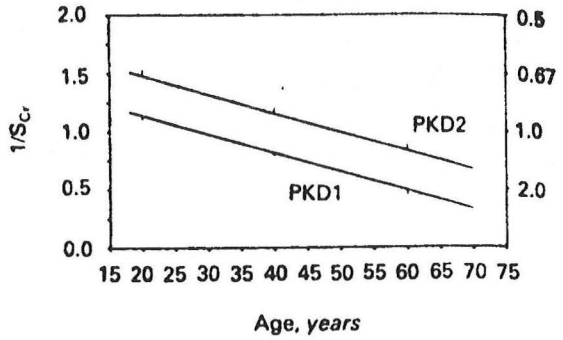
From Ref. 69

f. Progression, Prognosis and Management of Patients with ADPKD

Several variables have been determined to herald a poorer prognosis in patients with ADPKD. Among these, the presence of the PKD-1 gene, a younger age of diagnosis, male gender, hypertension, increased left ventricular mass, hepatic cysts in

women, 3 or more pregnancies, gross hematuria, urinary tract infections in men, and renal size has expressed as renal volume have all been associated with a poorer prognosis (71). Among the characteristics not associated with a worse prognosis are the gender of the affected parent, mitral valve prolapse, intracranial aneurysms, any pregnancy, hepatic cysts in men, and urinary tract infections in women. Thus, there are several factors (the PKD-1 gene and male gender) that cannot be changed, but there are several others that are potentially remediable (for example, hypertension, the number of pregnancies, and recurrent urinary tract infections). The effect of the PKD-1 gene on survival versus the PKD-2 gene is shown in **Figure 19.**

Figure 19. The Effect of Gene Type of Renal Function.



From Ref. 71

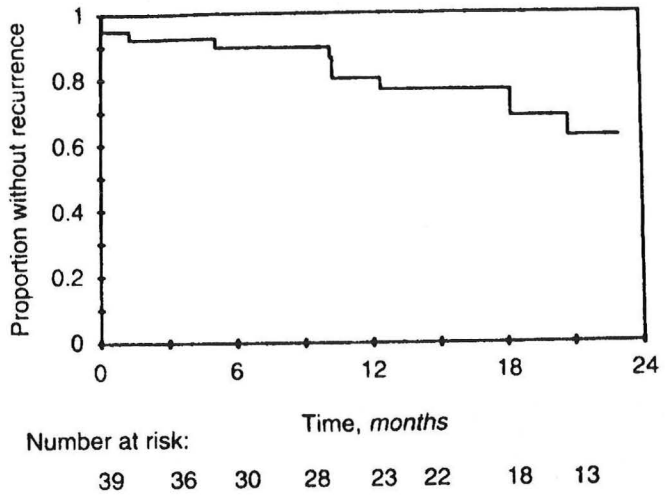
Several reports have detailed a relationship between renal cell carcinoma and ADPKD. A recent review by of this subject by Keith et al (72) did not show any male gender to be a risk factor for development of carcinoma in the 25 patients who met the inclusion criteria. The age of presentation of the cancer was earlier than that seen in the general population (45 vs 61 years). Fever, night sweats, and weight loss were prominent at presentation, with fever being a presenting symptom of renal cell cancer in 32% of ADPKD patients vs the general population of 7%. The diagnosis of renal cell cancer was very difficult in patients with ADPKD because of the imaging problems even using computed tomography and magnetic resonance tests. One interesting feature of renal cell cancer and ADPKD is that it occurred bilaterally more often (12 vs 1-5%), was more commonly multicentric (28 vs 6%), and featured sarcomatoid features in histology (33% vs 1-5%). Several of these features are represented in **Table 9.**

Table 8. Results of Multiple Variable Analysis Separated by Gender

	Males	Females
Significant variables	Age at diagnosis	Age at diagnosis
	Hypertension	Hypertension
	Gross hematuria	3 or more pregnancies
	Urinary tract infections	Hepatic cysts
	Mean renal volume	Gross hematuria
		Mean renal volume
Non-significant variables	Gender of affected parent	Gender of affected parent
	Hepatic cysts	Urinary tract infections

