AMERICAN RENAL TRAINING CENTERS

DESCRIPTION OF THE NEPHROLOGY TRAINING PROGRAM—UNIVERSITY OF CHICAGO PRITZKER SCHOOL OF MEDICINE

The program in nephrology at the University of Chicago dates to the 1940s and has been headed by such outstanding clinician-scientists as Louis Leiter, Alf Alving, and Theodore Pullman. Hemodialysis and kidney transplantation were initiated at our institution in 1967, and in the last year, more than 200 renal failure patients were dialyzed in our busy outpatient unit and 70 obtained renal transplants here. The section flourishes with 13 full-time faculty and 9 trainees in postdoctoral fellowships.

The clinical program is marked by diversity, and fellows gain valuable experience managing renal disease of all kinds, hypertension, chronic and acute hemodialysis (including continuous forms), peritoneal dialysis, renal transplantation, nephrolithiasis, metabolic bone disease, as well as hypertension and renal disease in pregnancy. The nephrology service benefits from close interactions with two renal pathologists and two pediatric nephrologists. A full-time transplant nephrologist is an integral part of the section, with an active transplant service performing cadaver and living-related kidney transplants, in addition to combined pancreas-kidney transplants for selected diabetic patients.

The University of Chicago has a strong research mission with an emphasis on using basic science principles to gain an improved understanding of the mechanisms underlying disease. Areas of current interest in the nephrology section include determinants of early events in nephrolithiasis; the role of growth factors in renal proliferation and regeneration after injury; bone, mineral, and vitamin D metabolism; vasoactive factors and blood pressure regulation; tubular transport of ions; and volume homeostasis and vascular reactivity in pregnancy. Clinical research parallels the laboratory focus and includes studies of epidemiology and treatment effects of nephrolithiasis; cardiac function in uremia; nutritional assessment during peritoneal dialysis; evaluation of treatment adequacy and drug kinetics in hemodialysis patients; and vascular reactivity in preeclampsia.

Not only do trainees at the University of Chicago gain an impressive clinical experience, but they also initiate and complete original clinical and basic research protocols, with the potential to use techniques of molecular and cell biology, protein chemistry, and renal microdissection. Of the 50 trainees at the University of Chicago during the past 10 years, 50% are currently in an academic environment. We are pleased by the opportunity to participate in this educational series.

Autosomal Dominant Polycystic Kidney Disease[1]

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is an important cause of medical morbidity in the United States that affects one-half million persons and accounts for ESRD in about 10% of the chronic dialysis population. In addition to its effects on the kidney, the disease has important manifestations in the cardiovascular system (aneurysms, hypertension) and the gastrointestinal tract (hepatic cysts). Clinically important renal complications can develop as the disease progresses that require specialized attention, such as urinary tract infection, pain, and nephrolithiasis. The underlying cellular defect that causes ADPKD has eluded investigators thus far, but abnormalities in cellular proliferation, the tubular basement membrane, and cell fluid secretion appear important in pathogenesis. Factors that mediate progressive interstitial fibrosis and failure of

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renal function are undefined, although rigorous control of blood pressure appears to be an important therapeutic measure. Recent advances in molecular biology have localized the abnormal gene to chromosome 16 in 90% of families, making early genetic screening of asymptomatic family members possible in many cases. A positive diagnosis may have important effects on employment status, as well as health insurance, so that family members sometimes refuse to be assessed for the presence of the disease. Because of such complex social factors, counseling of an asymptomatic individual by his or her physician is required when considering the use of screening tests for ADPKD. Inadequate patient education may still represent an impediment to early detection, genetic counseling, and timely treatment of disease complications.

Key Words: *Renal cyst, hepatic cyst, genetic screening, cyst infection, hypertension*

A 47-yr-old white woman was first diagnosed with autosomal dominant polycystic kidney disease (ADPKD) at age 10 yr on an excretory urogram. There was a strong family history of the disease that included the patient's mother, grandmother, one sister, an uncle, and three cousins; many had cerebral aneurysms. The patient had one episode of pyelonephritis at age 26 yr and developed hypertension when she was 32 yr old. A screening cerebral angiogram was negative at age 36 yr. She saw her internist irregularly and was intermittently treated with antihypertensive agents. In 1991, she was referred to the Renal Clinic at the University of Chicago for evaluation of progressive abdominal pain and distention of 1 yr duration. She described a bloating sensation, most severe late in the day, especially after eating a large meal or fatty foods. Frequently, she was forced to lie down at the end of the day for relief. Medications at the time of referral included furosemide, ranitidine, and tenormin. There was no history of oral contraceptive use or replacement estrogen therapy.

