

# Q & A on PKD

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# ADPKD Genes and Proteins: What We Now Know

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The gene that is mutated in more than 85% of ADPKD patients is called “PKD1.” The DNA sequence for PKD1 has been completely determined and, as a result, we have been able to identify a large number of mutations that can cause ADPKD. How these mutations cause the cysts that characterize ADPKD is now a subject of intense study. The second ADPKD gene, PKD2, is responsible for approximately 15% of ADPKD cases. Like PKD1, PKD2 has been completely sequenced, and many mutations have been found. Genetic testing for ADPKD is now available using DNA obtained from a single blood sample.

Once the ADPKD genes were identified and sequenced, it was possible to predict the sequence of the proteins, so-called polycystins, whose manufacture is directed by PKD1 and PKD2. Exploiting this new information, scientists immediately began to guess at the function of the polycystins and to devise experiments to test their hunches. In the past three years, several breakthroughs have been made to enhance our understanding of how polycystins work and what goes wrong when they don't. As we understand these molecules better, our ability to work toward a cure becomes immeasurably enhanced.

ADPKD typically progresses over decades. Animal models of the disease will be important for studying the progression of the disease and will be valuable for testing potential therapies. Since the ADPKD genes were found, PKD researchers have been applying cutting-edge technology to generate animal models that mimic the human disease. Several animal models of PKD1 and PKD2 mutations have been generated in the last five years. There are now knock-out (the PKD genes have been knocked out of the animal!) models for both PKD1 and PKD2 to start testing different strategies to slow or halt cyst enlargement and progression.

The first real insight into the role played by polycystins in each cell came from the discovery of the function of a PKD-like gene which scientists call PKDL. PKDL makes a protein, known as polycystin-L, which is very similar to polycystin-2, the protein made by PKD2 protein. It was discovered that polycystin-L is a “channel” through which calcium—and some other ions—can move through cell membranes. It now turns out that polycystin-2 is also a channel that allows ions to travel through cell membranes.

Very recently, scientists found that PKD1, which codes for a protein called polycystin-1, acts as a G-protein coupled receptor. There is strong evidence that polycystin-1 and polycystin-2 are coupled to each other. The next steps are to figure out how these two proteins communicate with other proteins in the cell and with the world outside the cell. Understanding of these communications, called signaling networks, will be a key to the search for molecules that drugs can target to halt the development of renal cysts and to treat ADPKD.

# The Autosomal Recessive Polycystic Kidney Disease (ARPKD) Gene and Protein; What do we know?

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ARPKD is the infantile form of polycystic kidney disease with the typical presentation of greatly enlarged cystic kidneys diagnosed in utero or neonatally. The disease can, however, present later with less severe kidney disease and only become clinically relevant due to complications of fibrosis of the liver that invariably accompany the disorder.

Genetic linkage studies indicate that ARPKD is caused by mutation to one gene, PKHD1, that is localized to chromosome region 6p12. ARPKD is a recessive disorder so a child is affected when they inherit one mutated copy of the gene from their mother and one from their father. The disease is usually found in just one generation in the family and there is a one in four risk that a sibling of an ARPKD case will also be affected.

The ARPKD gene, PKHD1, was identified by two separate research groups in 2002. We identified the gene using a rat model, the PCK rat, that had arisen spontaneously in a few years earlier in Japan, and has progressive kidney and liver cystic disease. Using a gene mapping approach we were able to show that PCK is a model of ARPKD and this led to a very precise localization of the gene, highlighting one clear candidate. Mutation analysis in ARPKD patients (and the PCK rat) showed that this was the disease gene in humans and the rat model. The second group used the genetic method of positional cloning in human ARPKD families and came to the same conclusion about the identity of the gene.

PKHD1 is an unusually large gene that covers nearly 500,000 base pairs of genomic DNA (0.017% of the DNA total) and encodes a large protein called fibrocystin. Mutation studies by many different groups have shown that multiple different mutations cause ARPKD with over 250 different changes described in approximately 600 patients. This complexity complicates molecular diagnostics but services providing mutation based diagnostics are now available. It is clear that the combination of disease-causing changes influences the presentation with cases with two mutations that truncate the protein having the most severe disease. Cases with one or two substitution mutations often are less severely affected. However, it is likely that environmental and other genetic factors also influence the presentation and course of the disease.

The precise role of the ARPKD protein, fibrocystin, is not yet known but, in common with many other PKD proteins, it has been localized to primary cilia and the basal body in the renal epithelial cell. Primary cilia (that are rooted in the basal body) are hair-like projections that extend from the surface of cells lining tubules in the kidney and liver and are thought to have a sensor role, possibly detecting fluid flow. The structure of fibrocystin suggests that it may sense cues from the extracellular environment necessary for proper development and maturation of renal and biliary tubules. Studies are already underway to better understand the role of fibrocystin and use this knowledge to develop rational therapies to treat this devastating disorder.