The management of pain is challenging in many patients with ADPKD. In general pain has a relationship with kidney volume, but there are many exceptions to this rule. Thus, patients with cysts smaller than 3 cm in diameter may still experience severe pain while some individuals with very large cysts have no pain. Pain is usually dull and constant and localizes to the flank or lateral anterior abdomen; on occasion it may be colicky or even very sharp. Before attributing the episode of acute pain to the presence of cystic disease per se, ureteral obstruction due to stone, clot or neoplasm should be excluded. Acute and severe exacerbations may occur for which there is no explanation. Hemorrhage into cysts or into the renal parenchyma can cause acute pain, which is usually self limited. If increased pain is accompanied by weight loss or fever, a search for malignancy or infection is warranted. The management of pain is generally conservative since most episodes are limited in time. In some cases the pain can be managed by percutaneous ultrasound-guided cyst puncture if the quality of life is altered (73, 74). The pain relief from cyst puncture is relatively long lasting with a likelihood that freedom from pain will be greater in 80% two years post surgery or cystic aspiration. This is depicted in **Figure 20**.

Figure 20. Kaplan-Meier time to event curve showing the probability of being pain-free following cyst reduction surgery.



From Ref. 68.

Hematuria is particularly common in ADPKD. About 20% of patients with hematuria of new onset will have nephrolithiasis as the cause (see above). New episodes of hematuria should also trigger a suspicion of a possible renal malignancy. The management of hematuria is usually conservative with heavy dependence upon adequate volume repletion, bed rest and analgesics as needed. Most episodes of acute hematuria resolve spontaneously in a few days and are managed without the need of transfusion.

Urinary tract infections are also common in patients with ADPKD, particularly in women. If instrumentation of the patient with ADPKD is needed with either a catheter or cystoscope, then the patient should be covered by antibiotics before and for 24 hrs after the procedure. The diagnosis for renal cyst involvement in infection should be entertained if the patient has fever, flank pain and leukocytosis, even if the urine cultures are persistently negative since infected cysts may not communicate with the urinary space. Occasionally, the CT scan can aid in the diagnosis. The information obtained from blood culture data suggests that the majority of cyst infections result from gram negative organisms (75). Infections with s. aureus and s. epidermis have also been reported (76). Lipophobic antibiotics that are usually used to treat pyelonephritis are poor penetrators of cysts, especially when the GFR is low. **Table 9** list some of the characteristics of antibiotic penetration of the cyst fluid. On occasion cyst infections respond well to percutaneous cyst drainage (76) and with a 4 week course of antibiotics. Chapman and colleagues (76) have recently reported that intravenous chloramphenicol is effective in treating such an infection. Oral chloramphenicol was also used in this particular case. Trimethoprim-sulfamethoxazole and norfloxacin have also been useful in this situation.

Table 9. Antibiotic Penetration into Cyst Fluid

	Gradient	Non-gradient	In vitro efficacy in cyst fluid from patients after treatment
Aminoglycosides	—	—[c]	NT
Beta lactams	—	+[a]	NT
Chloramphenicol	+	—	NT
Clindamycin	+	+	NT
Erythromycin	+	+	NT
Fluroquinolones	+	+	E[b]
Metronidazole	+	+	NT
Tetracyclines	+	+	E
Trimethoprim-sulfamethoxazole			
Vancomycin	+	+	NT

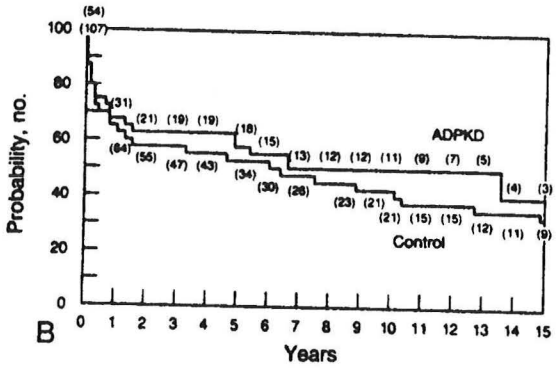
Symbols are: (+) concentration greater than minimum inhibitory concentration (MIC) of likely organism; (---) concentration less than MIC of likely infecting organism. Abbreviations are: NT are tested; E, increased titer from pre-treatment of at least fivefold.
[a]Some congeners such as ampicillin and cephalosporins achieve adequate levels with prolonged therapy (7-10 days)
[b]Ciprofloxacin more effective than Norfloxacin
[c]Isolated report of adequate concentration with Amikacin
From Ref. 68

The specifics of ADPKD in children will not be discussed in this review other than to say that there are several excellent new reports available on this subject (77, 78). As mentioned above, the concept of anticipation is a valid one in some families and the risk for this appears to occur predominantly in young female children who develop the disease in utero (77). On the other end of the spectrum, patients who developed symptoms of ADPKD after the age of 50 years have a similar course of those patients who develop the disease in their 30's and 40's (79).

