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Polycystic kidney disease

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Case presentations

Patient 1. A 37-year-old man developed hypertension at age 18 when he weighed 120.5 kg. He lost 50 pounds on a weight-reduction diet, and his blood pressure fell to within normal range. At age 26, routine physical examination disclosed a blood pressure of 140/100 mm Hg and weight of 108.4 kg. Urinalysis was unrevealing; BUN was 18 mg/dl. An intravenous pyelogram was reported to be normal. From age 26 to 32, he was treated for hypertension with phenobarbital. At age 33, blood pressure was noted to be 170/115 mm Hg. Administration of 50 mg of hydrochlorothiazide daily and 10 mg of hydralazine three times daily resulted in a fall in blood pressure to 120 to 130/88 to 90 mm Hg. At age 36, 4+ albuminuria was found for the first time; BUN was 26 mg/dl and the serum creatinine was 1.7 mg/dl. Intravenous pyelography revealed large kidneys with multiple bilateral cysts, and polycystic kidney disease was diagnosed. This diagnosis was confirmed by ultrasound and the patient was referred to New England Medical Center (NEMC) for further evaluation. When first examined, he was asymptomatic. There was no family history of polycystic kidney disease. He weighed 94 kg and the blood pressure was 145/100 mm Hg (supine) and 130/110 mm Hg (standing). The rest of the physical examination was unremarkable.

The patient was encouraged to follow a weight-reduction diet, and his dose of hydralazine was increased to 25 mg three times daily. Blood pressure remained in the range of 130 to 140/100 to 105 mm Hg over the next year, and the dose of hydralazine was increased to 50 mg three times daily. When last examined at age 40, the patient's blood pressure was 140/100 mm Hg and the serum creatinine was 1.8 mg/dl.

Patient 2. A 40-year-old woman, followed for many years at NEMC for polycystic kidney disease, came from a family with a well-documented history of polycystic kidney disease. Her father and six of his siblings had died of the disease between 30 and 36 years of age, and the patient's older sister was known to have polycystic kidney disease. When the patient was first evaluated at age 23, intravenous pyelography revealed kidneys measuring 19 to 20 cm and containing multiple renal cysts. Physical examination was normal except that palpation disclosed bilaterally enlarged kidneys. Serum creatinine was 0.8 mg/dl. There was no history of hypertension, urinary tract infection, hematuria, or abdominal pain.

Three years after the diagnosis was established, labile hypertension was noted. Good blood pressure control was achieved with moderate doses of various antihypertensive medications. The patient had no evidence of urinary tract infection over this period save for a brief episode, when she was 26 years old, of dysuria and pyuria with sterile urine cultures. Serum creatinine remained in the 0.8 to 1.0 mg/dl range until it rose to the 1.2 to 1.5 mg/dl range when the patient was 38 years old.

At age 40 she developed progressive low back pain, lower abdominal pain, fever to 103°F with shaking chills and diaphoresis, dysuria, and increased urinary frequency. Physical examination was notable for a blood pressure of 90/60 mm Hg with orthostatic changes, a pulse of 88, and a temperature of 37.9°C. The patient had warm skin with slightly decreased turgor. The abdomen revealed bilaterally enlarged kidneys that were minimally tender, and there was moderate bilateral costovertebral angle tenderness greater on the left than on the right. The remainder of the physical examination was normal.

Laboratory data revealed normal electrolytes, a BUN of 19 mg/dl, a serum creatinine of 1.3 mg/dl, a white blood cell count of 23,200 mm^3 with a shift to the left, and a hematocrit of 37%. Results of urinalysis revealed a specific gravity of 1.012; pH, 6; and a trace of protein. Examination of the sediment revealed sheets of white blood cells, 5 to 10 red blood cells per high-power field, and 2+ bacteria on an unspun specimen.

The patient was admitted to NEMC with a diagnosis of acute pyelonephritis. She was given intravenous ampicillin and tobramycin, and was rehydrated. Urine culture subsequently grew 50,000 to 100,000 colonies of *E. coli* sensitive to ampicillin, and tobramycin administration was discontinued on the second hospital day. She remained febrile to 39°C and had continued tenderness of the left kidney. A CT scan of both kidneys on hospital day 6 showed an area of possible abscess formation in the lower pole of the left kidney; the area was aspirated but was culture negative. The fluid was turbid. The patient did not become afebrile until day 8. She received a total of 2 weeks of intravenous ampicillin therapy (8 g/day) followed by an additional week of oral ampicillin. Urine culture was sterile at the time of discharge. When examined 6 weeks after discharge, she had no urinary tract symptoms and she had stable renal function and sterile urine.

Patient 3. A 48-year-old man had been in good health until age 31 years, when routine physical examination disclosed his blood pressure to be 170/120 mm Hg. Physical examination also was remarkable for palpable kidneys bilaterally and a ventral hernia. Intravenous pyelography revealed polycystic kidney disease; renal size was described as "three times normal." The family history was unremarkable for polycystic kidney disease or other renal diseases.

Over the next 14 years, the patient did well save for one brief episode of total, gross, painless hematuria. During this interval, the serum creatinine rose to 5.4 mg/dl. Renal function continued to deteriorate and

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when at age 40 the serum creatinine was 9.3 mg/dl, hemodialysis was instituted. At this time the patient's kidneys could be palpated easily and they extended to the iliac crests. He remained well on dialysis except for an exacerbation of preexisting asthma and a brief episode of abdominal pain thought to be due to a ruptured hepatic or renal cyst.