On physical examination, the blood pressure was elevated at 136/94 mm Hg with evidence of long-standing hypertension; there was copper wiring and arteriovenous nicking of retinal vessels and an S4 gallop without jugular venous distention. The lungs were clear to auscultation and percussion. Abdominal examination revealed a mass in the right upper quadrant extending to the left flank, and the liver span was in excess of 20 cm. The liver was nontender with easily palpable subcutaneous cysts. There was no pedal edema. The laboratory examination was notable for a serum creatinine concentration of 1.4 mg/dL, a hematocrit of 38.5%; normal bilirubin, albumin, and liver enzymes; and a normal urinanalysis.

An abdominal computed tomographic (CT) examination revealed that each kidney was more than 15 cm in its greatest dimension and was largely replaced with cysts; little normal parenchyma was present (Figure 1). The liver was massively enlarged and contained multiple large cysts, extending far into the left upper quadrant (Figure 2). In contrast to the kidneys, cystic changes in the liver were localized and interspersed with areas of relatively preserved normal architecture. Under CT guidance, fluid in

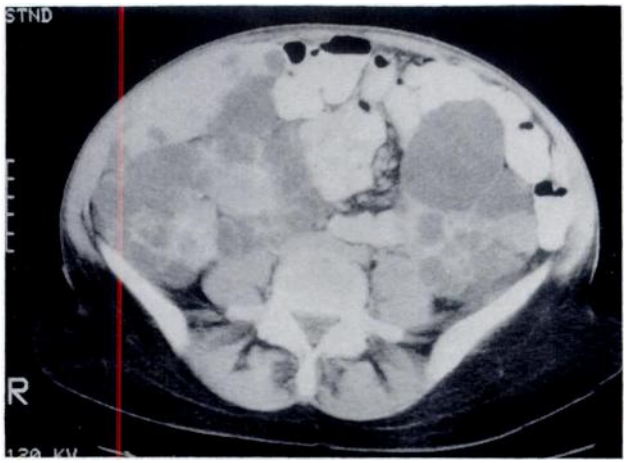

Figure 1. Abdominal CT examination from a patient with ADPKD. This section through the pelvis reveals massive enlargement of each kidney to a diameter of more than 15 cm. Renal tissue is largely replaced by cysts, which appear darker than preserved normal parenchyma. Also visualized just below the abdominal wall is a portion of the right lobe of the enlarged liver, which also contains cysts.

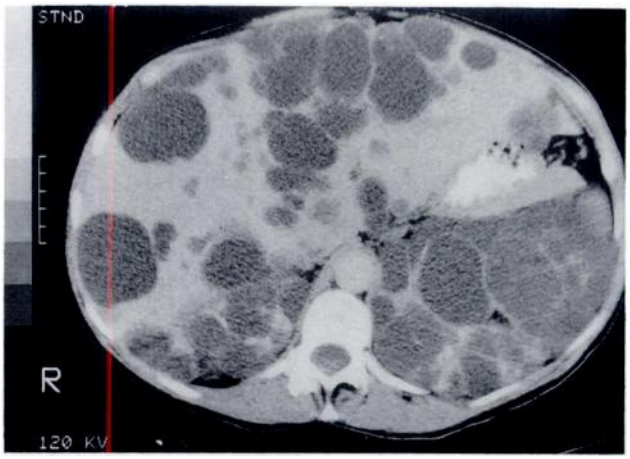

Figure 2. Abdominal CT examination from the same patient. This section through the upper abdomen demonstrates that the massively enlarged liver contains multiple dark cystic structures. The left kidney is increased in size and is largely replaced by cysts. Note that a greater fraction of the liver parenchyma is preserved compared with the portion of the kidney that is visualized.

several of the largest liver cysts was aspirated and alcohol was then instilled into the cysts to sclerose them. After cyst decompression, the patient noted decreased intensity of each abdominal symptom. Six months after the initial evaluation, her blood pressure was reduced to 110/70 mm Hg with the administration of an angiotensin-converting enzyme (ACE) inhibitor (lisinopril) in place of tenormin; the serum creatinine concentration was 1.7 mg/dL. Creatinine clearance measured with the patient taking cimetidine was 25 mL/min. Her two children, both in their twenties, are asymptomatic and knowledgeable about ADPKD but have refused screening by ultrasonography or genetic analysis for diagnosis.