# Strategies to Treat Hypertension and End-organ Damage in ADPKD Patients

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Although ADPKD is an inherited disease, not all patients progress to end-stage renal disease in their lifetime. Approximately 50% of patients will begin dialysis or require a transplant in their sixth decade of life. The most important factors that determine if someone with ADPKD will progress to renal failure include being a man vs a woman, the PKD1 vs the PKD2 gene, and the presence of hypertension. Given that gender and genotype cannot be modified, strategies for the best way to treat hypertension in ADPKD have been tested and established.

New guidelines were set forth in 2001 by the High Blood Pressure Education Program at the National Heart, Lung and Blood Institute at the National Institutes of Health regarding the appropriate blood pressure level for patients with all types of renal disease, including ADPKD. Current recommendations are for blood pressure to be kept to less than 125/75 mm Hg. These recommendations have been developed mostly for patients with renal disease with large amounts of protein in the urine. Importantly, when protein is present in the urine in ADPKD patients, progress to renal failure tends to occur more quickly. Although large amounts of protein in the urine do not happen very often in ADPKD, it is reasonable to adopt these same blood-pressure goals when treating hypertension in ADPKD.

We know that a blood pressure-regulating system present in all people is activated more than usual in patients with ADPKD. This system is called the renin-angiotensin-aldosterone system. Even early, when ADPKD patients still have normal renal function, this system is turned on. When this happens, blood pressure rises often to hypertensive levels. As well, when this system is turned on, it is more difficult for the kidney to get rid of salt in the diet, and blood pressure rises even more. Also, this system appears to promote cyst growth and expansion in animal models of PKD. So, for a variety of reasons, if this system were to be blocked, it may be possible to slow or halt the progression of renal disease in ADPKD.

There are medicines that are indicated for the treatment of hypertension (as well as congestive heart failure and high levels of protein in the urine) that interrupt the renin-angiotensin-aldosterone system. There are two families of drugs: one is the angiotensin converting enzyme inhibitor (ACE inhibitors), and one is the angiotensin receptor blocker (ARBs). ACE inhibitors have been available and used for more than two decades and ARBs have been available for approximately seven to eight years. Therefore, most of what we know about these medicines and successful treatment of hypertension in ADPKD is with the ACE inhibitors.

ACE inhibitors lower blood pressure in ADPKD patients, as do other antihypertensive medications, but they also improve blood flow to ADPKD kidneys. These salutary effects are present in ADPKD patients who have taken medicine for as little as four hours and tested in patients who have taken the medicine for up to six weeks (a very short period of time). Given these positive results, ACE inhibitors should also help to slow or halt the rate of progression of renal disease in ADPKD (a long-term effect).

However, this long-term benefit or halting the progression of renal disease has not been demonstrated in three different clinical studies in patients with ADPKD. Why is this? Is it because ACE inhibitors really do not help ADPKD patients, or have the studies been carried out inadequately? Most researchers believe the latter. The studies have been relatively short in duration (2.2-7 years) for a disease like ADPKD and the number of patients studied (64-222 patients) relatively small. As well, two of the three studies were trying to answer more than one question at the same time (for example both the benefit of lower blood pressure targets and dietary protein intake were being tested simultaneously in one large study where ACE inhibitors were used).

Even so, with such a promising effect seen with short use of ACE inhibitors, one should see some indication of its benefit in long-term studies. This indeed has been demonstrated with regard to end-organ damage related to high

blood pressure in ADPKD. In studies that have been carried out for up to 7 years, ACE inhibitor benefit has been demonstrated in ADPKD patients with regard to reducing the level of protein in the urine and the size of the heart (left ventricular mass). Long-standing hypertension will result in increased thickness of the heart muscle. This is unhealthy and called left ventricular hypertrophy. Not only do ACE inhibitors reduce this enlarged heart muscle back to its normal size better than other antihypertensive medications, but so does rigorous blood pressure control (<125/85 mm Hg). As well, protein in the urine, which can be a marker of uncontrolled blood pressure, is reduced to almost undetectable levels in ADPKD patients who receive ACE inhibitors. Both of these findings indicate the importance of ACE inhibitors and most likely blockade of the renin-angiotensin-system in preventing end-organ damage due to hypertension in ADPKD patients. Bigger and longer studies are needed to determine if blockade of the renin-angiotensin-aldosterone system (perhaps with additive therapies where ACE inhibitors and ARBs are combined) slows or halts the progression of renal disease in ADPKD patients.

## Diagnosis/Genetics

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### What is a multicystic kidney? Are multicystic and polycystic kidneys the same?

