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NEPHROLOGY FORUM

Complications of polycystic kidney disease

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Case presentation

A 33-year-old white man first presented to the Royal Infirmary Stirling, Scotland, 24 years ago with a history of recent-onset hematuria. Intravenous urography at that time showed a filling defect in the right kidney; a subsequent aortogram demonstrated a single simple cyst in the right kidney.

Over the next nine years he suffered from occasional episodes of back pain, particularly on the right side. His renal tract was further investigated at the Borders General Hospital 14 years ago because of recurrent urinary tract infections. His blood pressure at that time ranged from 130/100 mm Hg to 170/110 mm Hg. His hemoglobin was 15.7 mg/dl, with a hematocrit of 45.6%. Plasma urea and creatinine were normal at 5.1 mmol/liter (normal, 2.5–6.5 mmol/liter), and 75 μmol/liter (normal, 55–150 μmol/liter) respectively. Cystoscopy showed only moderate bladder inflammation, but a further aortogram at the Royal Infirmary Edinburgh demonstrated enlarged cystic kidneys bilaterally. The right kidney was significantly larger and more cystic than the left; a diagnosis of polycystic kidney disease was made.

Until 11 years ago, the patient's condition was characterized by recurrent episodes of back and abdominal pain, but he was able to continue in his job as a supervisor in a knitwear factory. Cyst aspirations on two occasions conferred some relief of pain. Eleven years ago, he was admitted to the Borders General Hospital with acute-onset chest pain. Acute myocardial infarction was diagnosed on the basis of an increase in cardiac enzymes and anterior T-wave inversion on the electrocardiogram. His hemoglobin was 15.6 g/dl, with a hematocrit of 44.7%; his renal function remained normal. At discharge, therapy with metoprolol, 50 mg twice daily, and isosorbide mononitrate, 40 mg twice daily, had lowered his blood pressure to 110/60 mm Hg. Because of subsequent episodes of chest pain, coronary angiography was performed in Edinburgh. The test showed a dilated left-ventricular cavity with apical hypokinesia and moderate left-ventricular function. The right and left anterior descending coronary arteries were mildly diseased (40%), and a moderately severe stenosis of the circumflex coronary artery (90%) was present. Continued medical therapy over the ensuing few months relieved his chest pain. Unfortunately, his abdominal and back pain continued; upper gastrointestinal tract endoscopy was normal, and an abdominal CT scan confirmed the presence of polycystic kidney disease with no other organ involvement. His blood pressure was well controlled by metoprolol and amiloride.

Six years ago he was again admitted to the Borders General Hospital with an acute right hemiparesis consisting of expressive dysphasia and weakness of his right arm and leg. His blood pressure and renal function were normal, but the hemoglobin was 20.4 g/dl with a hematocrit of 60.6%, and a platelet count of 220×10^9/liter. Blood urea was 8.5 mmol/liter, and serum creatinine was 125 μmol/liter. A cerebral CT scan, showing an axial slice at the level of the pineal, disclosed an ill-defined area of reduced attenuation adjacent to the anterior horn of the left lateral ventricle. No mass effect was associated with this finding and the scan was compatible with a recent infarction (Fig. 1). He made a gradual but satisfactory recovery from his stroke, and regular venesection during the next six months reduced and subsequently maintained his hemoglobin within the normal range. Antihypertensive therapy was continued with metoprolol and amiloride, and aspirin was added to the regimen.

Recurrent back pain continued to dominate his life. As a consequence of his stroke, his job had been downgraded, and increasingly persistent pain was threatening his ability to continue in employment. Episodes of depression responded to medication; intermittent relief continued to be obtained from cyst puncture and removal of fluid from the right kidney. The length of the periods of relief gradually decreased, however, and by last year cyst aspiration was being performed at less than 3-month intervals. Upper and lower gastrointestinal tract endoscopy were normal. A CT scan (Fig. 2) of an axial slice at the level of the left renal hilum disclosed multiple cysts affecting both kidneys, but the left kidney was less severely affected. Most of the cysts lay anteriorly, and the renal parenchymal tissue was well preserved posteriorly. The scan revealed no other organ involvement. Analgesia with a range of therapies was unsuccessful.

Because of the continuing pain, he was seen at the Royal Infirmary Edinburgh late last year for further assessment. He was a 57-year-old nonsmoker who apart from his back pain (particularly on the right side) suffered from occasional angina controlled by glyceryl trinitrate spray. He had a mild expressive dysphasia but no other neurologic deficits. Review of the family history indicated that his mother had died from a ruptured cerebral aneurysm at the age of 67 and might have had renal disease. His father was unknown. He was married with three sons, in one of whom abdominal ultrasound at the age of 28 had revealed no renal or liver cysts. The other two sons had declined medical investigation. The patient's creatinine clearance was 70 ml/min, and a recent isotope renogram showed 29% of function on the right and 71% on the left. His hemoglobin was 16.5 g/dl with a hematocrit of 50.4%. Ambulatory blood pressure monitoring confirmed excellent blood pressure control, although there was loss of diurnal variation (Fig. 3). A T2 weighted cerebral magnetic resonance image (MRI) of an axial slice at the level of the bodies of the lateral ventricles (Fig. 4A) showed a high signal in the ventricles and cortical sulci. In addition, the MRI revealed focal areas of increased signal in the left frontal and temporo-parietal regions; these areas corresponded to areas of gliosis and atrophy secondary to previous infarction. A magnetic resonance angiogram of the intracranial arterial system (Fig. 4B) showed a reduction in the size and number of the branches of the left middle cerebral artery compared with the right. The overall contours of

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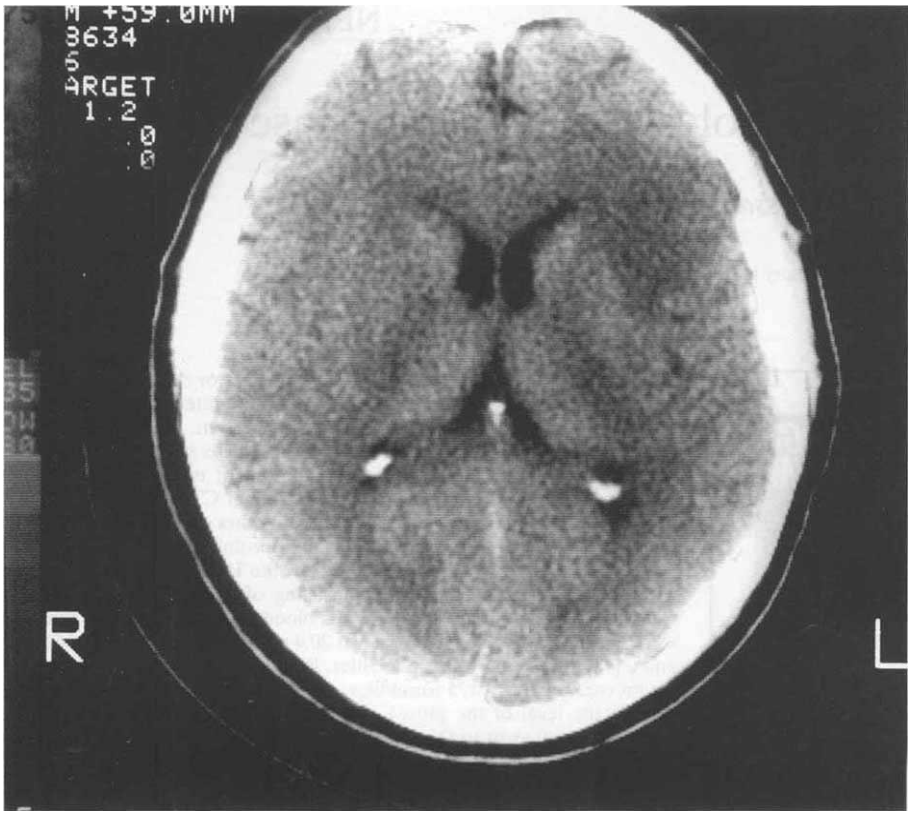

Fig. 1. *Cerebral CT scan at time of developing a right hemiparesis.*

the vessels were smooth, and no focal irregularities suggested the presence of an aneurysm.