Finally, it should be said that their are several distinguishing characteristics of renal replacement therapy in patients with ADPKD. For example, the main cause of morbidity in the patients is infections (80). Other characteristics of the patients on dialysis are

similar to the non-diabetic ESRD population and the overall mortality in terms of relative risk of deaths is comparable to other diseases (**Table 10**). With regard to renal transplantation in these patients, similar survival curves are reported for ADPKD patients and in non-diabetic patients with renal disease (81, **Figure 21**). Cyst recurrence is not a problem in the transplanted allograft in ADPKD patients. Thus, the long term outcome for ADPKD patients with regard to transplantation is excellent. Good results are obtained with transplant of these patients with the native kidneys in place.

Figure 21. APKD Patient Survival After Transplant



From Ref. 81

Table 10. Relative death risk in the ESRD population by etiology of renal disease[1]

Etiology of renal disease	Relative death risk	x^2	p
Chronic glomerulonephritis	1.0	-	-
Diabetic nephropathy	2.10	16.73	0.0001
ADPKD	1.15	0.21	0.64
Hypertensive nephrosclerosis	1.16	0.60	0.44
B/L small kidneys	1.54	2.37	0.12
Lupus nephritis	1.83	1.86	0.17

[1] Relative to a 45-year-old white female with no risk factors and a diagnosis of chronic glomerulonephritis. B/L = Bilateral

From Ref. 80

III. Nephronophthisis-Medullary Cystic Disease

The juvenile nephronophthisis-medullary cystic disease disorder refers to a group of cystic renal abnormalities characterized by medullary cysts associated with progressive

renal insufficiency, usually before the age of 35. This disease can be inherited either as an autosomal recessive (which occurs the majority of the time and appears first between the ages of 5 and 20 years of age) or as a sporadically inherited disorder that appears later in life (see **Table 11**). In another group of patients, the disease has been called retinal-renal dysphasia. Medullary cystic disease is an autosomal dominant inherited cystic disorder that begins in the second decade of life and can be sporadic in some

Table 11. Patient Groups Within the Nephronophthisis-Medullary Cystic Diseae Complex

Classification	Mean Age at Presentation
Nephronopthisis	**9-10 yr**
Autosomal recessive	
Sporadic	
Retinal-renal dysplasia	
Medullary cystic disease	**28-30 yr**
Autosomal dominant	
Sporadic	

kindreds. The pathogenesis of the disease is unknown. There is no experimental model of medullary cystic disease available. The overall incidence of the disease is also unknown, but the problem is a considerable one in the pediatric population because nephronopthisis accounts for 10% of patients with ESRD. It is estimated that between 1 and 2% of patients on dialysis in the U.S. have medullary cystic disorders as the cause. One of the features of the disorder is that, in addition to the medullary cysts that are present in the kidney, there is also a striking amount of fibrosis in the interstitium. Another interesting feature of this disorder is that renal cysts are not absolutely necessary for the diagnosis of the disease; in fact, distal tubule cysts are found only in 75% of post-mortem exams and are often heavily scarred. The cysts usually communicate with other nephron segments. The other associated features of this disorder include the fact that hepatic fibrosis may also be present and there may be retinal changes including retinal dysplasia. The clinical manifestations of this disorder include polyuria, and enuresis and polydypsia. These features are typical because they point to a defect in renal concentrating ability and sometimes an associated sodium wasting that can be seen. In fact, a decrease in the maximum urinary concentration is the earliest detectable abnormality in renal function in patients with this disorder. Patients have nephrogenic diabetes insipidus because they do not respond to exogenous vasopressin. **Table 12** list several of the clinical manifestations of the nephronophthisis-medullary cystic disease complex. Several of these characteristics have been reported in detail elsewhere (82). Another associated disorder with medullary cystic disease include gout and epilepsy (82).

In view of the confusing terminology of this syndrome, some have suggested that the nomen clature be simplified to simply divide medullary cystic disease into childhood and adult types, while others suggest a system that simply distinguishes between the autosomal dominant or recessive form. There are several synonyms that have been used in the literature for medullary cystic disease and several of these are shown in **Table 13.** Renal ultrasonography is helpful in the diagnosis (83). There is no specific treatment for medullary cystic disease; cystic do not recur in renal aligraphs.