Multicystic kidneys differ from polycystic kidneys in a number of ways. They occur sporadically, or happen by chance, in the general population. Multicystic kidneys rarely appear as a normal kidney and are misshapen and deformed. Even though kidneys enlarge in ADPKD and are cystic, the shape of a normal kidney is still apparent. These are the differences that help to distinguish multicystic kidneys from polycystic kidneys.

Typically, multicystic kidney disease is diagnosed at or shortly after birth and occurs in one kidney only. When multicystic kidneys occur in both kidneys (bilaterally), there is no kidney function, and the baby rarely survives. Multicystic kidneys are a consequence of abnormal embryonic development, where the blood supply is never a part of the developing kidney.

My wife has been diagnosed as having fibrocystic breast disease. She has been involved in a study for at least 10 years in Canada. I believe that 10-13,000 women have been a part of this study. The protocol involves the ingestion of a specific type of Iodine (a type that bypasses the thyroid). The results are staggering. The cysts are more or less deflated, thus reducing the pressure and discomfort associated with the disease. My question is this...is a cyst a cyst?

By definition, a cyst is just a cyst. A cyst is a descriptive term for a fluid-filled sac that is lined by a single layer of epithelium. The cysts seen in fibrocystic breast disease result from different pathways than the cysts seen in ADPKD. However, the end result is the same, a cyst. Just as there are many different diseases responsible for cystic disease in the kidney, such as tuberous sclerosis, chronic renal insufficiency, dialysis, and von Hippel Lindau disease, there are other diseases responsible for cysts in other organs in the body.

I have several simple cysts in my kidneys. What causes these cysts? Is there any treatment?

Simple kidney cysts develop in about 50 percent of individuals over the age of 50 years. They are not inherited like autosomal dominant PKD or autosomal recessive PKD, but develop from microscopic kidney tubules (called nephrons) in much the same way that hereditary cysts form. These tubule segments expand progressively and fill with fluid, and sometimes reach the size of a hen's eggs or oranges. They can be confused with renal tumors and cancers, but they are otherwise usually harmless. In some uncommon cases, it may be necessary to operate on the kidneys to rule out cancers or remove an infected cyst, but in most cases no treatment is needed.

Can PKD manifest itself in other ways? For instance, can a person have cysts in the liver or have some of the other PKD symptoms, but not have cysts in the kidneys themselves? Or can the cysts affect only one kidney?

There is a broad clinical spectrum or phenotype to polycystic kidney disease. Some individuals have liver cystic disease as the main feature of their disease, and in some polycystic kidney disease is the predominant feature. However, cystic disease of the kidneys is always present in ADPKD even when polycystic liver disease predominates. Other systemic or extra-renal manifestations of ADPKD include mitral valve prolapse, intracranial aneurysms, inguinal

or ventral hernias and polycystic ovaries. In ADPKD individuals, cysts can appear in one kidney only (unilateral involvement), usually when the individual is very young. This is frequently at the time of initial presentation. However, invariably, cystic involvement occurs in both kidneys.

There are families with polycystic liver disease without any evidence of polycystic kidneys affected by a separate disease unrelated to ADPKD. Polycystic liver disease without polycystic kidney disease is not caused by the same mutation as PKD1 or PKD2. Just like ADPKD, isolated polycystic liver disease is a dominantly inherited condition. This means that each child of an affected individual has a 50:50, chance or the flip-of-a-coin chance, of inheriting the disease. The gene responsible for polycystic liver disease disorder has been located on chromosome 19.

### **Do all patients within a family suffering from ADPKD develop renal failure at approximately the same time in the course of their disease?**

ADPKD is a disease in which individuals within a family can demonstrate a wide range of disease severity. Sometimes there are three generations of individuals alive: the grandparent is not on dialysis, doing well, while their offspring have reached ESRD or dialysis and their grandchildren are found at birth to have advanced disease. This suggests that other genetic or environmental contributions besides the inherited gene are important with regard to progression of renal failure in ADPKD. These contributors could be other unrelated genes, or environmental factors or other second-hit processes (mutations in the good copy of the PKD1 or PKD2 gene) that affect the kidneys in these individuals.

### **Is it possible that an apparent “spontaneous onset” of ADPKD is due to a dormant gene in the family?**

Spontaneous mutations occur in the PKD1 and PKD2 genes. The chance of this occurring is approximately 1 in 10,000 in the PKD1 gene and even less frequently in the PKD2 gene. This does not mean the PKD gene mutation is present in others in the family and lying “dormant” without a clinical diagnosis, but rather that, at the time of conception, a mutation spontaneously occurs somewhere in the PKD gene leading to ADPKD. Lying dormant implies that there is an affected parent with ADPKD. Such a situation can occur in particularly young affected individuals with no known family members with the disease. In this situation, when parents undergo screening for ADPKD, cysts are present in one of the parents. This situation indicates that the mutated gene was not dormant but present and in an affected parent not clinically diagnosed.