Further attempts were made at controlling the back pain with analgesia, but these were unsuccessful. He underwent a laparoscopic right nephrectomy at the Western General Hospital, Edinburgh, early this year with complete relief of symptoms. The kidney contained many large cysts, some containing pus. Histologic examination of the fragments of renal tissue confirmed the presence of polycystic kidney disease. His creatinine clearance of 65 ml/min six months later indicated that his renal function had not changed significantly.

Discussion

DR. MICHAEL L. WATSON (*Consultant Physician, Department of Medicine, Royal Infirmary of Edinburgh, Edinburgh, Scotland*): The patient presented is instructive because of the number of different issues raised in relation to management of patients with polycystic kidney disease and the impact of recent advances in our knowledge of the condition. Although the dominant feature of his recent clinical course has been progressive, intractable back pain, the early part of his history relates to the initial diagnosis of autosomal dominant polycystic kidney disease (ADPKD) and the subsequent acute cerebrovascular event.

Diagnosis

The ready availability of abdominal ultrasound and CT scanning has transformed our ability to diagnose ADPKD. Cysts, however, develop at varying rates and in some instances may not be evident until well into the adult years. For this reason, the usual criteria employed are that there should be two cysts present in one kidney and one in the opposite kidney in those patients with a family history of ADPKD.

Genetic counseling is most valuable if a reliable diagnosis is possible by the patient's reproductive years. Bear et al estimated that a positive diagnosis of ADPKD is possible in 68% of gene carriers under age 30 and 89% over age 30 [1]. Other estimates based on a comparison of gene linkage analysis and ultrasound detection in at-risk families suggest that a sensitivity of detection of 88.5% is possible in individuals under age 30 and 100% in those who are older [2]. As a result of this high sensitivity of detection, Ravine et al suggest a modification of diagnostic criteria on renal ultrasound in patients known to be at risk for the disease. If a patient is less than 30 years old, two cysts whether unilateral or bilateral are sufficient, two cysts in each kidney in the 30- to 59-year-old group, and at least four cysts in each kidney after age 60 [2]. The patient presented is unusual in that only one cyst was evident on arteriography at age 34, but nine years later he had the classic appearance of polycystic kidney disease. This delayed development of cysts might relate to the genotype of his disease.

Cerebral vascular disease

The major concern in any young patient with ADPKD presenting with a stroke is subarachnoid hemorrhage. An association between the two conditions has been known for many years. Recent data from a population of patients with ADPKD suggest that 12% of all affected patients died from a neurologic event, 6% of them from a subarachnoid hemorrhage (mean age, 37 ± 3 years) [3]. Data on the prevalence of unruptured cerebral aneurysms are more difficult to obtain, but will gradually improve as more widespread screening is undertaken. In a large autopsy series, unruptured intracranial aneurysms were identified in 4% of

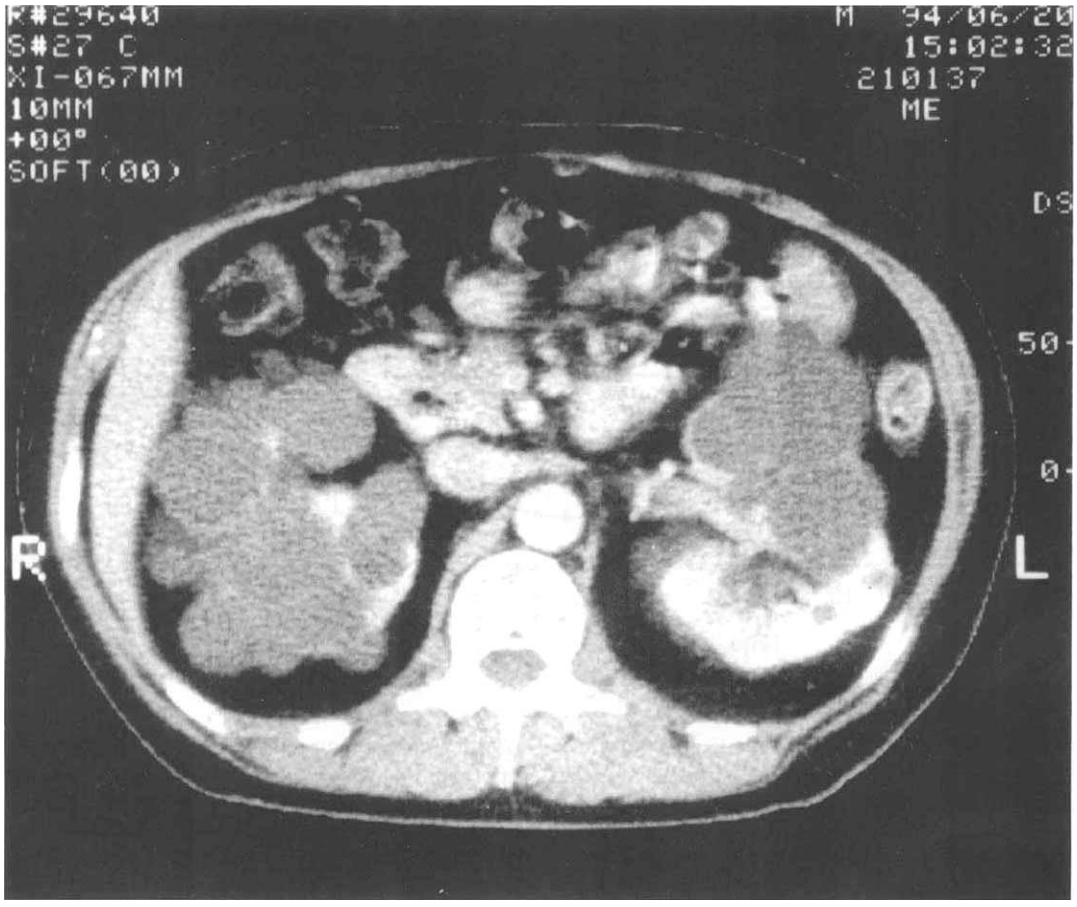

Fig. 2. *Abdominal CT scan showing extensive cyst formation in both kidneys.*

patients with ADPKD who died from unrelated causes [4]. Although this rate is higher than that in the general population, the difference was not significant. Asymptomatic intracranial aneurysms can be identified with either thin-section CT scanning or magnetic resonance angiography (MRA). Combined data from three large prospective studies suggest a prevalence of approximately 8% in the ADPKD population; this figure doubles in ADPKD patients who have a family history of intracranial aneurysm [5–7]. Morbidity and mortality after rupture of an aneurysm are high. In the autopsy series from the Mayo Clinic, mortality six months after rupture was 55% [4], although in a more selected European population, overall mortality was 10%, but 43% of those surviving beyond three months after rupture had severe neurologic disability [8].

The patient discussed today had no clear evidence that a ruptured cerebral aneurysm caused his stroke. Subsequent investigation of his cerebral circulation by MRA was justified, however, both because of the positive family history and the high risks associated with the presence of an unruptured cerebral aneurysm. The most important determinant of whether an aneurysm will rupture appears to be its size. In a series of otherwise normal patients with unruptured cerebral aneurysms followed for eight years, all the ruptures occurred when the aneurysm was greater than 10 mm in diameter [9]. Similar data are not yet available for a population of ADPKD patients, but prospective studies are currently underway.