Table 12. Clinical Manifestations of Nephronophthisis-medullary Cystic Disease Complex

Polyuria
Polydipsia
Azotemia
Anemia
Urinary sodium wasting
Hepatic fibrosis
Retinal dysplasia

Table 13. Synonyms for Medullary Cystic Disease

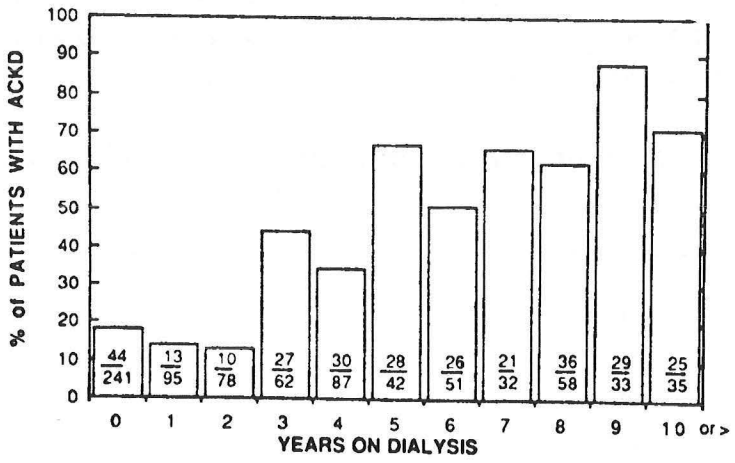
1.	Juvenile Nephronophthisis
2.	Cystic disease of the renal medulla
3.	Congential cysts of the renal medulla
4.	Microcystic disease of the renal medulla
5.	Uremia sponge kidney
6.	Fanconi's nephronophtisis
7.	Salt-losing nephritis
8.	Renal-rentinal dysplasia
9.	Polycystic kidney (medullary type)
10.	(Erroneously) medullary sponge kidney

IV. Acquired Cystic Disease

Acquired cystic disease is a disorder that is found in patients with renal failure. Usually the disease becomes manifest after the patient has begun dialysis, although some cysts may be detectable prior to initiating dialysis. The etiology of the disorder is unknown. Cystic structures appear to form in conjunction with progressive nephron loss and compensatory hypertrophy that leads to both epithelial hyperplasia and tubular diverticula. Whether or not concomitant ischemia or the presence of growth factors in higher concentrations favors the development of more renal cysts is really not clear. Most of the cysts in this disorder are small (< 100 grams), but there are many of them throughout the entire kidney parenchyma. The cysts are usually > 1 cm in diameter; large cysts can approach 5 cm in size. The prevalence of acquired cystic disease is shown in **Figure 22** from a paper by Matson et al (84). Acquired cystic disease is

present in both long term hemodialysis and peritoneal dialysis patients (85). The natural history of acquired cystic disease has been studied and there is a progressive increase

Figure 22. Epidemiology of Acquired Cystic Kidney Disease



From Ref. 84

in cyst volume over time (86). Bleeding into cysts is common in this disorder and the occurrence of subcapsular hematomas and massive retroperitoneal hemorrhage have been reported. Acquired cystic disease is usually asymptomatic and not detected without screening or autopsy. The complications of acquired cystic disease are listed in **Table 14.** In addition to the bleeding mentioned above, a few patients have manifested erythrocytosis as a complication of cysts in the kidney (87).

Table 14. Complications of Acquired Cystic Kidney Disease

None
Flank Pain
Nephrolithiasis
Infection
Erythrocytosis
Bleeding, hematuria or retroperitoneal hemorrhage
Tumors, benign or malignant

Obviously the worst complication of acquired cystic disease is renal cell carcinoma. The overall prevalence of all renal tumors appears to be about 3.5% with a prevalence of renal cell cancer of about 3.2% (87). The risk of developing a cancer has also been prospectively evaluated, with a risk of about 7% noted over a variable follow-up period (87-89). The clinical and prognostic features of renal cell carcinoma occurring in patients with acquired cystic disease appear to be similar to those of patients with primary renal cell carcinoma. Presenting symptoms of bleeding, flank pain, and polycythemia should lead to a work-up for renal cell cancer. A large tumor size seems to predict a greater