BACKGROUND

ADPKD is the most common genetically inherited disease in the United States. It affects 500,000 persons and accounts for about 10% of patients starting chronic hemodialysis (1). The gene is transmitted as an autosomal dominant trait with a frequency in the population of ~1:1,000 and has nearly complete penetrance (2). Up to 40% of patients initially deny a family history, although with careful screening of pedigrees, perhaps only 10% of these individuals lack an affected relative (2). The gene associated with ADPKD has recently been localized to the short arm of chromosome 16 in the majority of patients (2). Despite this well-publicized information, only 23% of dialyzed ADPKD patients in one American city were aware of the hereditary nature of their disease (1). Thus, patient education is an important but often neglected part of managing ADPKD patients and their relatives.

RENAL MANIFESTATIONS: CLINICAL PRESENTATION

The major symptoms that cause those patients not detected by family screening to seek medical attention are hypertension, flank pain, urinary tract infection (UTI), hematuria, and nephrolithiasis, each accounting for ~20 to 30% of cases (1). Hypertension is the most important of these, as it was present in *92%* of patients at the time of initial presentation if they later developed end-stage renal failure (1). Overall, hypertension occurs in 60% of patients with ADPKD before the need for dialysis (1). The increase in blood pressure appears to be mediated by activation of the renin-angiotensin system (RAS), in a manner that is analogous to a two-clip, two-kidney animal model (3). Narrowing of the arterial tree is evident in angiograms of polycystic kidneys, and prominent renin granules have been identified in cells of the macula densa (3). Early in the disease, there may be volume expansion with an inappropriate lack of suppression of the RAS (4), whereas later in the disease, when renal function declines, extracellular fluid volume returns towards normal (5), perhaps because of a loss of renal sodium conservation, as is seen in other forms of chronic renal failure. Thus, the pathogenesis of hypertension may be mediated by different mechanisms during the course of the disease. In the case presented above, an observed rise in serum creatinine concentration from 1.4 to 1.7 mg/dL while on an ACE inhibitor for blood pressure control could have reflected suppression of an activated RAS (6) that served in part to increase glomerular filtration.

Hematuria can be acute, severe, and painful. Often it is caused by one or more kidney stones, which can be detected by a CT scan if a plain abdominal x-ray does not provide the diagnosis (3). If the presence of a stone leads to urinary tract obstruction, the cysts make urologic procedures more difficult and thereby increase the risk of surgical complications. Acute flank pain is often due to intracyst hemorrhage that is unaccompanied by hematuria (3). In contrast, chronic flank pain may result from progressive accumulation of fluid within cysts, which increases intraluminal pressure, although the cause of the pain is often unclear. CT-guided needle placement for cyst decompression may provide symptomatic relief (3). In cases of severe intractable pain, surgical decompression of cysts provided relief of 2 yr duration for 62% of 26 patients, without a deleterious effect on renal function (7).

UTI occurs in about one third of patients with ADPKD during their lifetime, much more commonly in females (72%) than males (26%) (8). Instrumentation of the urinary tract poses a major risk of subsequent infection, which occurs in up to 40% of cases if no antibiotics are given (8). Asymptomatic renal infection, as evidenced by bacteria in the parenchyma, was present in up to 50% of ADPKD patients in one autopsy series and is of uncertain importance, as is the asymptomatic pyuria that occurs in up to 43% of patients (8). The diagnosis of cyst infection can be difficult because often neither pyuria nor bacteriuria are detected. On the other hand, flank pain and hematuria can occur without infection. Renal infections can be subclassified as pyonephrosis (infection of the upper collecting system), acute bacterial interstitial infection (infection of the renal parenchyma), or pyocyst (infection confined to a cyst). Pyocysts are the most serious of the three and are usually diagnosed by the failure of a short course of antibiotics to be curative (8). They are in most instances accompanied by the appearance of new back tenderness and positive blood cultures. Usually gram-negative enteric organisms are responsible, which suggests an ascending route of infection. Perinephric extension is the most feared complication because it is associated with a 60% mortality (8).

X-rays and tomograms may reveal evidence of perirenal infection, although a CT scan is often required to make the diagnosis. In difficult cases, a gallium scan may help localize and define the lesion, although this diagnostic tool only detects about half of the pyocysts present (8).