The annual incidence of rupture in the general population seems to be much the same whether or not the patient has had a previous episode of rupture: approximately 1.4% [10]. Similar observations have been made in a group of ADPKD patients followed for a mean of eight years after surgical clipping of a ruptured aneurysm [8]. Followup screening by MRA after an episode of rupture therefore seems fully justified in this population, but the broader issue of the risks and benefits of routine screening of the cerebral circulation in all patients with ADPKD remains more controversial [11].

Other potential causes of stroke in today's patient were an intracerebral hemorrhage or cerebral infarction. Intracerebral hemorrhage is much more likely if hypertension is present, accounting for nearly one-half of the deaths from neurologic events in the Denver series [3], with a significantly higher age at death (51 ± 3 years) by comparison with deaths from subarachnoid hemorrhage.

It is perhaps surprising that cerebral emboli are not more commonly associated with ADPKD. A variety of studies have indicated a high incidence of cardiac valvular abnormalities, both in life and at autopsy [3, 12, 13]. The mitral valve is most commonly affected, with as many as 26% of affected patients showing evidence of valve prolapse, whereas tricuspid prolapse was present only in 6%. Interestingly, although there was no evidence of aortic valve prolapse on two-dimensional echocardiography, there was a significant increase in aortic regurgitation

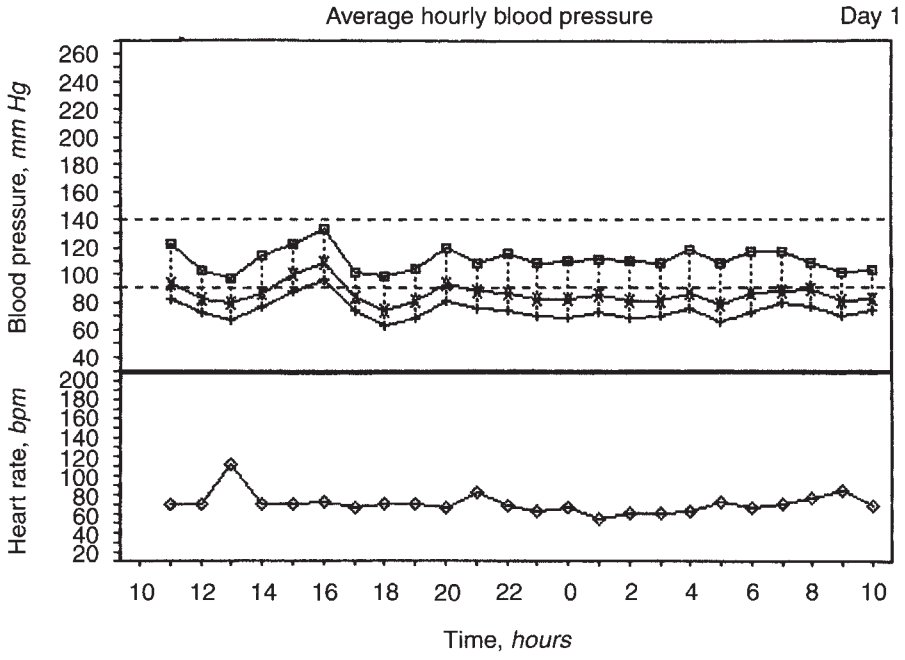

Fig. 3. *Ambulatory blood pressure profile while patient was on therapy with metoprolol and amiloride, therapy being taken at 0900 hours.* Symbols are: (■) systolic BP; (+) diastolic BP; (×) mean BP; (◇) heart rate.

compared to controls [13]. Yet little evidence indicates that these abnormalities are a major cause of death, or that the valve defect acts as a source of cerebral emboli.

It is highly likely that secondary polycythemia in this patient contributed to his stroke. Polycythemia is a rare but well-described complication of ADPKD [14, 15]. Most likely it relates to excessive production of erythropoietin [16], probably from interstitial cells adjacent to cysts. It is interesting that after the initial reduction of his hemoglobin, further increases could be prevented by comparatively infrequent venesections. From the patient's perspective, perhaps the most encouraging features of his illness were the extent of recovery since his stroke and his ability to continue in a demanding occupation until chronic pain disrupted his work pattern.

Chronic pain

Chronic intractable pain, at least in the early stages of ADPKD, is well documented [17]. This patient suffered from loin pain for 18 years although cyst puncture, at least initially, provided long periods of relief. The value of cyst aspiration in relieving the pain was clear, but characteristically the relief provided by further cyst aspirations lasted for shorter and shorter periods [18]. In my experience, injection of a sclerosing agent such as alcohol, while of value in the treatment of a single cyst, has not been successful in ADPKD [19]. For this patient, continued treatment of pain with a variety of agents was increasingly ineffective. The opiate-based analgesic led to drowsiness and a restricted ability to work.

No satisfactory studies exist on the best analgesic for use in patients with ADPKD; the best guidance, therefore, is to follow the principles used in other forms of chronic pain relief [20]. The persistence of severe pain in ADPKD is well known [21] and the complication of associated depression, as in this case, is not uncommon. Tricylic antidepressants can be useful both as an antidepressant and as an adjuvant analgesic. Clearly, therapy has to be tailored to the individual. In this case, the persistent severity of the pain so disrupted the patient's quality of life that a surgical approach finally was used to relieve the problem.

Laparoscopic cyst decompression versus nephrectomy

In today's patient, a relatively noninvasive surgical approach was desirable because of the history of myocardial infarction and a major cerebral event, although control of blood pressure was unlikely to be a problem during anesthesia. Surgical decompression has been used effectively for pain relief [22]; a decline in renal function following decompression, which has been of concern, is probably not of great significance [23]. Laparoscopic cyst decompression has been used effectively for treatment of pain [24]. In our patient, the absence of guidance as to which of the multiple cysts might be responsible, and the patient's unwillingness to undergo further cyst decompression (because of his persisting doubts as to the long-term benefit), led us to choose a complete laparoscopic nephrectomy. The subsequent finding of infection in the resected kidney probably contributed to the severity of the pain. Urinary tract infection is very common in ADPKD, and infected renal cysts are difficult both to diagnose and treat [25].

Laparoscopic nephrectomy is an established procedure, but its use for removing a polycystic kidney has not been documented. The subsequent success of nephrectomy in providing almost complete symptomatic relief was satisfactory, but there were and there remain concerns about the effect of nephrectomy on the rate of decline of renal function in the remaining kidney.

Blood pressure, renal function, and cardiovascular disease

The patient's blood pressure always was easy to control, and his renal function was reasonably well preserved. I will discuss the implication of these findings in relation to the underlying gene defect later. Part of the reason for the relative ease of blood pressure control might have been the myocardial infarction 10 years previously, but other factors such as the presence of large kidneys [26] suggest that hypertension could have been more of a