### **What are the criteria for diagnosis of polycystic kidney disease in patients with negative family history?**

Parents of an individual with ADPKD should be screened with an ultrasound exam. If the ultrasound does not show renal cysts, a computed tomographic (CT) or magnetic resonance (MR) exam has better resolution and can identify very small renal cysts in 5%. Paternity issues need to be addressed in ADPKD patients whose parents do not demonstrate evidence of ADPKD. Given that a spontaneous mutation is responsible for approximately 15% of all ADPKD, there are individuals with no other affected family members. In an ADPKD individual with a truly negative family history, the minimum number of cysts required for a diagnosis is five in each kidney. This number is slightly more than the number of cysts required to make a diagnosis in young at-risk individuals for whom a parent with ADPKD has been identified. In addition, other manifestations of ADPKD should be sought after, including liver cystic disease, mitral valve prolapse, inguinal hernias or intracranial aneurysms. For example, hepatic fibrosis, a feature of ADPKD, is rarely seen in ADPKD and can be used to distinguish different cystic disorders. Importantly, renal enlargement is a feature of ADPKD only and not a feature of another inherited cystic disorder. Solid tumors are found in the kidneys of patients with von Hippel Lindau and tuberous sclerosis and are not found in ADPKD. These are the clues that help to distinguish ADPKD from other inherited cystic diseases of the kidney. After careful clinical characterization, if there is still doubt, mutation detection can be used to confirm the presence of ADPKD.

## **Now that both autosomal PKD genes have been isolated, will it be possible to determine if a fetus has the disease? How early in the pregnancy can testing be done?**

Yes, it is possible to determine if a fetus has the disease. Testing can be done if properly planned, and a center where this is available prenatally or at 5-8 weeks gestation. Not only have both PKD genes been isolated, but mutation-detection strategies have been developed that work for PKD1, PKD2 and ARPKD (PKHD) as well. The accuracy of the mutation-detection strategies differ between the two ADPKD gene types, with mutation-detection strategies being the most accurate in PKD2 individuals. Close to a 90% mutation-detection rate is observed in PKD2. In PKD1, mutations are successfully identified in approximately 65-70%. The lower success rate in PKD1 is because the gene is larger and more difficult to analyze, given the long polypyrimidine tract. Additionally, pieces of the gene so similar to PKD1 lie nearby on the same chromosome that it is difficult to separate the pieces from the PKD1 gene. The ARPKD gene has been identified in 2002 and mutations found; however, it is too early to tell the best way to screen all individuals for mutations in ARPKD and the success rate of mutation detection.

## **Would the diagnosis “medullary sponge kidney” be the same as or part of polycystic kidney disease?**

Medullary sponge kidney is common and occurs in 1:100 to 1:200 individuals. The diagnosis is only a radiological one. It is characterized by the presence of dilated or enlarged collecting tubules in the medulla or middle of the kidney. This occurs in many unrelated kidney disorders and has been reported to occur in ADPKD. The cause of medullary sponge kidney is not entirely understood but in ADPKD is probably secondary to the distortion of the collecting system by the presence of cysts in that area of the kidney. Medullary sponge kidney increases the risk of renal stone disease, probably from alterations in urinary flow and may, in part, account for the high frequency of renal stone disease (approximately 25%) in ADPKD individuals.

## **I am a 36-year-old woman, diagnosed with PKD at age 22. Except for high blood pressure and a full abdomen, I have no symptoms. Neither of my parents had this disease; both were tested. No other relatives have PKD. I assumed that I have the recessive form of PKD. How rare is it for someone to have recessive disease and live past childhood?**

You may or may not have autosomal recessive polycystic kidney disease (ARPKD). You could also have a form of autosomal dominant polycystic kidney disease (ADPKD) that is due to a spontaneous mutation. This typically occurs in 15% of ADPKD patients, which is in approximately 1:10,000 individuals. Given that ARPKD occurs in 1:20,000 individuals, it is twice as likely that you have ADPKD. However, ARPKD can present in childhood or in adulthood. The two forms of presentation are different, with adults having signs and symptoms related more to liver disease or congenital hepatic fibrosis. This is not a cystic form of liver disease but a dilated form of the bile ducts of the liver. The kidneys in ARPKD are rarely large, and this helps to differentiate between ADPKD and ARPKD. The signs and symptoms of liver disease related to ARPKD can be serious and life-threatening and include bleeding from the stomach and infection in the liver. The best non-invasive way to tell if you have ARPKD is to undergo a magnetic resonance angiography with cholangiography. This will determine non-invasively if congenital hepatic fibrosis is present and also determine the relative size and cystic involvement of the liver and kidneys.