Cysts in ADPKD kidneys can be divided into two populations on the basis of their fluid content; one has characteristics of the proximal nephron and the other has characteristics of the distal. With regard to the treatment of an infected cyst, the antibiotic chosen should be active against gram-negative organisms and likely to penetrate the tight junctions found in a distal tubule-like cyst wall, *i.e.*, it should be lipophilic. Among the available antibiotics, chloramphenicol, trimethoprim-sulfamethoxazole, and ciprofloxacin fulfill these criteria and are therefore useful for the treatment of both proximal and distal tubule-like cysts. Even so, a prolonged course of 4 to 8 wk of either agent will likely be required to clear a pyocyst (8). Percutaneous drainage of antibiotic-unresponsive pyocysts has also been successful (7). Nephrectomy is a last resort. After renal transplantation, infection of native polycystic kidneys is rare if there was no prior history of it but is common if there was a prior history of UTI. Such posttransplant infections have a high morbidity and mortality, so that native nephrectomy is recommended before transplantation in patients with a prior history of recurrent UTI (8).

Despite a high incidence of hyperplastic renal polyps (90%) and microadenomas (24%), autopsy studies have failed to demonstrate an increased risk of renal cell carcinoma in patients with ADPKD (1,9). On the other hand, excluding renal cell carcinoma in a polycystic kidney in the presence of intrarenal hemorrhage or in an affected patient over age 50 with new-onset hematuria is a diagnostic challenge. In these instances, angiograms or possibly nephrectomy may be required (1).

Kidney stones occur in 15 to 20% of patients with ADPKD. The stones are composed primarily of urate and calcium oxalate and are associated with an abnormally low urinary pH, reduced urinary citrate excretion, and elevated excretion of uric acid (10). These alterations in urine chemistries are not specific for the presence of renal cysts but are more likely a reflection of the presence of chronic renal insufficiency.

Renal function is normal for many decades in patients with ADPKD, and the prognosis for retaining normal function may be better than previously believed with current treatments of complications such as hypertension (11). In a recent analysis of a large series of patients, only 25% had reached ESRD by age 50, 43% by age 58, and 53% by age 73 (11). The presence of specific clinical factors such as hypertension may influence these statistics (1), and in some series but not others, females have been found to have a more benign course of renal disease (12). The pathophysiologic event(s) that initiates the loss of renal function is not known. Arteriolar sclerosis and interstitial fibrosis are the most prominent histologic features, which suggests that hypertension is an important factor in the progression of renal failure (13). Scarring after repeated infections or rupture of cysts followed by repair may underlie the interstitial fibrosis. Alternatively, an as-yet-unidentified stimulus for the proliferation of interstitial fibroblasts may be a result of the underlying cellular defect in ADPKD. Widespread tubular atrophy is *not* seen, an observation that does not support the idea that cysts compress normal kidney tissue thereby causing atrophy and subsequent scarring (13). The absence of focal sclerosis appears to rule out glomerular hyperfiltration of residual functional nephrons as an important factor (13).

Persons with ADPKD do well after kidney transplantation, with graft and patient survival scores similar to that of the general renal transplant population (14). There appears to be an increased incidence of complications specific to the underlying cystic disease, such as ruptured cerebral and aortic aneurysms and infection of hepatic cysts.

EXTRARENAL MANIFESTATIONS: CLINICAL PRESENTATION

Saccular cerebral aneurysms were present in 10 to 40% of asymptomatic patients with ADPKD examined by angiography or at autopsy (3). A statistical risk-benefit analysis determined that screening cerebral angiograms in asymptomatic ADPKD carriers were not justified (3). Not considered in this analysis was the possibility that the risk of cerebral aneurysms may be increased among certain affected families with ADPKD (3). Thus, one diagnostic strategy is to recommend cerebral angiography only in a patient with ADPKD who has a family history of subarachnoid hemorrhage. Alternatively, high-resolution CT or magnetic resonance imaging of the head with 3-mm sections through the circle of Willis is an alternative test to screen for intracranial aneurysms in high-risk individuals (15). When these relatively noninvasive tests were used to screen 96 low-risk patients, no aneurysms were identified (15), thereby providing further evidence that such unselective screening of all ADPKD patients would have a low yield.

An increased incidence of valvular abnormalities such as mitral prolapse (26%), aortic incompetence (8%), and tricuspid prolapse (6%) have been detected in ADPKD patients (3). Aortic aneurysms may also occur with increased frequency in association with ADPKD (12). Thus, careful attention to the cardiac examination is warranted in ADPKD patients and

standard prophylaxis to prevent subacute bacterial endocarditis should be carried out in family members with valvular abnormalities (3).