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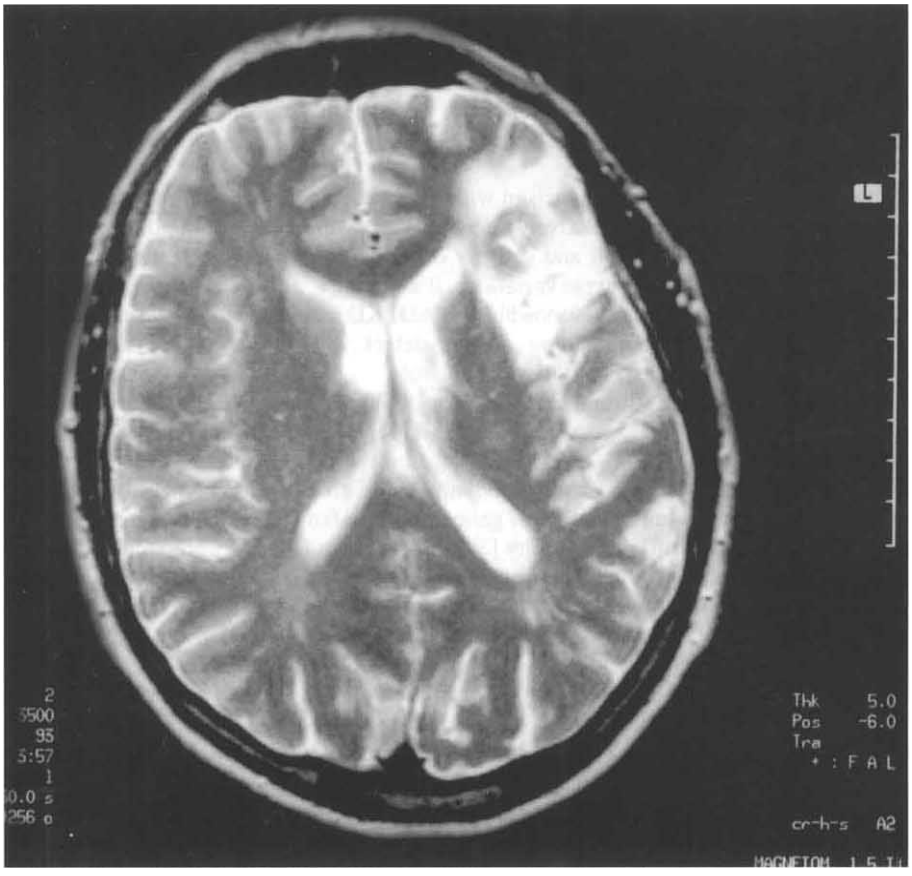

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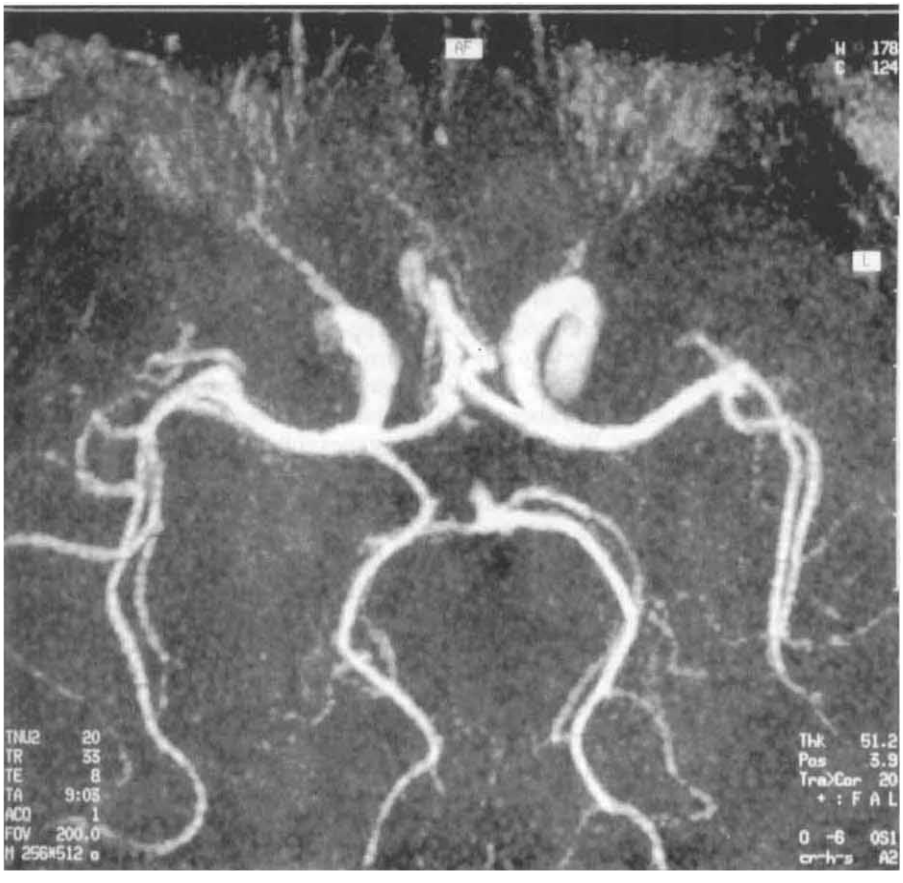

Fig. 4. A. *Cerebral magnetic resonance imaging five years after cerebral infarction.* **B.** Cerebral magnetic resonance angiogram.

problem. The importance of hypertension relates both to the acceleration of renal impairment and also to progression of concomitant vascular disease. Hypertension develops very early in the course of ADPKD; significant increases are evident by adolescence [27], with a subsequent progressive rise with age [28]. The early rise in blood pressure correlates with the presence of target organ damage in the form of left-ventricular hypertrophy [27]. A significant factor contributing to the development of target organ damage also might be an increased "blood pressure load" over 24 hours as a consequence of the loss of the usual nocturnal fall in blood pressure [29] or an elevation in nocturnal pressure [27]. Although overall blood pressure control was very good in this patient, he did have a loss of diurnal variation of blood pressure in the 24-hour recording. The extent to which good blood pressure control in this patient has delayed the progression of renal failure must be speculative. It is disappointing, however, that the studies available to date in patients with ADPKD do not show any value of tight control of blood pressure, at least over a relatively short time period (2 years) in patients with established renal failure [30].

Much of the focus of blood pressure research has been in relation to preservation of renal function, but as survival with dialysis and after transplantation improves, broader issues emerge. This patient had significant atherosclerotic vascular disease at an early age that led to myocardial infarction and probably cerebrovascular disease. While these events might reflect only the high incidence of atherosclerotic vascular disease in the Scottish population, evidence suggests acceleration of vascular disease in ADPKD [3, 31–33]. The extent to which a long-standing modest elevation in blood pressure contributes to vascular disease is unclear, but it does emphasize the importance of considering delayed progression of generalized vascular and particularly coronary artery disease as one of the potential benefits of good blood pressure control.

End-stage renal failure is reached more rapidly in males affected with ADPKD than in females [34], with a mean age of reaching dialysis of 52.5 years in males and 58.1 years in females. Recent clarification of genetic heterogeneity does indicate, however, a separate group of patients (type-2 disease) in which progression to end-stage renal failure is delayed, and hypertension is less severe [35]. Knowledge of the individual genotype of patients therefore will assist in providing a firmer basis on which to judge their prognosis. I'll return to this issue shortly.

In the patient we are discussing, the clinical desirability of removing the right kidney to control pain had to be tempered by the potential for more rapid progression to end-stage renal failure. Not only was a small, albeit significant, amount of functioning renal tissue being removed, but also the possibility existed that the removal of one kidney might, as a consequence of glomerular hyperperfusion, accelerate the decline in renal function of the remaining kidney. Reassurance was gained from the collaborative study by Zeier and colleagues, who demonstrated that the rate of decline of renal function after uninephrectomy in ADPKD did not differ significantly from the rate of decline of renal function in patients with two kidneys [36]. In this case, the right kidney provided only 29% of function, giving an estimated glomerular filtration rate (from creatinine clearance) of 41 ml/min in the left kidney. In fact, measurement of creatinine clearance six months post nephrectomy suggested that the renal function had not significantly declined further. Uninephrectomy has been reported to exacerbate hypertension [36], but in this case the hypertension was not difficult to treat and renal function, at least in the residual kidney, was well preserved.

Genetics

In comparison with many affected individuals, this patient has had a relatively benign course with respect to the decline in renal function and severity of hypertension. Before we examine these phenotypic variations, it is perhaps worth considering the genetic defect responsible for ADPKD and the way in which improved understanding of this defect will in due course allow better characterization of patients.