There is a strong pattern of PKD in my family. At age 18, I was told (after kidney X-rays) that I did not have PKD. There is confusion in our family about who will and who will not have this disease later in life, even if an initial exam proved negative, as in my case. I am 28 years old.

PKD has a variable age of onset, but, in general, most patients with the adult form of PKD will show X-ray signs at age 18, even if they have no symptoms. The standard dye test (IVP) that you probably had is the least sensitive of the tests now available.

In most centers, ultrasound (sonography) is sensitive enough to detect most cases of PKD, but not sensitive enough, in the view of most specialists, to completely exclude the diagnosis. The computed tomography (CT scan) combined with the dye infusion is the most sensitive test available. If, at age 28, you have a negative sonogram and CT scan, current data indicates that you do not have PKD and will not pass it on.

## **Is either race or ethnic background a factor in the development of the disease? Are all races affected equally?**

ADPKD occurs with equal frequency in all races and genders. There is no difference in how often ADPKD occurs in populations whether they are Japanese, Caucasian, African American or Mexican. It is not clear yet whether disease severity differs in different races. It has been suggested the disease severity is greater in Japanese and African Americans as compared to their Caucasian counterparts. However, the data to support this are less than complete. African Americans with ADPKD and a poor renal outcome also have sickle cell disease, which can affect renal function independent of ADPKD. When large groups are reviewed with regard to age of onset of dialysis, African Americans do not appear to be different from their Caucasian counterparts. Small studies suggest that African American patients with ADPKD are diagnosed with hypertension an earlier age than their Caucasian counterparts and have higher serum creatinine values, suggesting worse disease. However, creatinine levels are greater in African Americans with the same level of renal function as Caucasians. Currently, it is difficult to say if ADPKD is more severe in African Americans than Caucasians.

## **Why do people in the same family vary in the intensity and manifestations of PKD?**

This question has not yet been answered fully. There are a number of explanations, however. It is now known that the cysts in patients with ADPKD not only have an inherited PKD1 or PKD2 mutation but that they also have an acquired mutation in the PKD1 or PKD2 gene inherited from the unaffected parent. In up to 70% of all cyst cells, this “second hit” takes place. This suggests that cysts in ADPKD kidneys and livers not only have an inherited gene but also have a mutation, in the non-inherited PKD gene. Given that the second hit, or somatic mutation, is a random event (this could occur at age 1, 5, 15, 45, etc.), this introduces a lot of variability into how a disease expresses itself within a family. This is one possible cause. The second cause is that other genes are also contributing to disease severity in ADPKD. For example, a high blood pressure gene or a diabetes gene or a cancer gene may be in the same family as the ADPKD gene, and, when combined, the disease is more severe in that individual and not in another family member with ADPKD who did not inherit both genes together. Finally, environmental exposures are important risk factors for progression of many different renal diseases. It is possible that toxic occupational exposures are important risk factors for progression of renal disease in ADPKD. These risks have not been evaluated or established in the disease variability found in ADPKD but are worth considering.

## **If PKD is such a common hereditary kidney disease, why is it that I have talked to only one person who actually has the disease, and everyone else I have talked to has never heard of it?**

Good question! One of the mysteries of PKD is why so few have ever heard of this condition. It is much more common than cystic fibrosis, sickle cell anemia and Down’s syndrome, conditions that Americans are much more aware of than PKD. Your question affirms one of the important goals of the PKD Foundation, which is to increase the awareness of PKD among laypersons.

## **I have PKD, but my sister does not have it. She is interested in genetic counseling, and her question is: Can PKD skip a generation?**

If your sister is more than 25 years of age and does not have cysts in the kidneys and/or the liver when examined by computed tomography scan (CT scan) with contrast enhancement, it is most unlikely that she has PKD. There are no

documented instances to our knowledge that PKD has skipped a generation. In other words, if your sister does not have PKD at age 25, there is very little chance that her offspring will have the disease, provided, of course, that her husband does not have PKD.

**I understand that there is a blood test for all family members of a PKD patient to determine who else in the family has PKD and/or to determine which family member is a potential donor. Please provide more information about the test.**

A test is commercially available that depends on the linkage of PKD to a marker known to occur on chromosome 16 or 4. This is called gene-linkage analysis. There are also mutation-detection strategies now available. In order for the test to be informative, one must have one, and preferably, two or more living family members available who have the disease in order to determine which asymptomatic subjects in the family have the PKD gene. If you are interested in being tested, you can contact the genetics department of medical schools in your area, or you can write to the National Center for Education in Maternal and Child Health, 3520 Prospect St., N.W., Washington, D.C., 20057 and request a copy of its pamphlet entitled “Comprehensive Clinical Genetic Services Centers: A National Directory.” This is a listing of genetic service centers throughout the United States, which provide comprehensive diagnostic services, medical management, counseling and follow-up care.