Hepatic cysts probably originate from the biliary epithelium and appear about 10 yr later than renal cysts, eventually occurring in about 50% of patients with ADPKD (16). These cysts are often inconsequential but may cause symptoms if they become very large. Although male and female patients are equally likely to have liver cysts, women are more likely to have more than 15 cysts and to have larger ones (16). There is an increased incidence of hepatic cysts in women who have been pregnant, and the number of cysts correlates positively with the number of pregnancies, suggesting a role for female steroid hormones in cyst development. The presence of hepatic cysts is associated with relatively poor *renal* function but surprisingly not with hepatic dysfunction (16). Massive hepatic cystic disease is primarily a disease of women, but it is rare. Symptoms arise as the liver enlarges and compresses adjacent structures. Complaints include increasing abdominal girth, dull abdominal pain, early satiety, weight loss, and respiratory compromise. Cyst puncture and aspiration, followed by sclerosis, have provided prolonged relief in some cases, such as the one presented. In more severely affected patients, a combined cyst resection–fenestration procedure was deemed successful in seven of nine patients for relief of symptoms (17). As in our case presentation, the highly cystic portion of the affected liver is often distinct from hepatic parenchyma with preserved architecture, which makes cyst resection feasible. Because hepatic functional failure is rare, liver transplantation has not been carried out in these patients. The longer survival of patients with ADPKD in the dialysis era may allow other conditions related to hepatic cysts to develop. In one population of ADPKD patients on maintenance hemodialysis, complications related to hepatic cysts (infection, portal hypertension, or cholangiocarcinoma) accounted for 10.5% of all deaths (18).

Colonic diverticulae were reported in more than 80% of patients with ADPKD in one series (19). The risk of complications arising from these diverticulae such as rupture was also increased (19). For this reason, some recommend evaluation for the presence of such diverticulae before renal transplantation, with consideration of partial colectomy if extensive disease is found.

PATHOBIOLOGY OF CYST FORMATION

In patients with ADPKD, cysts appear as localized "outpouchings" of intact tubules or collecting ducts. Cyst formation requires proliferation of tubular epithelial cells, on the basis of the mathematical considerations imposed by cyst surface area and cell size (20). The basement membranes of cysts are morphologically and compositionally abnormal (13). Table 1 summarizes the characteristics of three model systems used to study the disease and highlights cellular defects that have been uncovered. Studies of patients with ADPKD have been carried out on excised renal tissue and in cells derived from it grown in primary culture (13,20). Mice with congenital polycystic kidney (cpk) disease are an inbred strain with an autosomal *recessive* syndrome characterized by cystic deterioration of the kidneys and death in the first month of life (21). Rats fed diphenylthiazole (DPT) exhibit progressive cystic changes along the collecting duct during a period of about 30 wk (13). Unfortunately, none of the available models for the study of ADPKD are truly analogous to the human disease and there appear to be multiple pathways to cyst formation. Thus, one must be wary about drawing firm conclusions concerning the pathogenesis of cyst formation in ADPKD from these experimental investigations.

Alterations in tubular basement membrane composition are prominent in each of the three models. During normal murine organogenesis, renal mesenchymal cells stop secreting type I and III collagens and begin to secrete type IV collagen and laminin to produce basement membranes. The timing of this switch in the transcription of genes encoding basement membrane proteins is altered in developing cpk mice so that less messenger RNA for type IV collagen and laminin is present early, whereas later in development, amounts of each are more than expected (21). Conversely, the quantity of basement membrane proteins encoded by these genes is normal soon after birth, but as cysts develop, less laminin and

TABLE 1. Cystic kidney diseases: Similarities amongst models[a]

	ADPKD	cpk Mouse	DPT Rat	ATN
BM Thinning + Altered Composition	+	+	+	
Marked Interstitial Fibrosis	+	?+	+	
Loss of Cell Polarity	+	+		+
Decreased ADH Binding to its Receptor	+		+	
Decreased EGF in Urine and/or Tubular Fluid	+	+		+
Decreased EGF mRNA	+	+		+
Increased EGF Binding to its Receptor	+			+
Increased c-*myc* Oncogene and/or Proto-oncogene Expression	?+	+		+

[a] Abbreviations used: ADH, antidiuretic hormone; BM, basement membrane; ?+, equivocal or suggestive evidence.