Although the pattern of inheritance of ADPKD was described many years ago [37], the identification of linkage between alpha globin and ADPKD located the gene defect on the short arm of chromosome 16 [38] and led to an explosion in investigative work. Initial studies of gene linkage in families failed to detect evidence of heterogeneity [39], but as more families were studied, heterogeneity was confirmed, and further linkage analysis studies have led to the localization of a second gene (type-2 disease) to chromosome 4 [40–43]. The relative prevalence of type-1 versus type-2 disease is approximately 85% to 15%, but a paucity of families with type-2 disease has restricted an understanding of its clinical significance. Increasing evidence suggests that type-2 disease has a better prognosis than type-1, particularly with regard to development of end-stage renal failure [35]. Appearance of the kidneys on ultrasound examination is similar, although more extensive cyst development often occurs in type-1. Therefore, without genetic studies, identification of patients with type-2 disease must be speculative. In today's patient, the late development of cysts, the mild hypertension, and the relative preservation of renal function favor type-2 disease, as does the absence of renal failure in the known affected relative. Confirmation of the presence of type-2 disease requires a larger pedigree for analysis than was available in this instance. In practice, genetic testing in a family such as this must await the delineation of mutations in the relevant genes that can then be identified in affected individuals. Recent identification of other pedigrees unlinked to either the type-1 or type-2 locus raises the possibility of yet further genetic heterogeneity (type-3 disease) [44].

Because of technical difficulties, it has taken almost 10 years to clone and sequence the type-1 ADPKD gene since its initial localization to the short arm of chromosome 16. It is a large, complex gene with large regions of the gene being reiterated three times elsewhere on the same chromosome—homologous gene areas. Whether these other genes code for specific proteins is not yet known. The presence of the homologous gene areas has caused considerable confusion when researchers have attempted to isolate cDNA relating to the ADPKD gene alone [45, 46]. The crucial breakthrough in isolating the gene came with the identification of a family with tuberous sclerosis type II (TSCII) and polycystic kidney disease [47]. Polycystic kidneys have been described both in tuberous sclerosis type I and type II [48]. Because TSCII and ADPKD are linked to loci on the C16 chromosome, a causative link between the two has been suggested [49], but renal cysts also occur in patients with TSCI, which is linked to chromosome 9 [50]; this finding makes such a direct relationship unlikely. Using a positional cloning strategy, the European Chromosome 16 Tuberous Sclerosis Consortium identified the gene for TSCII on chromosome 16 [51]. One particular family from Portugal,

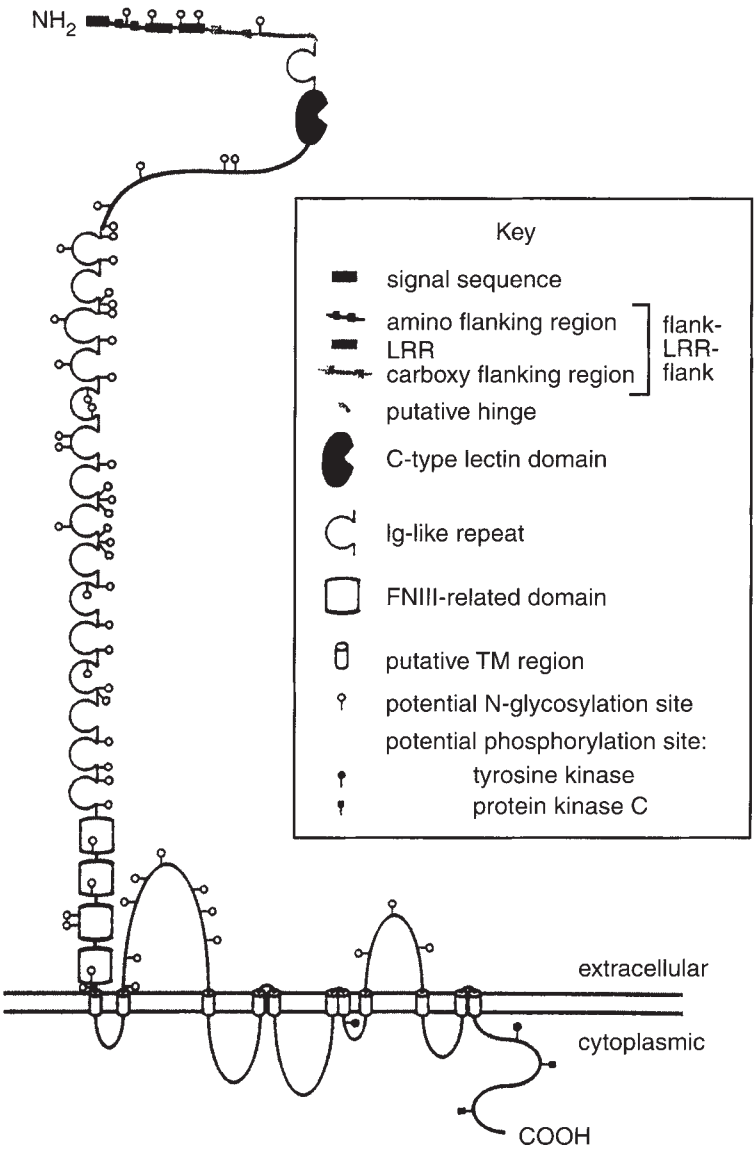

Fig. 5. *Predicted molecular structure of polycystin (from Ref. 46).*

however, had a pedigree in which different family members exhibited one or both of the typical phenotypes of ADPKD and TSC. Family members in two generations showed a 16:22 balanced chromosome translocation; both these individuals had ADPKD. The break point for the translocation on chromosome 16 was localized within 16p13.3 (the area known to contain the PKD1 gene), and the gene disrupted was labeled the polycystic break point gene (PBP). In another family member, the translocated section of 16p13.3 16pter was deleted, resulting in TSCII. This finding confirmed the extremely close proximity of the PBP and TSCII genes. The PBP gene is in fact the PKD1 gene [47].

A number of point mutations or small deletions have been identified in the type-1 gene, but because of the technical difficulties associated with eliminating the homologous gene sequences, all these are located towards the 3′ end of the gene [46, 52]. To date, the mutations identified account for only a small number of the presumed mutations in affected families. The ADPKD 1 gene is large, containing 14,148 base pairs divided into 46 exons. Thus it is possible that some of the mutations identified to date merely represent polymorphisms that do not significantly disrupt the normal functioning of the gene. It also is possible that some mutations lead to only a partial loss of gene function and a relatively mild phenotype, whereas complete deletion of the gene, as seen in certain infantile cases of ADPKD associated with TSCII, leads to a very severe form of cystic kidney disease [53]. It seems likely that large numbers of mutations remain to be identified and probably will reflect a relatively high new mutation rate.

Cloning of the PKD1 gene rapidly led to detailed nucleotide sequencing and prediction of the protein structure. Very similar results were reported by independently operating groups [45, 46, 54]. The PKD1 protein has 4302 amino-acid-containing sequences that have characteristic functions in other known proteins (Fig. 5). The two leucine-rich repeat sequences close to the 5′ end are placed between cysteine-rich flanking regions. This placement is characteristic of proteins in extracellular locations involved in

protein-protein interactions, such as cell recognition, signal transduction, or binding to components of the extracellular matrix [55].

The type C lectin domain probably binds carbohydrates in the presence of Ca^{++}, permitting interaction with other glycoproteins involved in cell recognition and adhesion functions [56]. The immunoglobulin-like repeat sequences and fibronectin III-related domain reported by Hughes et al [46] differs slightly from the sequences reported by the International Consortium [45]. Differences in the reported length of the transmembrane domain also make it difficult for us to be sure whether polycystin is totally extracellular or membrane bound. The charged residues in the C-terminal end would certainly be consistent with a cytoplasmic terminus. Whatever its exact function, polycystin likely plays an important role in the interaction between tubular epithelial cells and the basement membrane.