**My mother has polycystic kidneys, as does my sister. I have a polycystic liver, and one polycystic kidney was removed because of infection. The remaining kidney is O.K. Do I have PKD, since only one kidney seems to be involved?**

In view of the strong family history and the evidence of cysts in the liver and one kidney, there seems to be little doubt that you have the hereditary form of PKD. There are a few reports of “one-sided” PKD in the medical literature, but these are extremely rare. A CT scan of the remaining kidney would resolve the issue.

**Do you believe that it is possible for me to be the only child of nine who has PKD?**

In each child of an affected parent, autosomal dominant polycystic kidney disease is a 50/50 proposition. It is like flipping pennies. Occasionally three, four, or five or more heads will turn up in a row. If one flips the pennies a sufficient number of times, the odds will always even out—50 percent heads, 50 percent tails. Many families seem to have a lopsided experience with polycystic kidney disease. In your case, it is a low statistical probability that you are the only one of nine children who has the disease, but not an impossibility. We have communicated with other families in which nearly all of the members seem to have polycystic kidney disease and only a few escaped without it. Large-scale studies of many PKD families have always confirmed the 50/50 ratio.

**Though the gene of polycystic kidney disease is autosomal dominant, isn't there occasionally incomplete penetrance?**

In dominantly inherited diseases, 50 percent of the offspring of an affected parent may inherit the defective gene. If the disease is dominant, then it should be seen in all patients who have the defective gene. In a number of studies (done by performing radiographic studies on all patients at risk for PKD whether they had symptoms of the disease or not), ADPKD has been clearly shown to be an autosomal dominant condition. Incomplete penetrance is a term used to describe a genetic disorder that does not always show up in every sequential generation of a family. Incompletely penetrant genes cause the particular disease to “skip” generations. ADPKD appears to “skip” generations in some families, but incomplete penetrance is not the reason why. If sensitive radiographic tests are not performed, some subjects who have the ADPKD gene and a mild form of the disease may never become aware that they have it. They can, however, pass the gene on to their offspring, and it may resurface there. Thus, because ADPKD has mild forms of presentation in some individuals, it has incorrectly been grouped by some doctors among incompletely penetrant genetic disorders.

## **You indicate in PKD updates that a milder form of PKD exists. I would like to know if a nephrologist can order a test to determine which form of PKD an individual has?**

Two genetic types of autosomal dominant PKD are now recognized. PKD-1 affects the vast majority (85%) of individuals who have polycystic kidneys. Another genetic form, now called PKD-2, appears to have a milder clinical course than PKD-1 (at least 14%). There is a genetic test available for the PKD-1 and PKD-2 type, either through gene-linkage analysis, which requires at least two affected individuals in the family along with the individual who is at risk. As well, mutation-detection strategies are available. These tests are performed at only a few centers scattered throughout the United States.

## **Extrarenal Manifestations**

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My wife has just found out she has congenital hepatic fibrosis. Is there any cure for this condition? We have not been able to find out much on this condition and would like to know more.

Congenital hepatic fibrosis is a pathological diagnosis of the liver in which fibrotic tissue surrounds the biliary ducts. The cause of this is due to an abnormality during embryogenesis when the ductal plates of the liver are formed. This condition can occur in isolation or in association with cystic diseases of the kidney, most commonly in autosomal recessive polycystic kidney disease. Rarely, congenital hepatic fibrosis has been reported to occur in association with autosomal dominant polycystic kidney disease. The biliary ducts of the liver become dilated and deformed. The ducts can appear cystic. Because of these changes, the bile ducts are prone to developing stones or infection. The liver becomes progressively worse over time, and the fibrosis results in ultimate failure of the liver or cirrhosis with portal hypertension. These changes result in other complications, including varices of the esophagus. Varices can cause bleeding from the stomach and the esophagus, which is a life-threatening condition. Varices may require medication, banding of the esophagus, and eventually, transplantation of the liver.

## **What is known about pancreatic cysts in patients with autosomal dominant polycystic kidney disease (ADPKD)? How often do they occur, and what symptoms do they cause?**

Pancreatic cysts are reported to occur in ADPKD. They occur in approximately 11% of ADPKD patients. Typically, they are solitary, and it is unusual to find multiple pancreatic cysts in ADPKD patients. If multiple pancreatic cysts are present, the possibility of other diagnoses should be raised, including von Hippel Lindau disease. Pancreatic cysts in ADPKD have not been reported to cause clinical problems and have been incidental diagnoses made during ultrasound, computed tomography or magnetic resonance imaging examination. Pancreatic cysts have not been found to cause abnormalities in pancreatic function or pancreatic inflammation.