chance of a metastases. The overall 5 year survival in patients who have acquired cystic disease and renal cell cancer is approximately 35 to 40%, a figure not significantly different from patients who have primary renal cell cancers (87). The major methods of detection of multiple renal cysts remain renal ultrasound and CT scanning. Ultrasound can detect cysts or masses as small as 0.5 cm in ESRD kidneys. CT scanning enhances the resolution to sizes as small as 0.3 cm. The use of contrast can help to characterize the mass. The possibility that magnetic resonance imaging with the use of gadolinium may allowing MRI to supplant CT scanning as the best tool for diagnosing renal cell carcinoma is currently under study. Recently, Levey and colleagues (87) undertook a detailed decision analysis in order to determine the value of routine CT or ultrasound screening for cancer in asymptomatic patients with acquired cystic disease. The results of the study showed that CT or ultrasound screening for asymptomatic patients who have acquired cystic disease prolongs the average patient survival. However the gain is small even among the healthiest and youngest patients. Levey found that the average life expectancy in young dialysis patients who were not screened was about 15 years versus an average life expectancy of 15 years and 3 months in patients who were screened. In patients 65 years of age on dialysis the average life expectancy is 5 years; the screening of patients with CT scanning could theoretically prolong the life of a person by only about 2 weeks. Hence, the role of routine CT scanning in the management of patients with acquired cystic disease is not presently resolved. Clearly the development of any symptoms or signs suggestive of renal cell cancer, or a change in ultrasound or CT scan appearance warrants a full investigation of these masses. Further, the diagnosis may be enhanced by MRI using gadolinium.

V. Simple Renal Cysts

With the increased frequency of highly accurate abdominal imaging studies the diagnosis of simple cysts of the kidney has become prevalent. In one recent study of 729 patients referred for investigation of symptoms unrelated to the urinary tract who had normal renal function, the prevalence of renal cysts were carefully noted (90). The prevalence of individuals with at least 1 renal cyst was 0% in those aged 15-29 years, 1.7% in those aged 30-49 years, 11.5% in those aged 50-70 years, and 22.1% in those aged 70 years or above. Bilateral renal cysts also became more common as patients aged as 1% of patients between the ages of 30 and 49 years had a bilateral cyst, 4% of those aged between 50 and 70 years had bilateral cyst, and 9% of those above the age of 70 had bilateral renal cyst. The 95% confidence intervals for the prevalence of renal cysts is provide in **Table 15**. Simple cysts are lined by a single layer of epithelium and may arise as a consequence of tubular obstruction or concurrent ischemic damage. The composition of non-infected cyst fluid is parallel to that of serum (91). Penetration of antibiotics into the fluid of cyst may be poor and therefore may warrant the drainage of cyst fluid on occasion. The clinical manifestations of simple cysts include occasional flank pain, hematuria, urinary tract infection, spontaneous rupture, intestinal obstruction, the presence of an abdominal mass and hypertension. The diagnosis of simple cysts is

made by ultrasonography and by CT scanning. On CT scans simple cysts are characterized by a homogenous water-like attenuation value, a thin cyst wall, smooth interfaces with tissues, and the lack of cyst enhancement after administration of contrast material. Calcification within the mass is a marker for malignancy. The use of magnetic resonance imaging may help distinguish between tumors and cysts and between hemorrhage and cysts in cases that are difficult to call by CT scanning. The use of cyst puncture has largely been abandoned as a routine procedure. Cyst are usually asymptomatic and do not impair kidney function. Over the course of years, simple cysts grow quite slowly and generally increase in number rather than size.

Table 15. Frequency of Cysts by Age Group

	Age Groups			
	15-29(%)	30-49(%)	50-69(%)	70+(%)
Unilat. Cyst	0	1.7	11.5	22.1
Two Cysts	0	0.6	1.8	11.7
Three Cysts	0	0.6	0.7	4.5
Bilat. Cysts	0	0.6	1.4	5.4
1 Cyst, 2 Cysts	0	0.6	0.7	3.2
2 Cysts, 2 Cysts	0	0	0	1.9