Soon after dialysis was begun, the patient was evaluated for renal transplantation. Because of the enormous size of the kidneys, bilateral nephrectomy was performed to provide space for the grafted kidney. The right kidney measured 32.0 cm in length, 20 cm at greatest width, and it weighed 3550 grams. The left kidney measured 30.5 cm in length, 15 cm at maximum width, and it weighed 3030 grams. Intraoperative examination of the liver revealed multiple large cysts measuring between 0.5 cm and 6 cm. The patient was discharged on the 10th postoperative day. His postoperative course had been complicated only by transient hypotension 3 days postoperatively that responded to intravenous fluid administration. Ascites and pedal edema were noted 4 weeks postoperatively, but these resolved with aggressive dialysis. Cadaveric renal transplantation was performed after one year of hemodialysis.

Discussion

DR. WADI N. SUKI *(Professor of Medicine and Chief, Renal Section, The Methodist Hospital, Baylor College of Medicine, Texas Medical Center, Houston, Texas):* The three patients summarized here illustrate some interesting features of polycystic kidney disease. The first and the third patients presented with hypertension, not the most common mode of presentation in this disorder. In the first patient, hypertension was recognized at age 26; 10 years passed before polycystic kidney disease was first diagnosed. In many instances, the diagnosis is only made postmortem, although the patient may have suffered from any one of the consequences of the disease. The second patient, a woman with a strong family history of polycystic kidney disease, was diagnosed at age 23. It was not until 3 years later that she became hypertensive, and 12 years later her serum creatinine predictably was elevated. Two years subsequent to that she developed an abscess, which responded only after about 3 weeks of treatment; I will comment on this feature subsequently. Polycystic kidney disease was diagnosed in the third patient during an evaluation for hypertension when his kidneys were found to be palpable. Nine years later dialysis was begun because the patient was in renal failure, and nephrectomy was performed. The need and indications for nephrectomy, particularly in preparation for transplantation, will be addressed later in the discussion. Other interesting features of these 3 patients include the normal IVP in the first and the fact that 2 of the 3 had negative family histories. This may seem unusual for an autosomal dominant inherited disease, but a negative family history is frequent in this disorder.

Incidence of polycystic kidney disease. Adult polycystic kidney disease is a fairly common disorder. It accounts for approximately 1 in 3000 hospital admissions and has been described in 1 in 200 to 1 in 1000 autopsies, with an average of 1 in 500 [1]. The disease is clinically recognized much less frequently, however. In fact, only a small proportion of patients are diagnosed during life. Clear-cut adult polycystic kidney disease was diagnosed premortem in only 25% of patients shown to have the disease postmortem [2]. Of the other 75%, at least one-third had a clinical manifestation, such as hypertension or renal insufficiency, that should have led to recognition of the disease. Dalgaard, in a study of Scandinavian patients, estimated that by age 80 years, everyone who has inherited the gene for polycystic kidney disease will have some manifestation of the disease [3]. But a patient could die at age 80 of unrelated causes never having had overt clinical evidence of the disease and yet cysts could be found at autopsy.

Dalgaard found the pattern of expression to be fairly uniform in a particular family; in other words, the age at which clinical expressions of the disease become manifest and the severity of these expressions are fairly uniform among family members who inherit the gene [3]. We have encountered several exceptions to this assertion, however.

The disease, usually recognized in the third and fourth decades of life, has been described in patients of all ages, from neonates to the elderly. Involvement by cysts is usually diffuse and bilateral, although occasional cases of unilateral disease [4] and of highly localized disease [5] also have been described.

Clinical features of polycystic kidney disease. I shall restrict my remarks about the clinical features to adult polycystic kidney disease (Table 1). I should point out immediately that the term adult polycystic kidney disease is a misnomer; we know now that "adult" polycystic kidney disease can occur at any time from birth [6] to old age. For this reason, the term autosomal dominant polycystic kidney disease has been proposed to distinguish it from the autosomal recessive, or so-called infantile type, which also occurs in adults [7].

In the study by Rall and Odell, the most common presenting complaint was heaviness and pain in the flank and abdomen [8]. The pain, often a pulling or tugging discomfort, usually is moderate in severity but can be severe when associated with bleeding, infection, or malignancy. The presence of pain seems to correlate with the weight of the kidneys and the size of the cysts. In one study, 50% of patients with pain had at least one cyst measuring 3 cm or more in diameter; cysts of this size were found in only 20% of asymptomatic patients [2]. Funck-Brentano, Vantelon, and Lopez-Alvarez have reported, however, that frequency and nocturia were the most common initial complaints in their experience [9]. This observation is interesting, especially because impaired concentrating ability is one of the functional hallmarks of this disorder [10]. Hematuria is the second most common presenting complaint in this disease [3]. Gross hematuria frequently continues to punctuate the course of patients with polycystic kidney disease. The bleeding can lead to clot formation, obstruction, and renal colic-type pain. Finally, hypertension occurs in approximately 70% of patients who manifest the disease [3]; another common clinical manifestation is palpable kidneys [3].

Proteinuria is the most common laboratory finding [3, 8], but it is rarely substantial and even more rarely in the nephrotic range. Ackerman described 2 polycystic patients with advanced renal failure, massive proteinuria, and hypoalbuminemia [11]. Whether the proteinuria in these patients was solely the consequence of polycystic kidney disease or whether it was due to some superimposed process was not studied. Indeed, glomerulonephritis superimposed on polycystic kidney disease has been reported [12].

Stone disease occurs with some frequency in patients with polycystic kidneys. The incidence in various series ranges from 5% to 15%, with an average of 10% [3, 13]. In my experience and in that of several others, the stones usually contain calcium. Hamburger and coworkers, however, report that the stones may be composed mostly of urate [14]. The composition of

Table 1. Manifestations of adult polycystic kidney disease

Pain (most common complaint)
Urinary frequency
Palpable kidneys
Hematuria
Proteinuria (most common laboratory finding)
Stones
Malignancy (unilateral or bilateral)
Infection (sometimes abscess)
Hypertension

renal calculi in polycystic kidney disease and their pathogenesis deserve more thorough investigation.