## **Are patients with ADPKD more likely to have diverticulosis? What is the difference between diverticulosis and diverticulitis?**

Diverticulosis has been reported to occur in ADPKD individuals with increased frequency. Diverticulosis is an out-pouching of the wall of the intestine. The intestines are the bowels that carry food and help with digestion. Diverticuli usually develop in the large bowel towards the end of the digestive system. They look like grapes or pouches attached to the wall of the intestine. These pouches have narrow necks where they attach to the bowel or intestine. Sometimes these necks become blocked, and this results in inflammation or diverticulitis. This is a painful condition, and patients usually have abdominal pain, fever and sometimes constipation associated with it. This condition may require the use of antibiotics to heal properly. The way to avoid diverticulosis becoming diverticulitis is to keep your bowel regimen as regular as possible and to avoid episodes of constipation. As many as 70% of dialysis patients with ADPKD have diverticular disease, and it has been suggested but not proven that ADPKD patients with diverticular disease suffer from complications such as diverticulitis or rupture of a diverticuli more often than patients without ADPKD.

## **Is there a relationship between malabsorption of food and nutrients in the GI tract and polycystic kidney disease?**

There is no direct relationship between malabsorption of food and nutrients and polycystic kidney disease. However, in patients with very large kidneys or livers, compression of the gastrointestinal system can occur that then results in difficulty with digestion of food. This is a form of malabsorption that is related to polycystic kidney disease.

## **What is polycystic liver disease (PLD)? Can someone have PLD without having PKD?**

Polycystic liver disease is defined by the presence of multiple cysts in the liver. Liver cysts are present in the majority of ADPKD patients, and the frequency of these occurring increases with age. Hepatic cysts have been reported to present approximately 10 years after renal cysts appear in ADPKD. Women and men are equally affected; however, liver cysts appear earlier and more severely in women. Estrogen exposure in the form of pregnancy and birth-control pill use have been shown to increase the likelihood that liver cysts will develop in ADPKD women. PLD has been reported to occur in individuals without evidence of polycystic kidney disease. This disease is not caused by genes than cause ADPKD and should be considered a separate disorder. Importantly, polycystic liver disease found in ADPKD and polycystic liver disease in isolation do not usually result in liver failure.

## **What information exists about the relationship between hernias and polycystic kidneys? I am a female who was diagnosed with an inguinal hernia at age 18 but was not diagnosed with PKD until age 24. I was wondering if the hernia was a result of the PKD.**

Hernias are found in increased frequency in ADPKD. The hernias are typically inguinal or ventral. The reason for this association has not been well worked out. It is most likely both a developmental error and an abnormality in extracellular matrix. Women are not as likely as men to develop hernias, so the presence of a hernia in a young woman with ADPKD suggests that this is a result of a mutation in the ADPKD gene.

## **I am a 44-year-old woman with polycystic kidney and liver disease. I have heartburn, and my physician ordered x-rays of the stomach, which showed that I have a hiatal hernia. Is the hiatal hernia related to polycystic kidney disease?**

Hiatal hernias are very common in the general population. However, hiatal hernias have been found in ADPKD individuals with increased frequency, particularly those with polycystic liver involvement. Polycystic livers can become quite large and cause compression of the stomach. It is most likely that the hiatal hernias develop as a result of the pressures caused by the presence of polycystic liver disease. This is usually a benign condition and will get better with early evening meals, sleeping with two or more pillows, and using medication to reduce the acidity of the stomach.

## **I am a patient with PKD, and I have had a kidney transplant. I also have polycystic liver disease. What are the reasons that I should avoid estrogens, and what is the latest research about estrogens in polycystic liver disease?**

Polycystic liver disease is aggravated by increased exposures to estrogen. Pregnancy number and birth-control pill use are associated with the presence of polycystic liver disease. Post-menopausal estrogen replacement therapy has been demonstrated to be associated with increases in liver cystic volume, parenchymal volume and total liver volume as compared to ADPKD women not receiving hormone replacement therapy. These changes were seen over a one-year time period. One way to avoid high estrogen exposures in the liver is to take estrogen if necessary in a dermal delivery system or as a skin patch. This tends to avoid high liver estrogen exposures after absorption of estrogen pill use (called the first-pass effect)

and may reduce the effect on progression of polycystic liver disease. The use of estrogen after renal transplantation in which prednisone use may diminish bone density, is an important issue. Estrogen is clearly effective in maintaining bone density in post-menopausal women.