type IV collagen are present than in normal mice. Although these alterations in collagen and laminin production may not be necessary or sufficient for cyst formation, abnormalities in the formation of the basement membrane may be important in the pathogenesis of polycystic kidney disease. Ultrastructural study of tubular cells from DPT-treated rats reveals an early increase and prominence of organelles involved in protein synthesis and secretion, with an associated thinning of the basement membrane and loss of sulfated proteoglycans (13). In human kidneys, the tubular basement membrane is thickened in cyst walls and its content of heparan-sulfate proteoglycans is reduced (13). After 30 wk of DPT treatment, the most remarkable histologic changes are dilated collecting ducts and atrophy of nonaffected tubules with marked interstitial fibrosis but *normal* glomeruli and blood vessels (13). Interestingly, the deformability and compliance of isolated basement membranes from the kidneys of humans with ADPKD and rats treated with DPT do not differ from that of normal tissue (13). It is uncertain how structural and compositional defects in the basement membrane mediate cyst formation, but it appears more complex than simply an increase in mechanical stretch due to structural weakness. Interstitial fibrosis appears to be a common finding in each model of cystic disease. Pathologic study of human ADPKD kidneys reveals prominent interstitial fibrosis out of proportion to the accompanying nephron loss, suggesting that interstitial fibrosis contributes to the decline of GFR late in the disease (13). In the cpk mouse model, messenger RNA encoding the gene for type IV collagen is present within interstitial fibroblasts but is absent in these cells in kidneys from control animals (21). This observation suggests a specific abnormality in the interstitial cell in this model of the disease.

Loss of polarity has been demonstrated in cells of the cyst wall (20). In human ADPKD cells in primary culture, the enzyme Na:K ATPase is found on the apical surface, apparently the result of translocation of the enzyme from its normal basolateral location. The abnormal location of the enzyme on the apical surface could permit reversal of sodium transport so that the ion is pumped into the tubular lumen, as well as the interstitium. This may explain in part the accumulation of fluid within cysts. Similar alterations in the distribution of Na:K ATPase are found in cpk mice (21).

Aberrations in cAMP production may contribute to increased fluid secretion by cells of the cyst wall. Under specific conditions, canine renal epithelial cells of the MDCK line form cystic structures that accumulate fluid (20). In this model system, compounds that increase intracellular cAMP also enhance the secretion of fluid into the cyst, whereas agents that block the accumulation of cAMP inhibit fluid secretion. In humans with ADPKD, puncture of renal and hepatic cysts *in vivo* followed by administration of the hormone secretin increased the amount of fluid secreted (20). Although the mechanism of augmented fluid secretion is not known, the hormone does increase intracellular cAMP. Taken together, these observations suggest that pharmacologic agents that reduce intracellular cAMP content could have a potential therapeutic role in ADPKD to reduce cyst size.

Another abnormality of plasma membrane protein function is the reduced capacity of antidiuretic hormone to stimulate receptor-mediated activation of adenylate cyclase in cells from patients with ADPKD as well as from rats treated with DPT (3,13). This provides a potential mechanism for the early loss of renal concentrating ability in patients with ADPKD. An additional aberration of membrane protein function in cells from humans with ADPKD is an increased binding of epidermal growth factor (EGF) to its cell surface receptor, despite a decreased amount of the factor in tubular fluid and urine (20).

Enhanced cellular proliferation has been observed in primary cultures established from ADPKD cysts by some investigators (20), but not by others (13). In cpk mice, the expression of the c-*myc* proto-oncogene, which is associated with enhanced cell growth, is markedly stimulated (20), and transgenic mice expressing the c-*myc* transgene develop polycystic kidneys (20). These findings support a role for increased tubular cell proliferation in the formation of cysts, although its contribution as an initiating factor in cystogenesis is uncertain.

ATN is a disease paradigm in which aberrations in cell polarity mediated by cytoskeletal changes have been described (22). Many of the cellular abnormalities reported in models of polycystic kidney disease (20,21) are found in ischemic tubular cells, including loss of polar orientation of Na:K ATPase. A decrease in the amount of mRNA encoding EGF and the quantity of protein in tubular fluid, along with enhanced EGF binding to its receptor, is observed in both conditions. The importance of these changes in EGF production and action are unclear in ATN, as they are in the models of cystic disease. It is intriguing to speculate that perhaps a subtle alteration in one of the components of the cytoskeleton, plasma membrane integrins, or extracellular matrix proteins could account for many of the seemingly unrelated abnormalities in polycystic kidney disease.