Renal cell carcinoma is bilateral in 20% of patients with polycystic kidneys, whereas it is bilateral in only about 5% of patients without polycystic kidney disease [15]. Therefore, if one encounters a tumor in one kidney of a patient with polycystic kidney disease, one should look carefully for a tumor in the other kidney. Even if none is found, one should follow the patient carefully.

Infection occurs frequently in polycystic kidney disease, especially in women; 50% to 75% of patients have infection sometime in the course of the disease [3, 8]. The high infection rate is only partly related to the increased frequency with which patients with polycystic kidney disease have instrumentation of the urinary tract. The polycystic kidney also is more susceptible to infection than is the normal kidney. Kime et al rendered the kidneys of experimental animals polycystic by chemical means, and when these animals were injected with microorganisms, the frequency of renal infection increased [16].

When hypertension complicates polycystic kidney disease, it can occur quite early in the course of the disorder, frequently at the time of diagnosis or soon thereafter. The onset of hypertension clearly antedates the onset of progressive renal functional insufficiency. Renin and angiotensin do not seem to play a role in the pathogenesis of the hypertension [17, 18]; indeed, the administration of the angiotensin II antagonist saralasin to these patients usually does not lower blood pressure. This finding supports the view that the hypertension in polycystic disease is not renin dependent [19].

Polycystic disease often involves organs other than the kidney. Extrarenal cysts most commonly occur in the liver, where they usually are inconsequential. The benignity of liver cysts in adult polycystic disease stands in sharp contrast to the course of liver involvement by cysts in infantile polycystic kidney disease. This latter disorder is often accompanied by hepatic fibrosis, cirrhosis, hepatic failure, and portal hypertension. I should point out, however, that an occasional patient with adult polycystic kidney disease has been described with portal hypertension and esophageal varices [20] or jaundice [21]. Pancreatic cysts and an array of cysts in other organs also occur.

Cerebral artery aneurysms occur in 5% to 16% of patients. When the aneurysm is greater than one centimeter in diameter, it generally is symptomatic and can rupture [22]. Two papers have reported abdominal aortic aneurysm in association with polycystic kidney disease [23, 24]. However, this finding may be merely an incidental occurrence in an adult disease associated with hypertension.

Of course, the most serious consequence of polycystic kidney disease is progressive renal failure. In transplantation registries, 5% to 8% of patients with end-stage renal disease who undergo renal transplantation have polycystic kidney disease [25, 26].

Functional aspects of polycystic kidney disease. Medical students and house officers are often taught that patients with polycystic kidney disease tend to be salt wasters. We have been unable to confirm this assertion [27]. We studied one group of patients with fairly well preserved renal function (7 patients with a mean creatinine clearance of 58 ml/min) and another group with severely impaired renal function (6 patients with a mean creatinine clearance of 10 ml/min). Patients in both groups were first given a diet containing 100 mEq of sodium and then a diet containing 10 mEq of sodium. The patients with well-preserved renal function conserved sodium appropriately on the low-sodium diet. The patients with advanced renal insufficiency could not reduce urine sodium concentration to the same level as did patients in the first group; also, they were in negative sodium balance. This response, however, does not differ in patients with the same degree of renal insufficiency from other causes [28]. Urine sodium concentration does not decrease abruptly to very low values in patients with advanced or end-stage renal disease. Whether the increased urinary sodium level is due to osmotic diuresis or to a natriuretic factor is a subject for a separate discussion [29, 30].

Because hyperkalemia has been observed in some patients with polycystic kidney disease and advanced renal failure, the possibility exists that these patients might not be able to handle potassium very well. In our studies, patients with severe renal impairment did not excrete as much potassium as did the patients with mild impairment [27]. If one calculates potassium excretion as a percentage of the filtered potassium load, however, the patients with severe impairment excrete a high percentage of the filtered potassium load.

Hypercalciuria was not a feature, but we have not studied patients with relatively well-preserved renal function who have calcium-containing kidney stones. The explanation for stone formation in these patients remains to be determined. Whether the stones are due to local factors, loss of an inhibitor, or excretion of a factor that promotes crystallization is not known.

The cysts in this disorder are functional and are also in a state of dynamic equilibrium [31–34]. The careful studies of Lambert [31] and other workers [32–34] suggest that the cysts can arise from any segment of the nephron, and that they have the characteristics of the particular nephron segment from which they are derived. Proximal cysts, for example, have inulin, creatinine, and electrolyte concentrations similar to those of blood. Distal cysts have a sodium concentration three- to four-tenths that in blood, whereas the concentration of inulin or creatinine in the cyst is several fold that in blood. Perhaps the only exceptions are glomerular cysts, which are "blind" and nonfunctional [31]. Both inulin and PAH appear in the cysts after intravenous administration; thus some communication with glomerular filtrate probably exists and the cells of the cyst lining likely are functional [31, 32].

Hyperchloremic acidosis occurs in patients with polycystic kidney disease, and Preuss et al reported that 2 of 4 patients could not acidify the urine maximally [35]. In this respect, these patients do not seem to differ from patients with other forms of