A number of different groups have raised antibodies to polycystin. Because of the difficulty of the homologous gene sequences, however, all these antibodies are related to the C-terminal end of the molecule. Polycystin is expressed in renal tissue early in fetal development, but results vary regarding the exact location within the kidney, particularly whether expression is restricted to the distal tubular epithelial cells or present in the glomerulus and proximal tubule [57, 58].

Recent cloning of the PKD2 gene has provided further insights into the complex role played by membrane proteins in the genesis of polycystic kidney disease [59]. Flanking markers for PKD2 gene were first reported in 1993 [42, 43]. The genetic interval subsequently has been further refined by identification of other polymorphic markers, allowing the construction of a contig of approximately 680 kb spanning the region of interest. A candidate gene that was expressed in most adult and fetal tissues was isolated from this region. Moreover, analysis of potential reading frames demonstrated homology to significant proportions of the amino acid sequences with those in polycystin. Confirmation that this site is likely to be the PKD2 gene came from analysis of three separate type-2 families in which each affected individual was heterozygous for a single base pair change resulting in a nonsense mutation.

The as-yet-unnamed putative translation product is a protein with 968 amino acids; approximately 25% of the sequence is identical with polycystin and 50% is similar. Many of these similarities are in the transmembrane region, indicating a similar role as a membrane protein. Significant homology also exists between other regions of the PKD2 protein and a family of voltage-activated calcium^{++} and sodium$^{+}\alpha_1$ channel proteins. The authors speculate that PKD2 protein and polycystin function in parallel, perhaps as a common signal transduction pathway.

These extraordinary genetic advances are set to transform knowledge of the pathophysiology of PKD. Mutational analysis of PKD2 families will be rapid, whilst other advances are likely to overcome the confounding problems of the homologous gene sequences in detecting PKD1 mutations. The impact of these advances on the practice of nephrology will be significant.

Questions and answers

DR. JOHN T. HARRINGTON (*Dean ad interim, Tufts University School of Medicine, Boston, Massachusetts*): Thank you very much, Dr. Watson, for a superb review of some of the complications of polycystic kidney disease and for updating us on the genetics of PKD. We have several individuals in the audience who are quite knowledgeable about polycystic kidney disease and I hope they will participate in our question and answer period. Let me start by asking a question about the definition. I believe you defined PKD clinically as at least two cysts in one kidney and one cyst in the opposite kidney. Yet you also said that we need to distinguish patients with true PKD from patients with multiple benign cysts who do not have polycystic kidney disease. In the absence of genetic analysis, how does one manage that feat?

DR. WATSON: It can be difficult. The definition that you have given is satisfactory if there is a family history of ADPKD. If there is no family history, it is still relatively straightforward if there is widespread renal involvement with multiple cysts, but in milder forms, differentiation from simple renal cystic disease can be difficult. David Ravine's data do give some guidance by building in a correction for increased number of simple cysts that occur with age [2]. Therefore, by age 60, the requirement for diagnosis is four cysts in each kidney. With some cases, however, diagnosis can be difficult, and to some extent relies on the subjective impression of the radiologist. An additional problem is that cysts may develop more slowly in type-2 disease.

DR. HARRINGTON: Are there studies on the use of angiotensin converting enzyme inhibitors in patients with polycystic kidney disease and hypertension? We finally have evidence that ACE inhibitors delay the progression of renal disease in diabetic renal disease [60]. Are similar data available in patients with polycystic kidney disease?

DR. WATSON: Angiotensin-converting-enzyme inhibitors lower renal vascular resistance in patients with ADPKD and therefore might have beneficial effects in managing hypertension and preserving renal function [61, 62]. A long-term prospective study is currently underway in Europe to try to determine their value early in the course of the disease. Unfortunately, it will be some years before the results are available.

DR. YVES PIRSON (*Cliniques Universitaires Saint-Luc, Brussels, Belgium*): Congratulations on your interesting discussion covering many aspects of polycystic kidney disease. I also have a question relating to the management of hypertension. In view of the relative polycythemia, wouldn't an ACE inhibitor have been a better choice of antihypertensive than a diuretic?

DR. WATSON: I agree. I think first-line therapy for most patients with ADPKD would be an ACE inhibitor, a beta blocker, or a calcium antagonist, and this is particularly true in the presence of polycythemia.

DR. PIRSON: Could you comment on the disappointing results of the MDRD study in the United States regarding the management of hypertension?

DR. WATSON: The Modification of Diet in Renal Disease Study focused on patients who already had significant renal damage and whose glomerular filtration rate was 25–55 ml/min/1.73 m^2 [30]. Stringent blood pressure control and protein restriction appeared not to confer any advantage so far as limiting the rate of decline of renal function, when compared to patients managed with conventional blood pressure control and protein restriction. This result is disappointing, but it is worth emphasizing that most of the patients had significant renal impairment. We are particularly curious as to whether stringent blood pressure control provides benefits when begun very early in the course of disease, before impairment of renal function is detectable.

DR. EBERHARD RITZ (*Klinikum der Universitat Heidelberg, Heidelberg, Germany*): I would like to add an additional comment to

Dr. Watson's response. The MDRD study compared two regimens for controlling blood pressure. One was regarded as having acceptable clinical levels for blood pressure control in patients with renal disease (mean BP < 107 mm Hg in patients age 18–60) and the other a regimen that aimed to achieve stringent blood pressure control (mean BP < 92 mm Hg). What the study did not demonstrate was that blood pressure wasn't important in renal disease, but merely that stringent blood pressure control in patients with renal impairment did not confer an added advantage. The clinical imperative of satisfactory blood pressure control in patients with renal impairment remains.

DR. HARRINGTON: The cerebral MRA study was negative in this individual. Is there a higher false-negative rate if one compares MRA with conventional cerebral arteriography for the detection of cerebral aneurysms?

DR. WATSON: Dr. Allan, perhaps you would respond to that question.

DR. PAUL ALLAN (*Consultant Radiologist, Royal Infirmary, Edinburgh, Scotland*): Magnetic resonance angiography is coming along very nicely, but I don't think it is yet as good as digital radiographic images. Proponents of MRA say it's wonderful; I think the people who tend to be a little more objective about it would say that for some small aneurysms, less than about 3 mm in diameter, there is a significant risk of missing them with MRA.

DR. HARRINGTON: I have a followup question regarding MRA. In a patient like this, who had a major cerebral event and a negative MRA, should one proceed with conventional cerebral arteriography?

DR. ALLAN: The event on CT scan of the brain in this patient was typical of a thrombotic event rather than a hemorrhagic event. The clinical picture and the CT scan were not that suggestive of a subarachnoid hemorrhage, so I think probably in this case, no. Had there been the least suggestion that this patient had suffered a subarachnoid hemorrhage, but had a negative MRA, then it would be mandatory for us to do a conventional angiogram.

DR. ALEX DAVISON (*Consultant Renal Physician, St. James's Hospital, Leeds, U.K.*): This patient seems to be very unusual in that cysts totally destroyed one kidney and appear to involve just the anterior half of the left kidney, with quite a lot of normal-looking kidney behind it. How often do you see that sort of disparity in the distribution of cysts?

DR. ALLAN: Not that often. I believe that it would be most unusual to see this appearance in a 58-year-old patient with type-1 PKD. One of the reasons we chose this patient was precisely because of his unusual presentation, and because his renal function was relatively well maintained by the residual cortex. Normally it is a diffuse field change throughout the kidneys, and to see such a significant portion of normal kidney is, in my experience, rare in this age group.