GENETIC ASPECTS

Because the cellular defect that underlies ADPKD has eluded investigators, a reverse genetics strategy has been used to seek the gene and its product, which

is presumably abnormal in this disease (2). Initially, many genetic markers with known chromosomal locations were used to screen families with ADPKD to determine which markers segregated with phenotypic expression of the disease (presence of cysts). Because recombination between chromosome pairs occurs during meiosis, even if two genetic markers are on the same chromosome in a parent, they may not both be passed on to a single offspring together. In general, the closer together two regions of DNA are on a given chromosome, the less likely such recombination will occur. Markers that can be investigated include genes that encode specific proteins (such as ABO blood types), anonymous DNA sequences that do not encode a known gene product (such as the 3′ hypervariable region, 3′HVR), or a clinical phenotype (such as the presence of renal cysts). Variation between the two chromosomal copies (alleles) of a locus is necessary to trace the mendelian inheritance of each copy through a family (each marker needs to be polymorphic in order to define a linkage between them). To evaluate a given family, one can consider the gene responsible for ADPKD as occurring in disease-inducing or wild-type alleles as the first polymorphic locus, whereas another polymorphic marker (such as the 3′HVR) is the second locus. Then, cosegregation of the two markers (presence or absence of renal cysts, size of 3′HVR) can be assessed. Because random cosegregation of unlinked genes as well as recombination between linked genes can occur, statistical analysis is performed to test the significance of an apparent linkage. The "lod score," which is used to assess significance, is calculated as the logarithm of a ratio of the odds of two markers being linked or not linked. A score of 3 or greater indicates significant linkage (chances of linkage exceed 1,000:1). In this manner, an anonymous segment of DNA closely linked to the α-globin gene on chromosome 16, the 3′HVR, was found to be closely linked to the ADPKD gene, thereby localizing the ADPKD gene to the short arm of this chromosome. The 3′HVR region is an interesting region of the genome containing between 70 and 450 copies of a repeated 17-base-pair sequence (it is highly polymorphic). Each of two number 16 chromosomes from an individual is unlikely to have the same number of repeats in the 3′HVR, thus making it a very useful marker with which to study families.

Restriction fragment length polymorphisms greatly expand the repertoire of polymorphic markers available for linkage analysis. Restriction enzymes obtained from bacteria cleave DNA at specific nucleotide sequences. Point mutations that change the sequence within chromosomal DNA can remove or add restriction enzyme cleavage sites. A patient's genomic DNA, isolated from peripheral blood cells, can be cleaved by these enzymes and the fragments that result can be separated according to size by gel electrophoresis and transferred to nitrocellulose paper. Hybridization of the genomic DNA fragments with radioactive DNA probes (in this case, for anonymous DNA fragments in regions flanking the ADPKD gene) will reveal fragments of different sizes in persons having mutations that add or subtract enzyme cleavage sites on one or both copies of chromosome 16 (the restriction fragment length polymorphisms). DNA from several family members (at least two) is required to define these restriction fragment patterns that are generated by enzyme cleavage and that also segregate with the disease phenotype in that family. If a family member has a cleavage pattern similar to that of the affected individuals, he or she is considered to carry the ADPKD gene. By using multiple markers generated by DNA cleavage with other enzymes and subsequent hybridization with different radioactive probes on each side of the ADPKD gene, diagnostic accuracy is >95%. This analysis depends on the marker gene lying close enough to the ADPKD gene so that recombination between the two regions of DNA is unlikely to occur during meiosis. For the 3′HVR region, linkage to the ADPKD gene was established with a maximum lod score of 25 (odds of linkage are 10^{25}:1). If one assumes that the chance of recombination between the gene and each marker is approximately 2% (2), the use of two markers on each side of the gene reduces the chance of a false-positive or false-negative error to 0.04%. Because certain individuals will have inherited one disease marker but not the other, because of a recombination event, up to 4% of individuals in a given ADPKD family will not be diagnosed by this method. The above discussion and percentages assume that enough family members are available to ascertain the linkage patterns. Small family sizes, such as the presence of only the proband and an affected parent, often precludes such an analysis, and in these instances, one is forced to use traditional screening techniques such as renal ultrasonography.

Recently, several families with clinical polycystic kidney disease were described in which the disease is not linked to markers on chromosome 16, representing perhaps 4% of all cases (23). The gene in these individuals has been termed PKD-2; the designation PKD-1 is used for the gene known to be localized on chromosome 16. Others prefer the term "non PKD-1," because there may be more than two gene defects that result in clinical polycystic kidney disease. A recent prospective study of 17 families with ADPKD revealed 10 with PKD-1 disease, 2 with non PKD-1, and 5 in which a determination could not be made. Onset of renal failure was delayed from a mean age of 57 yr in PKD-1 patients to 69 yr in the non PKD-1 families, suggesting that the latter may represent a milder form of the disease.