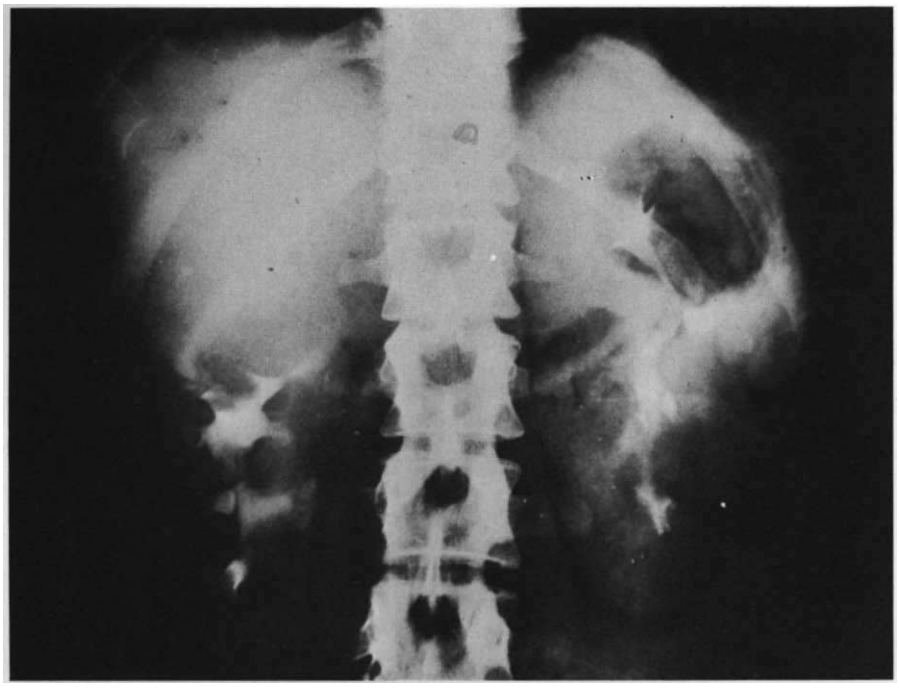

Fig. 1. *Intravenous pyelogram demonstrating enlargement of the renal contour, stretching of the infundibulae, and arched impressions on the infundibulae and calyces caused by the renal cysts.*

renal disease. Salt-restricted patients with renal parenchymal disease can acidify the urine when given sodium sulfate and mineralocorticoids. But because Preuss et al did not use this experimental protocol, it is not clear whether their patients with polycystic kidney disease had a defect different from that encountered in other patients with moderate to severe renal disease. In Preuss' study, ammonium excretion was decreased in 4 of 7 patients even when corrected for GFR; this finding suggests that a tubular defect does exist [35].

Several years ago we reported that with few exceptions patients with polycystic kidney disease tend to have an impaired ability to concentrate the urine, even when renal function is relatively well preserved [10]. The GFR in these patients ranged between 60 and 165 ml/min. Only 2 of 13 patients were able to concentrate the urine greater than 900 mOsm/kg; the other 11 had an impairment in the ability to concentrate the urine maximally. We investigated this observation further to determine whether concentrating ability becomes more impaired with advancing renal insufficiency. We found that the 8 patients with the most markedly depressed renal function also had the most severely impaired U_{max}. Only one patient, however, had what one might label as hyposthenuria or nephrogenic diabetes insipidus.

We studied the patients with an impaired U_{max} but well-preserved GFR by giving them hypertonic saline, thus raising their osmotic clearance. We then examined their capacity to reabsorb solute-free water ($T^c_{H_2O}$). We observed four patterns. In 2 patients, $T^c_{H_2O}$ was at the top of the normal range. These 2 patients had the best-preserved GFRs (143 and 165 ml/min). In 3 additional patients, $T^c_{H_2O}$ was at the bottom of the normal range. The GFR in these patients was 90, 102, and 117 ml/min. In one patient, $T^c_{H_2O}$ initially was at the bottom of the normal range, but at a very high osmotic clearance it began to decrease (GFR, 109 ml/min). In 2 others, $T^c_{H_2O}$ was lower than normal throughout the range of osmolar clearance (GFR, 60 and 97 ml/min). Although most of the patients with well-preserved GFRs had an impaired ability to maximally concentrate the urine, their ability to absorb solute-free water in the collecting tubule largely was well preserved until renal functional impairment became severe.

When the rate of flow in the distal nephron was increased by hypertonic saline infusion in the patients with severe renal dysfunction, osmotic equilibrium between tubular lumen and the peritubular environment did not occur, and hypotonic urine was produced; that is, free-water absorption became negative.

Free-water clearance measured during water diuresis was normal in both groups; the thick ascending limb and distal convoluted tubule, which are the major sites of dilution, apparently were functioning normally. The impairment in concentrating capacity therefore must have been the consequence of disordered function of the collecting tubules or of the medullary countercurrent multiplication system.

We investigated urinary concentrating ability in rats with experimentally induced polycystic kidney disease. Two chemicals are known to induce polycystic changes in the kidneys of experimental animals. One is diphenylamine and the other is 2-amino, 4,5-diphenyl thiazole HCl. Vernier and his group reported that rats treated with diphenylamine exhibited an impaired ability to concentrate urine even before cystic changes appeared in the nephron [36], and we confirmed that finding [37]. As in humans, however, the rat's ability to absorb solute-free water in the collecting tubule was intact. Also as in humans, their ability to dilute the urine and form solute-free water was normal. Other studies in these rats revealed that glucose, bicarbonate, chloride, and proximal tubular water absorption (the latter measured by micropuncture as TF/P inulin) were