DR. DAVISON: I have two questions that relate to the surgery. First, I found it interesting that you removed the kidney laparoscopically instead of with a more conventional approach. Second, was this specimen examined histologically to see whether there was malignant change in any of the cysts?

DR. WATSON: Perhaps it would be best if we asked the surgeon to respond to your question.

DR. DAVID TOLLEY (*Consultant Urologist, Western General Hospital, Edinburgh*): Thank you. First let me answer Dr. Davison's question about the pathology. Certainly it was an unusual kidney in that many of the cysts were full of infected fluid and were not full of blood as we so often see. In retrospect, I think that a lot of this man's pain was due to recurrent infection. There was no evidence of malignant change.

Now I will comment on some of the surgical aspects of this case. Our considerable experience with laparoscopic nephrectomy in Edinburgh confirms that this is a good and safe technique for patients with benign renal disease. A comparison of some 60 patients undergoing laparoscopic nephrectomy with a contemporary series of patients undergoing standard nephrectomy demonstrated that blood transfusion requirements and duration of hospital stay were significantly lower in the laparoscopic group [63]. Postoperative morbidity is reduced and the procedure is safe. In our hands, these benefits are at the expense of a minimally increased operating time of some 15 minutes. We believe, however, that the benefits to the patients who have a laparoscopic procedure are so great that the brief increase in operating time is of little or no significance. The difficulties in performing laparoscopic nephrectomy for polycystic disease relates largely to the size of the kidney and its subsequent removal. The cysts often obscure the renal pedicle, and thus it is necessary to puncture a number of cysts around the hilum to identify the vessels clearly. Having completed the dissection, one must then place the grossly enlarged kidney in an impermeable sac and then morselate the kidney whilst it remains in the sac, removing portions of the kidney piecemeal. The worldwide experience of laparoscopic nephrectomy for polycystic disease is limited to a handful of cases, but our experience with laparoscopic nephrectomy compares favorably with that reported in the literature and, in experienced hands, this technique offers significant advantages over conventional surgery [64].

DR. HARRINGTON: It seems that there was significant infection in a number of cysts. What techniques are available to identify cyst fluid, hemorrhage, or infection in cysts?

DR. WATSON: It is very difficult to detect infected material. Dr. Allan could comment on the scanning appearances, but I think it difficult to detect infection other than by direct aspiration, systemic features of infection, or both.

DR. ALLAN: It has been a great problem over the years, and my heart always sinks when I am sent a patient with polycystic kidney disease, because finding infection or hemorrhage is very difficult. Occasionally we identify on ultrasound a particular cyst that has increased echoes within it; we then put a needle into it and get back pus or blood, but echogenic cysts can have debris in them from previous episodes of infection. Quite often you can become disoriented; some of these large kidneys can be 22 cm long by 10 to 12 cm wide, and the ultrasound image does not reveal the whole kidney. I think we will probably look to MRI scanning in the future for these patients. Based on my anecdotal experience of two cases, I think that this technique has the potential to identify cysts with different fluid consistencies within them. One patient had apparently normal cystic appearances on CT and ultrasound. But an MRI scan on one of our old machines, a very low field strength machine, showed a cyst with fluid in it that we were able to identify on ultrasound and aspirate with a 20 gauge needle. I think that the development of MRI techniques offers great potential for our being able to distinguish an old from a recent hemorrhage and to identify the fluid in a cyst without pus or blood in it.

DR. LIAM PLANT (*Royal Infirmary, Edinburgh*): The literature contains quite a few studies from in-vitro systems on the transfer

of different types of antibiotics into cysts [25]. The suggestion has been made that aminoglycosides and penicillins concentrate poorly in some types of cysts and that quinolones perhaps do so better. Is there a clinical advantage to using antibiotics of that type in trying to eradicate infection?

Dr. Watson: In my experience, no. I couldn't say that there is an advantage either way. Most of the data from the literature rely on measuring antibiotic penetration in cyst models. I don't know of any clinical studies that have looked at the outcome of treatment of cyst infection with different antibiotic regimes.

Dr. Plant: Do you think ambulatory blood pressure monitoring should become standard clinical practice in light of the increased risk of end-organ hypertensive damage in these patients?

Dr. Watson: I am very impressed by the value of 24-hour ambulatory blood pressure monitoring for providing a much better assessment of overall blood pressure control. I think that quite often the random clinic pressures that we obtain do not give a clear picture. Questions remain about the significance of the lack of diurnal variation of blood pressure, and we are trying to obtain better evidence as to whether good control of nocturnal blood pressure assists in delaying progression of the complications of the disease. Clearly these would be difficult long-term studies, but in the meantime I think there is every clinical justification for trying to achieve smooth blood pressure control throughout a 24-hour period.

Dr. Harrington: What have we learned about the fundamental reason for the progression of polycystic kidney disease? I was taught many years ago that it might be cyst enlargement, that it might be interstitial damage, that it might be hypertension, and that it might be infection. Well, it's 30 years later and I still have all of these "might be's." What do we know now about the causes of progression of PKD beyond hypertension and infection?

Dr. Watson: Three main mechanisms apparently are involved in the progression of damage. Unfortunately, our knowledge of the relative contribution of each of these mechanisms remains poor. They are: epithelial cell proliferation, cyst fluid accumulation, and interstitial damage. Although the relationship among these three factors remains unclear, it can only be a matter of time before the recent work on polycystin and its role in membrane function and interaction with the interstitium will provide us with better answers about the underlying pathologic process.

Dr. Christopher Isles (*Dumfries and Galloway Hospital, Scotland*): How often do you see this rapid progression from someone who at 34 has one simple cyst and then nine years later has extensive bilateral polycystic kidney disease?

Dr. Watson: I think this is really unusual, and that is part of the reason why we presented the case. The possibility remains that some of the cysts weren't identified by arteriography because of the relative insensitivity of this technique for finding cysts, but it does seem remarkable that there was such an obvious progression over a relatively short period.

Dr. Isles: In that case, does this individual fall into a particular category or is he a "one-off" patient?

Dr. Watson: I think he more closely fits into a type-2 PKD category. The relatively low level of blood pressure, the preserved renal function, and the late development of cysts all point to type-2 PKD. Cases such as this demonstrate the potential value of a clear definition of the mutations in type-1 and type-2 so patients can be correctly categorized and counseled about prognosis.

Dr. Allan: It is worth emphasizing that intravenous urography and arteriography will show large cysts but will not show small developing cysts that are not yet big enough to distort either the vessels or the pelvicalyceal system. These examinations are fairly crude tests that have been supplemented by the more sensitive ultrasound and CT scans. It may well be that at the time of his original arteriogram, this patient did not have just a single cyst but in fact had one dominant single cyst and several smaller ones that were too small to be seen with these relatively crude diagnostic techniques.

Dr. Isles: I still feel a bit uncomfortable about diagnosing this condition in, say, someone with three cysts and normal renal function with no family history.

Dr. Watson: I agree with your sentiments, but I think that in the absence of satisfactory genetic information, this is when one has to rely on the subjective opinion of the radiologists.

Dr. Harrington: I alluded to this question earlier. Should we be doing genetic analysis in all these patients rather than trying to hazard a diagnosis on the basis of ultrasonography?

Dr. Allan Wright (*Western General Hospital, Edinburgh*): Mutational analysis is a major problem with the PKD1 gene for a number of reasons. First, the gene is unusually large. The coding regions of most genes cover 1000–2000 nucleotide base pairs (1–2 kb) of DNA; the PKD1 gene is 14kb long. Second, the coding regions are broken up into 46 exons, each separated by large non-coding or intronic regions. What one would normally do to look for mutations would be to analyze the exons in turn using DNA primers flanking each exon. There is a rather simple technique called single-stranded conformational polymorphism (SSCP), which is suitable for mutation screening in small exons. The gene from Marfan's syndrome, fibrillin, is another large gene that can be conveniently analyzed in this way, except that it is a big job, since there are also many exons.