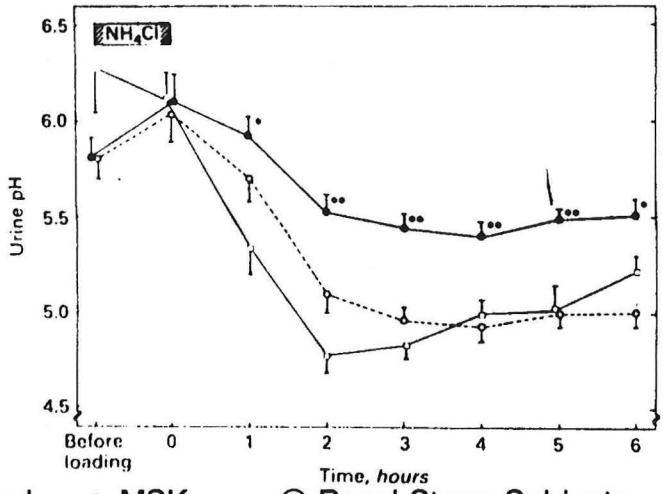
From Ref. 90

VI. Medullary Sponge Kidney

Medullary sponge kidney is a term applied to a cystic renal disease involving the renal papillae of one or both kidneys. The cysts are usually small (1 to 7.5 mm) and are located in the collecting tubules of one or more pyramids. It is not clear whether medullary sponge kidney has a hereditary basis or not, although the disorder has been demonstrated into two or more successive generations on several occasions. The disorder is believed to be due to a developmental abnormality in the medullary collecting tubules. The ectatic collecting tubules form cystic structures that do not progress in size. The disorder occurs in about 1 in every 10,000 people, and there is no gender or ethnic prediliction. The disorder is seen in about 1 and every 200 excretory urograms that are performed. As many as 20% of women with calcium urolithiasis are found to have medullary sponge kidney. The disorder appears in adulthood and is rare before the age of 25. Patients with medullary sponge kidney have a tendancy to develop calcium deposits in the ectatic tubular cyst. The environment is believed to be favorable for calcification in the cyst because of the cellular debris that collects there as well as the higher urinary pH seen in many patients with this disorder. In fact, about 80% of patients with medullary sponge kidney are unable to maximally acidify the urine in response to an ammonium chloride challenge (see **Figure 23**) (92). There may be an accompanying

accompanying interstitial fibrosis in the renal medulla adjacent to the ectatic tubular cyst. Hypercalciuria occurs in about half of the patients with medullary sponge kidneys and appears to affect women more frequently than men. Both renal and absorptive subtypes of idiopathic hypercalcuria have been observed in studies of patients with sponge kidney. In addition to the abnormal maximal urinary acidification, there is also a vasopressin-resistant concentrating defect present in some. Other patients with medullary sponge kidney have hyperparathyroidism; whether this is due to a primary increase in parathyroid hormone or rather a response to persistent hypercalciuria is not clear (93). Glomerular filtration rate is believed to be normal in most patients with medullary sponge kidney.

Figure 23. U_{min} in MSK



□ Control ● MSK ○ Renal Stone Subjects

From Ref. 91

The clinical manifestations of sponge kidney are manifest as symptoms in about half of the patients, usually as renal colic or flank pain and typically associated with a stone. The renal stones can occur in patients both with and without hypercalcuria. Hematuria occurs in about 20% of patients, and urinary tract infections are present in about 33% of patients at some point during their course. A number of other disorders are associated with sponge kidney including hyperparathyroidism, hyperaldosteronism, Marfan syndrome, and congenital hepatic fibrosis. Diagnosis is made in most cases by excretory urography. Renal ultrasound and CT scanning offer little help in the diagnostic evaluation. Kidney size is usually normal or minimally enlarged. There is a characteristic "paint brush" appearance to the renal papillae in sponge kidney. The linear radiations can be seen only briefly in the urogram. Some nephrocalcinosis is present in about 50% of patients. There is no specific therapy required for sponge kidney. Therapy for nephrolithiasis is the same as for patients without sponge kidney and includes thiazide diuretics and increased water intake. Alkaline therapy may be necessary in patients who manifest renal tubular acidosis. The long term prognosis is quite good provided that urinary tract infections are treated appropriately and stone recurrence is minimized to prevent obstructive uropathy.

Table 16 shows several of the important differences between medullary sponge kidney, polycystic kidney disease and nephronopthisis-medullary cystic disease.

Table 16. Clinical Differences Among Three Common Cystic Disorders of The Human Kidney

Diagnostic Criterion	Nephronophthisis–Cystic Renal Medulla	Polycystic Kidney Disease	Medullary Sponge Kidney
Flank pain	Usually absent	Usually present	Present only if complicated
Hypertension	Unusual	Frequent	Unusual
Hematuria[b]	Absent until azotemic	Often present	Present, if complicated (as with stone)
X-ray findings	Small kidneys	Large kidneys Cysts	Normal to large kidneys Papillary cavitations
	No calculi	Calculi	Medullary calcifications
Impaired glomerular filtration after onset	Frequent	Frequent	Absent unless complicated
Age at death	1st–4th decade	<5 or >50 yr	Normal life-span
Familial incidence	>75% of cases	>75% of cases	<20% of cases

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