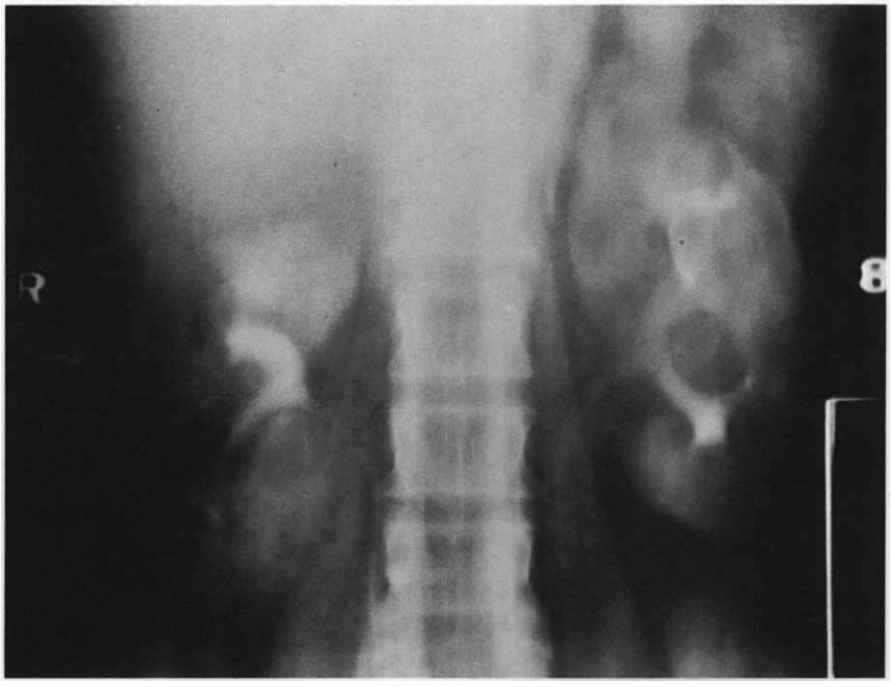

Fig. 2. *Nephrotomogram showing areas of diminished nephrogram density and distortion of the collecting system caused by the renal cysts.*

comparable to those in the normal rat; these findings suggested that the tubular defect was in the more distal segments of the nephron.

Diagnosis of polycystic kidney disease. Until recently, the diagnosis of polycystic kidney disease depended on intravenous pyelography and renal arteriography. Intravenous pyelography usually reveals enlarged kidneys with an irregular contour, stretching of the infundibulae of the calyces, and circular or arched impressions on the calyces causing flattening and distortion (Fig. 1). When the changes on standard intravenous pyelography are not diagnostic, one can complement the study with nephrotomography (Fig. 2). Arteriography has been used in establishing the diagnosis (Fig. 3) and is currently one of the mainstays in diagnosing some of the complications of polycystic kidney disease, particularly malignancy. In my view it remains the major method for detecting renal malignancy.

Ultrasonography [38] and computerized tomography [39] are new and important diagnostic tools. Ultrasonography, a noninvasive technique, has proved useful for screening patients' families (Fig. 4), and it sometimes can be of value when one suspects a solid tumor in the kidney. Computerized tomography can demonstrate the configuration of both the kidneys and liver (Fig. 5A, 5B), determine whether obstruction is present, assess whether there is a solid mass in the kidney, and evaluate whether an abscess is present, merely from the difference in the density of the fluid in a particular cyst.

Management of polycystic kidney disease. Because no one has been able to document salt-wasting in these patients, one need not urge the patient to ingest a high salt intake as one would in a patient with medullary cystic disease. When the patient is hypertensive, sodium intake should be reduced to 70 to 80 mEq/day. Patients with polycystic kidney disease have a high incidence of hiatal hernia; therefore one should recommend that the patient have small meals and not recline soon after eating. The patient should avoid contact sports, rough rides, seat belts, and tight belts around the abdomen. Whelton reported ruptured cysts and hematuria as a consequence of patients wearing automobile or airplane seat belts [40]. When hematuria occurs, bed rest alone is the best treatment. Occasionally the hematuria can be severe enough to cause obstruction of a kidney. This presents a problem, because introduction of a ureteral catheter to bypass the obstruction can lead to infection. One also could use fibrinolytic preparations in an attempt to lyse the clots and speed up their evacuation.

As I mentioned earlier, one of the presenting manifestations of adult polycystic kidney disease is pain. When the pain is severe and protracted, one should consider the possibility of a renal stone, infection, or tumor. It is difficult to diagnose a renal tumor in a patient with polycystic kidney disease because the manifestations of tumor—pain, hematuria, fever, and calcification—are features of polycystic kidney disease itself, especially when complicated by infection. When the index of suspicion is high, renal arteriography may be required if noninvasive tests fail to exclude a tumor.

At one time, the Rovsing procedure was performed on large cysts suspected of causing pain or when kidney size was very large. In 1957, Bricker and Patton studied renal function before and after this operation in patients with polycystic kidney disease [41]. Their comparison of operated patients with those who did not undergo operation disclosed a 20% loss of renal function in the operated group. Since then, this procedure has been discarded.

Infection deserves special comment, because clinicians agree neither on the method nor on the duration of treatment for this complication. Certain lessons can be learned from studies of cyst fluid obtained at the time of surgery. The cyst concentrations of antibiotics administered in standard doses prior to the procedure were not optimal, reaching only 10% to 25% of the