In the case of PKD1, there is a further complication. Because of the homologous gene areas, about 60% of the gene is duplicated elsewhere on chromosome 16. There are two or three copies in distinct genes at other sites on chromosome 16. These other regions are so homologous with PKD1 that it is currently impossible to distinguish which gene you are looking at when analyzing the exons that are duplicated.

The second approach, which is probably more promising, is analyzing the gene as a whole from a fresh blood sample. This is possible because even a low level of transcription of PKD1 within blood cells is detectable by polymerase chain reaction (PCR) amplification. The advantage of this technique is that the reverse transcribed/PCR amplified gene detected in blood is fully spliced with no intervening sequences remaining. However, it is still a major problem to analyze this gene for mutations because of the strong homology to other genes.

If mutation analysis cannot help with early diagnosis, what other approaches can be used? One is the conventional linkage approach. Generally this method requires the availability of at least two affected family members for sampling. The patient discussed did not have this setting, although it is possible that archival material on the presumed carrier relative who died—his mother—might solve the problem and make it possible to exclude chromosome 16 by linkage. Of course, this is a much easier analysis to carry out. It does raise the question, what is the current clinical relevance of isolating the PKD1 gene? Within a reasonable period of time, it might be possible to have specific primers

that can distinguish the true PKD1 from homologous genes and allow conventional mutation analysis. This advance in turn might give information on prognosis in the individual patient, since particular mutations may be associated either with a mild disease or a severe, early-onset condition. Such an advance might have implications for patients considering predictive testing and potential termination of affected pregnancies. In the case of this particular family, the disease is relatively mild, so termination would probably be inappropriate. Even in families segregating for severe, type-1 disease, however, most individuals decline prenatal diagnosis [65, 66]. I suppose it boils down to the fact that DNA-based prediction could be useful in establishing the prognosis for the three sons who are at risk of developing the disease. This information might help with their management, but the real value of genetics is yet to come, when we find out more about the function of the PKD1 gene and new ways of treating PKD1 patients.

Dr. John Donohoe (*Consultant Nephrologist, Beaumont Hospital, Dublin, Ireland*): I would like to ask one further question in relation to imaging and diagnosis of polycystic kidney disease. What added diagnostic value is the presence on ultrasound of liver and/or pancreatic cysts?

Dr. Allan: If you have, say, a 45-year-old patient with a few cysts in a kidney who has liver cysts as well, then you are well on the way to making the diagnosis. I think the whole question about diagnosis and definition is very difficult; the last thing you want to do is label someone as having polycystic kidney disease when they do not. We try to be very cautious. A 1983 study on the incidence of simple cysts in patients who were having CT scans for nonrenal disorders showed that having more than one simple renal cyst was very unusual in patients under the age of 40 [67]. I think that the presence of cysts in the liver does add more diagnostic weight than do cysts in other organs such as the pancreas.

Dr. R. Bernd Sterzel (*Universität Erlangen-Nurnberg, Erlangen, Germany*): There remains the clinical problem of what can be done to help these patients. Years ago, cyst puncture or surgical "deroofing" was a popular technique. This approach fell out of favor, particularly the aggressive surgical techniques, because of a suggestion that they may have either caused a deterioration in renal function or, at best, yielded no significant improvement. Have the advent of laparoscopic techniques and the ability to identify cysts more accurately changed this opinion, and should selective cyst aspiration be more widely used in the future?

Dr. Tolley: We are often called upon to perform nephrectomy for patients with unremitting pain from polycystic kidneys. There are the problems of operating on patients with polycystic renal disease and also the subsidiary issue of laparoscopic nephrectomy. The major problems we face as surgeons are being asked to deroof or decompress cysts and to identify which of the cysts are symptomatic and therefore require decompression. Laparoscopy is an all-too-convenient and easy way of examining the kidney; therefore the temptation to intervene surgically is perhaps much greater than it was four or five years ago. For *solitary* cysts we still recommend a relatively conservative approach with cyst aspiration and sclerosing therapy. If this fails, laparoscopic partial excision of the cyst wall is an effective treatment. However, it is difficult to adapt this technique for the patient with polycystic renal disease because of the difficulties of specifically identifying the cyst or cysts responsible for the patient's symptoms.

Dr. Allan: Could I make a comment on aspirating cysts? One of the reasons for aspiration, other than hemorrhage or infection, is pain and discomfort. The reason for the pain and discomfort is the stretching and pressure on the renal capsule. The problem about polycystic kidneys and also polycystic livers is that the cysts are almost "alive," and if you take one away you disturb the very fine balance of pressures and counterbalances present in the kidney. Then another cyst will enlarge over a period of a week or so to replace the missing volume; eventually you have quite a difficult problem. You end up putting needles into four, five, or six cysts and hoping that you are taking away enough mass to produce pain relief.

Dr. Ritz: I notice that two of the offspring refuse to have screening. What do you think is the importance of screening, and is there a price to be paid once the relatives have been screened? For instance, what would screening do to their insurance?

Dr. Watson: I think there are major ethical issues involved in screening, and these are likely to be increasingly important. In the absence of a specific clinical indication, it is doubtful whether patients should be screened before age 18. If a child from an affected family develops a symptom that could be a consequence of ADPKD, such as loin pain, urinary tract infection, or severe headache, screening can be justified, because our knowledge as to whether the patient is affected can significantly influence clinical management. In the absence of such symptoms, it is better to undertake screening with the informed consent of the individual, that is, ideally after the age of 18. The difficulty arises in relation to blood pressure and, to a lesser extent, renal function. We know from Heidelberg data that increases in left-ventricular mass index are already evident in affected adolescents [27]; this finding suggests that early treatment of even mild hypertension is appropriate. Alternatively, all the children of affected families should have their blood pressure and renal function checked at perhaps two-year intervals to allow early intervention. The key factor in favor of screening is whether effective therapy is available that can significantly alter the course of the disease in young affected individuals. We cannot yet answer this question.

The reasons against screening relate more to the moral question of the importance of individuals being able to make their own decisions about screening. Clear negative implications exist in relation to insurance ratings and job applications for affected individuals. If patients are faced with a fait accompli because of screening at their parents' or physician's behest early in life, they may well harbor significant anger at the penalties suffered in adult life.

We also should consider genetic counseling and its implications for parenting. Most physicians would advise that individuals be screened before marriage, particularly so that the unaffected spouse can be made aware of the implications for the future. Effective counseling requires significant patient education, because it is clear that most individuals, despite substantial family experience, have little understanding of the condition [66]. A program of education for potentially affected individuals is a prerequisite and should be undertaken, at least in part, before screening to allow the patient to make an informed decision. There has been little demand to date for prenatal screening. Although many parents wish to know whether their child is affected, few would opt for termination of pregnancy on the basis of a positive result. The same is probably not true for the recessive form of cystic kidney disease [68].

Dr. Brian Junor (*Western Infirmary, Glasgow, Scotland*): Could

I comment on the rate of decline of renal function in males versus females? In the Denver study [26], the lines of the rate of decline in each group are almost parallel, yet males overall have a higher incidence of renal failure at a younger age than females. This observation suggests that the decline starts earlier in males than females, but that the actual rate of decline is comparable. Could you comment on this?

DR. WATSON: Yes, the slope of the line for declining renal function in the Denver data is very similar for the two sexes [26], but presumably the entry point is different. The difficulty, of course, is obtaining accurate data on the early phase of decline in function in each group.

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