PRESYMPTOMATIC SCREENING

The sensitivity of ultrasound detection of renal cysts for the diagnosis of ADPKD increases with age. In patients determined to have the PKD-1 mutation by linkage analysis, 83% had renal cysts on ultrasonography if less than 30 yr old and 100% had cysts if older (23). For a definitive diagnosis, the presence of three to five cysts in each kidney is required. The DNA marker analysis described above can potentially identify affected persons from PKD-1 families earlier than can ultrasound examination, even *in utero*. The issue of prenatal evaluation is particularly complicated, given the fact that some affected individuals live nearly an expected lifespan and ever-improving therapies for disease complications exist. The benefits of screening a family member for the presence of the disease include enlightened family planning, careful blood pressure monitoring and treatment of hypertension if found, certainty of the diagnosis, the possibility of being a living-related transplant donor (if negative), and clarification of the risks of cerebral aneurysm and the need for detecting its presence in selected families. The drawbacks of a definitive presymptomatic screening diagnosis include possible subsequent difficulty in obtaining employment and insurance, anxiety, and the cost of the evaluation itself ($2,000 for genetic testing alone).

The experience of a large clinic in Great Britain illuminates the views of patients from affected families (24). Attitudes about screening were assessed in individuals between the ages of 18 and 45 from 139 families. In this population, 22% were considered high risk for ADPKD but had refused screening at the time of study. In the patients studied, knowledge of the clinical aspects, genetics, and therapeutic implications of ADPKD was fair at best, with 46% having poor knowledge of the genetics of the disease in particular. This is notable because it was routine in this clinic to educate all patients at age 18 about these issues. Among those who had previously been screened and found to have the disease, 74% felt they had suffered adverse psychologic or social consequences, including loss of job (19%) or insurance (33%). Only 17% of these affected individuals felt that certainty about their diagnosis altered reproductive plans. Of these, only 21% had declined to have any children at all, whereas the remainder elected to have smaller families. Thus, only 3.5% of 85 affected patients in this study decided not to have children because of their disease. Fifty-three percent of the high-risk group once again refused screening at the time of the study; half of these did not want to cope with the certain diagnosis of a disease without a cure. Overall, 75% felt that the development of a prenatal test was desirable, although only 29% said they would use such a test. Those interested in the test were more likely to consider the disease to be "extremely serious."

CONCLUSIONS

Polycystic kidney disease is the most common genetically inherited disease in the United States and presents nephrologists with challenging opportunities to manage its renal and extrarenal manifestations. As patients live longer because of improved management and renal replacement therapy, the extrarenal manifestations may become an even more common problem to be addressed, as exemplified by the cystic hepatic disease described in the case presented here. The factors that lead to a decline in renal function and interstitial fibrosis late in the disease are also unclear, although the appearance of hypertension may be one important cause. There is reason to suspect that aggressive control of blood pressure will retard loss of renal function. To date, experimental models of the disease have failed to identify the underlying cellular defect(s) responsible for ADPKD. Recent studies at the genetic level have localized the abnormal gene to chromosome 16 in the majority of patients, and continued efforts to clone the gene should eventually shed light on molecular mechanisms that are responsible for the disease. Through the use of linkage analysis of flanking DNA markers on each side of the gene on chromosome 16, affected family members (in PKD-1 families) can be identified before the radiologic detection of cysts in up to 95% of cases in which sufficient family members are available to assess linkage patterns. In non–PKD-1 families or where an insufficient number of family members are available to assess linkage patterns, ultrasound evaluation must be used. Because of adverse effects on employment and health insurance, as well as other negative attitudes concerning a definitive diagnosis of ADPKD, early genetic screening for the disease in family members occurs in only a small number of cases. Each of the two children of the patient in our case presentation refused screening for the presence of ADPKD, although if affected, cysts would likely be present on an easy-to-perform ultrasound examination at their ages. Presymptomatic diagnosis of ADPKD carries social risks, such as loss of health insurance, that might outweigh the benefits for an individual patient, given the minimal effect that knowledge of the disease appears to have on childbearing in practice. Education is important for several reasons: patients can better understand the genetics of inheritance and manifestations of the disease, make informed decisions about screening and family planning, and become aware of potential complications such as elevated blood pressure. All family members who refuse screening should be advised to regularly monitor their blood pressure. Past

experience suggests that patient education is an undertaking that requires continued emphasis.

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