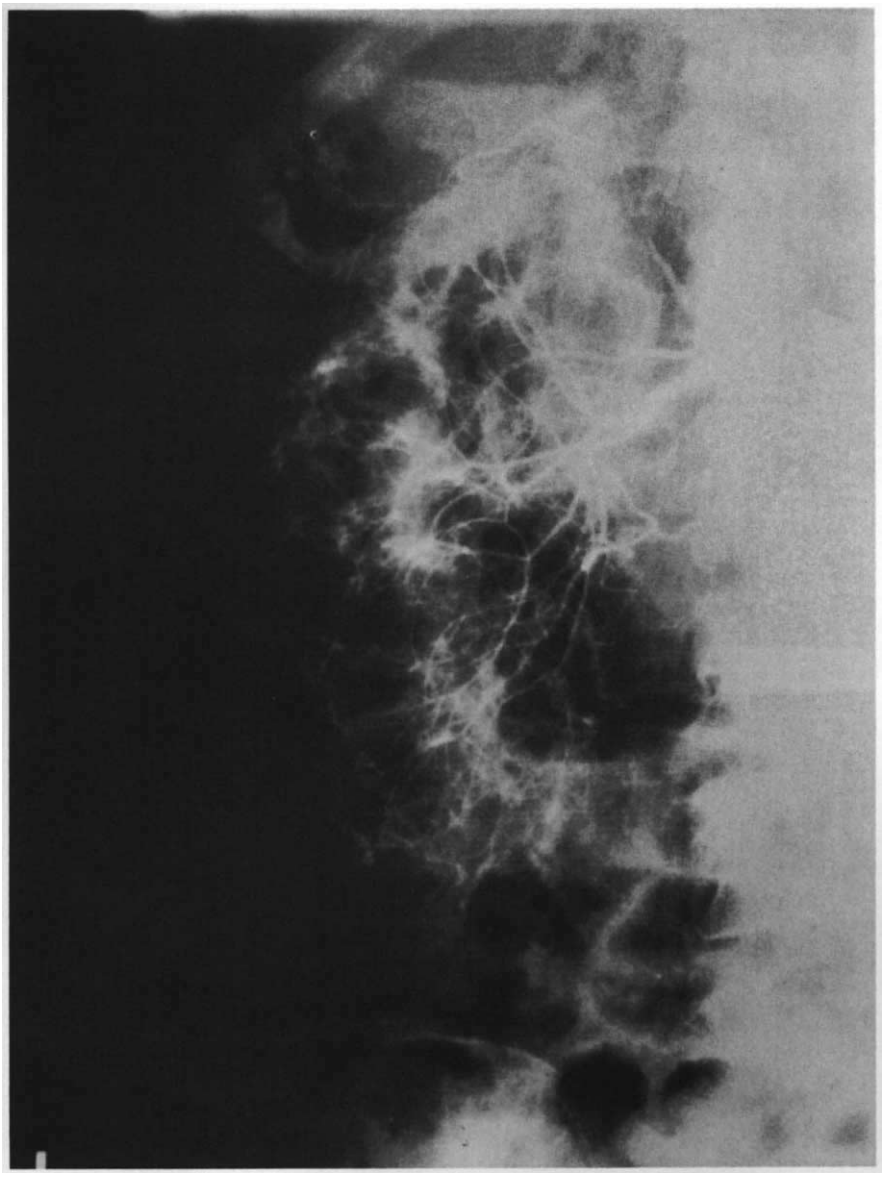

Fig. 3. *Selective renal arteriogram showing distortion of the intrarenal vasculature and the "Swiss cheese" pattern caused by the renal cysts.*

concentrations in blood [42]. The concentrations of the antibiotics in the distal tubular cysts were even lower than those in proximal cysts. These observations provide a rationale for treating patients with infected cysts with high doses of antibiotics for protracted periods.

Cerebral aneurysms generally do not lead to any harmful effects unless they are 1 cm in diameter or larger. Stones and hernias present other important challenges in management.

The management of renal failure is conservative until the patient requires renal replacement therapy. At that point, hemodialysis is an acceptable form of treatment and has been widely used [43]. Peritoneal dialysis also can be employed in these patients; unless the kidneys are huge—and the kidneys often do shrink as the patients go into renal failure or are dialysed [44]—I believe there is no contraindication to this form of dialysis [45].

Transplantation is another feasible therapy for these patients [43]. The patient's diseased kidneys should be removed not only when hypertension cannot be controlled by dialysis, but also for other major complications of the disease, including: *(1)* infection; *(2)* tumor; *(3)* severe, gross hematuria; *(4)* very large kidneys, with or without ascites; and *(5)* nephrolithiasis, because stones predispose to infection. I believe that every patient with polycystic kidneys should undergo arteriography prior to renal transplantation. If a potential transplant recipient is found to have neoplasia in one or both kidneys, bilateral nephrectomy should be performed. If after 1 to 3 years such a patient is free of tumor, renal transplantation can be reconsidered. Of 11 patients who had malignancy (several with hypernephroma) and who received renal transplants at least one year after tumor resection, tumor recurred in only one patient after transplantation [46].

In summary, polycystic kidney disease is a common cause of end-stage renal disease. Major advances in our understanding

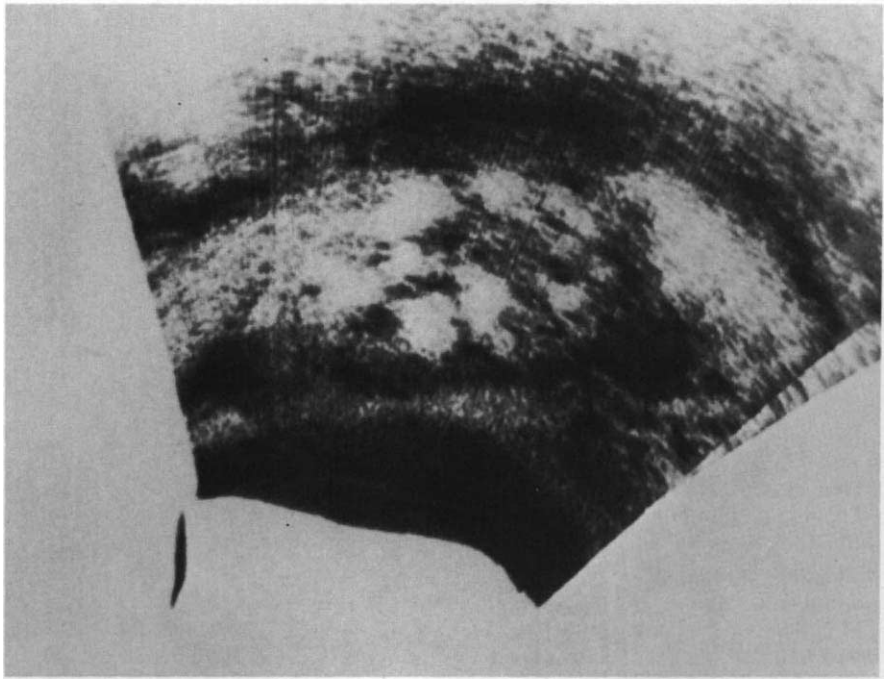

Fig. 4. *Ultrasonogram demonstrating enlargement of the kidney and the areas of sonolucency caused by the renal cysts.*

of the pathophysiology and pathogenesis of this disease have been made in the last 25 years. Unfortunately, we are not yet able to halt the progressive decline in renal function, but current methods of renal replacement therapy are as applicable in patients with this disorder as they are in patients with other types of renal disease.

Questions and answers

DR. JORDAN J. COHEN: You noted that an experimental model of polycystic disease can be produced by administering certain chemicals to an animal. This, of course, raises an obvious question: Does this disease in humans stem from the inheritance of a structural defect in the nephron that eventually results in cyst formation, or does it result from the inheritance of a metabolic defect that causes production of an injurious circulating substance? The latter possibility might more easily account for the variable age of onset of the disease and the variable distribution of cysts in other organs. Are there any data in humans that bear on this point, or are we left only with speculation?

DR. SUKI: It is really all speculation. It fascinated us that one of the earliest manifestations of this disease in humans is impaired renal concentrating capacity. Similarly, there is impaired concentrating capacity in the experimental model before there is any apparent structural change even by electron microscopy. Perhaps what we inherit is not a structural defect in the basement membrane of the nephron, but rather an abnormal chemical which, upon prolonged exposure to the basement membrane, dissolves it. I should add that one can perfuse an isolated tubule in vitro under standard pressure, and add collagenase to the medium, and the perfused tubule segment will balloon out.

Cuppage et al [34] and others have shown by electron microscopy that the basement membrane in these cysts is actually thickened and extensively laminated. The lingering question is whether a basement membrane abnormality resulting in excessive compliance is the primary reason for the development of the cyst, or whether cysts develop because of tubular obstruction.

DR. COHEN: Do these chemicals produce cysts only in young animals, or are adult animals affected as well?

DR. SUKI: The model can be produced most predictably when the chemical is administered to young rats, but adult rats also develop cysts.

DR. COHEN: It will be interesting, of course, to see whether patients with polycystic kidney disease who receive renal transplants develop recurrent cystic disease. Such an occurrence would provide strong evidence that a circulating factor is responsible.

DR. SUKI: To date I know of no evidence of recurrence of polycystic disease in transplanted kidneys.

DR. WARREN GOORNO *(Nephrologist, Emerson Hospital, Concord, Mass.):* Dr. Suki, given the high incidence of malignancy in patients with polycystic kidney disease, are there any data on the incidence of malignancy after transplantation in such patients? One would suspect that it might be even higher.

DR. SUKI: Tumors appear with some frequency in polycystic kidney disease, but the true incidence is not known. Only about 50 cases of malignancy have been reported in polycystic kidney disease. Whether the incidence of malignancy is exaggerated further by immunosuppression, I do not know. There are no good data regarding this point.

DR. JOHN T. HARRINGTON: I have another question on malignancy. You stated that you perform bilateral arteriograms before transplantation on all patients with polycystic kidney disease. If you find a malignancy on one side, do you recommend bilateral nephrectomy?

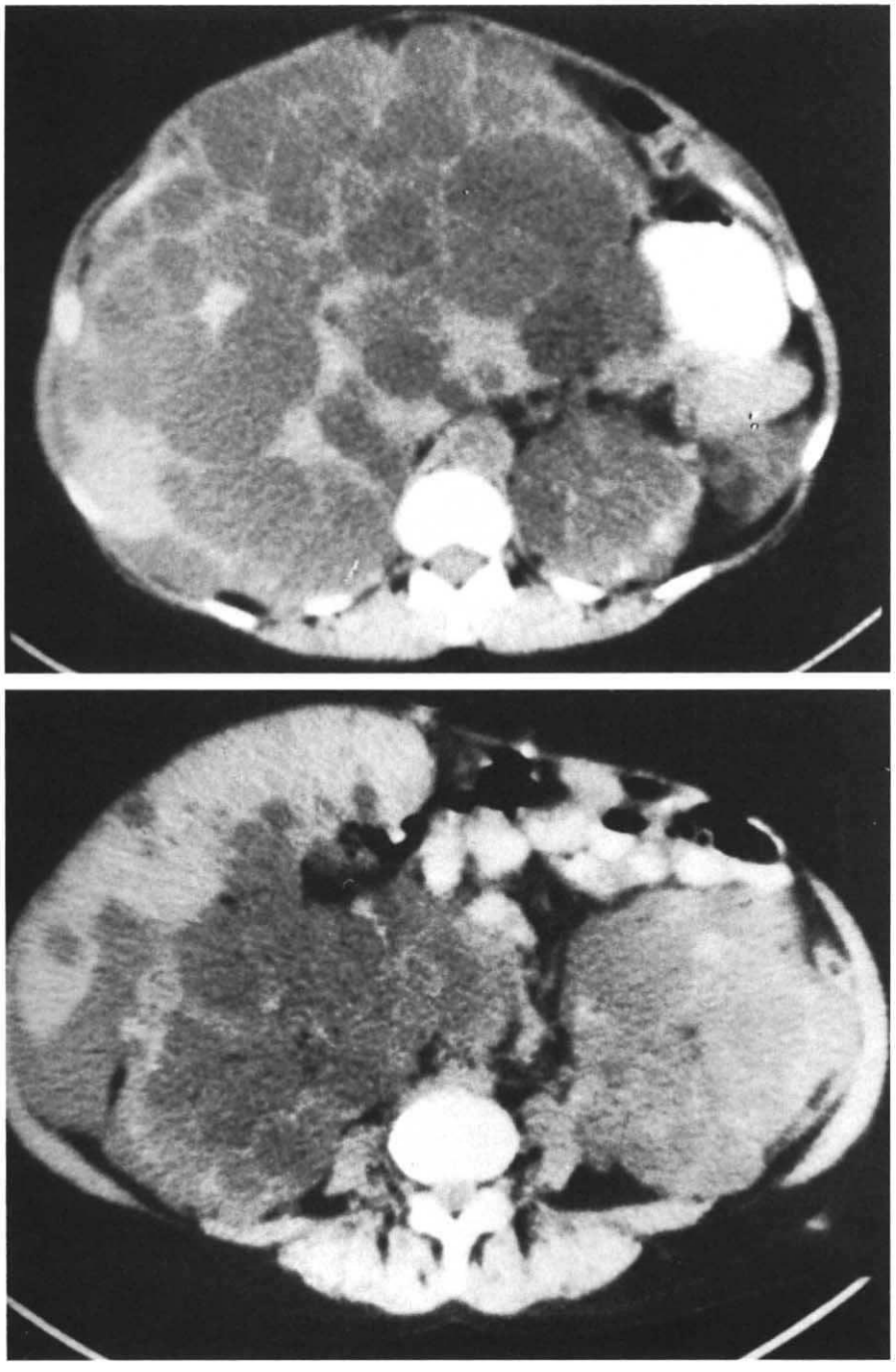

Fig. 5. (Upper) *CT scan demonstrating a massively cystic liver and cysts in the upper pole of the left kidney.* (Lower) *Lower level of the same CT scan demonstrating cysts in both markedly enlarged kidneys and a few cysts in the liver.*

DR. SUKI: Yes, for the following reasons. First, the chances are high that the patient has or will develop a tumor on the contralateral side. Second, this procedure avoids the need to undertake major surgery after transplantation. In my experience, the postoperative management of patients with polycystic kidney disease is difficult. They often develop ileus, ascites, and infections. It is difficult surgery. I therefore suggest nephrectomy and a waiting period of 1 to 2 months prior to transplantation.

DR. HARRINGTON: Let me turn to a different issue. Polycystic kidney disease always has fascinated me because it is one of the few renal diseases in which high blood pressure frequently develops in the absence of volume overload or a high renin-angiotensin state. Is there any new information on the pathogenesis of the hypertension in these patients?

DR. SUKI: None that I know of. As I indicated, the latest data with saralasin show no response to the drug [19]. The studies of Nash [18] and others [17] of the renin-angiotensin system also yielded negative results. One presumption is that the high blood pressure is related to subtle volume expansion; the blood

pressure does respond very well to diuretic administration.

DR. ANDREW LEVEY *(Renal Service, NEMC):* What do you do for patients with massive bleeding into the urine?

DR. SUKI: This may be an indication for interventional radiography. Embolization using autologous clot, balloons, or small coils has been used to control massive uncontrollable bleeding. I find the embolization technique an attractive possibility in some of these patients with huge kidneys. One should keep in mind, however, that pain may be a prominent complaint for a day or so after this procedure.

DR. COHEN: Dr. Suki, you mentioned that occasionally you find nephrotic-range proteinuria in patients with polycystic kidney disease. That brings to mind the recent suggestion that any form of chronic renal insufficiency can lead to secondary glomerular injury in the remaining nephrons because of hemodynamic alterations [47]. Is there any evidence of focal sclerosis or other primary glomerular abnormalities in patients with polycystic kidney disease?

DR. SUKI: None that I know of. As I said, there is one report of glomerulonephritis superimposed on polycystic kidney disease [12]. Also, Ackerman reported polycystic patients with the nephrotic syndrome in whom no histologic diagnosis was made [11]. It remains to be proven whether hyperfiltration really produces focal sclerosis. Hyperfiltration does cause focal sclerosis in the renal infarction model, as shown by Morrison and Hostetter [47–49]. In contrast, one does not see focal sclerosis in another model of hyperfiltration, diabetes.

DR. BARRY STRAUBE *(Renal Fellow, NEMC):* Patients with renal cysts generally have high red blood cell counts, and patients with polycystic kidney disease seem to have higher hematocrits for their degree of renal failure. Could you comment on this finding?

DR. SUKI: Relative erythrocythemia seems to be a feature of polycystic kidney disease [50]. Erythropoietic material has been found in the fluid contents of these cysts [51, 52]. The presumption is that these cysts produce the erythropoietic factor, which in turn enters the blood and stimulates erythropoiesis.

DR. JAMES STROM *(Chief, Renal Division, St. Elizabeth's Hospital, Boston):* Has the occurrence of unilateral polycystic kidney disease been well documented?

DR. SUKI: Yes, there are occasional reports of unilateral disease [4].

DR. LEVEY: How early in life can pathologic examination establish the diagnosis of the adult form of polycystic kidney disease?

DR. SUKI: It is difficult to know because there are no systematic studies. Some asymptomatic infants from families with known polycystic kidney disease have been screened by ultrasonography, and cysts have been found. We used tomography to evaluate 10- and 12-year-old children of patients with polycystic kidney disease and found cysts in many of these children.

DR. NICOLAOS MADIAS *(Chief, Renal Service, NEMC):* How about genetic counseling in this hereditary disorder?

DR. SUKI: This is very important to patients with polycystic kidney disease. What does one advise a couple about having children if one of them has polycystic kidney disease? If the disease could be detected in utero, one could theoretically offer the option of abortion in those instances. But at present there is no test to detect the disease in utero. Even if such a test were available, however, the course of the disease is so highly variable that the child might never have clinical disease. I explain the facts about inheritance of the disease and the consequences of having the disease and let the prospective parents make the decision.

DR. STRAUBE: Do you screen family members?

DR. SUKI: Screening is a debatable issue. One of the questions raised is, what is the purpose of learning that you have polycystic kidney disease if you are asymptomatic? The knowledge may evoke anxiety, decrease job opportunities, and diminish insurability. I therefore do not recommend routine screening of asymptomatic family members of patients with polycystic kidney disease. If an individual develops hypertension, hematuria or proteinuria, of course, studies should be carried out.

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