**I am a 46-year-old white male whose father died as a result of renal failure. I was diagnosed with polycystic kidneys at the age of 30 and subsequently found to have a cystic liver, and my right testicle is grossly enlarged due to cysts. Do you have any information on cysts involving the testicular region in polycystic kidney disease patients?**

Cysts in the testicular region have been reported in patients with ADPKD. The cysts are located in the seminal vesicle, which is in the scrotum adjacent to the testicle. If these cysts are in a specific position, they can stop sperm from traveling from the testicle to the prostate, where they can then be available for reproduction. If this occurs, and it is rare, those individuals can be infertile. If this is the case, this can be corrected surgically, or sperm can be obtained indirectly to be made available for fertilization. Overall, men with ADPKD do not have a decline in fertility, and their sperm appear to be normal. Therefore, if a case like this occurs, even though it is related to ADPKD, it is not very common.

**I am a 48-year-old man with ADPKD. I have a very large abdomen and have been told that my polycystic kidneys are particularly large. My renal function is only slightly reduced. My concern is that, during the last two years, I have experienced episodes of vomiting shortly after eating. Except for this, my health has been good. I don't feel particularly ill before or after vomiting. My physician has run some tests, but no obvious explanation has been found. Could my vomiting episodes be related to PKD?**

There are many causes for vomiting that are not related to ADPKD. Stomach ulcers, gastritis, reflux and even medications can cause vomiting. As well, systemic illnesses such as diabetes mellitus or post transplantation can be associated with abnormalities in gastrointestinal function that results in vomiting. With that said, given that your doctor has been thorough and ruled out these problems, there are situations where either polycystic livers or polycystic kidneys become big enough that the stomach becomes compressed. When this occurs, patients usually feel one of two things. Either they develop early satiety, which means they lose their appetite or can only eat small amounts of food and then feel full, or they have episodes of post-prandial (after meal) vomiting. This usually occurs soon after eating, within 30 minutes, and can include undigested food. The treatment for this is not complete but can include medications to help in gastric motility or stomach emptying, changing meal patterns to more frequent meals with smaller amounts, changing the position with eating to lie on the right side to help with stomach emptying and consideration for cyst-reduction procedures to help reduce compression on the stomach.

**A few years ago at a Friends seminar, a PKD researcher said that PKD is becoming thought of as a disease of the connective tissue, rather than just a kidney disease. I haven't seen much about this in the PKD Foundation literature. Did I misunderstand what I heard?**

No, you heard this correctly. The role of the PKD genes is complicated, but it appears that one of the functions of these two genes is to allow for communication between different cell types on the extra-cellular matrix. This component of tissue in the body is part of the connective tissue and may play an important role in the pathogenesis of disease in ADPKD. In support of this, inguinal and ventral hernias, which are disorders of connective tissue, have been found with increased frequency in ADPKD individuals.

## **I am 50 years old and have polycystic kidney disease. For some time now, I have been complaining of continuous ringing in the ears. My physician has made a diagnosis of tinnitus. Can this be a manifestation of an intracranial aneurysm?**

Tinnitus is usually not associated with intracranial aneurysms. The causes of tinnitus are local and in the area of the auditory canals next to the ears. Typically, the symptoms associated with intracranial aneurysms include headaches, change in vision or functional neurological loss. However, intracranial aneurysms that are symptomatic can present in many different fashions, and so one cannot rule out with certainty that tinnitus is not related. The way to make sure that an intracranial aneurysm is not present is to have a magnetic resonance angiogram of the brain performed. This test can detect even small intracranial aneurysms.

## **Is a brain cyst part of autosomal dominant polycystic kidney disease?**

Cysts have been reported in the brain with increased frequency in polycystic kidney disease patients (usually in 3-5% of patients). These cysts are usually in the pineal region, are incidental findings and do not cause trouble to patients. The protein polycystin, which is produced by the ADPKD gene, is found in very high concentrations in the brains of patients with ADPKD. Whether this accounts for the cysts found in the brains of ADPKD patients is unclear.

## **My mother and her brother had PKD, and both had ruptured brain artery aneurysms in their 50s. I am 42. Should I have an X-ray test for brain aneurysms?**

Current estimates indicate that, in the absence of any symptoms, the risk of a PKD patient having an aneurysm is between 5 and 10 percent. Aneurysms tend to run in families. Current studies suggest that there are no compelling reasons to screen all persons with PKD for aneurysm; however, if there is a family history of aneurysm, screening by angio magnetic resonance imaging (MRI) is indicated. Patients with PKD who note a change in symptoms involving the head region (blurred vision, dizziness, severe headache) should consult their physician.

## **Can you please tell us symptoms of aneurysms of the brain and abdomen?**

Aneurysms (ballooning) of brain blood vessels will occasionally cause recurrent, severe headaches. Patients have also reported eye disturbances, nausea, vomiting, and stiff neck. Fortunately, aneurysm of the brain vessels is relatively uncommon. The aneurysms tend to occur within families of patients who have polycystic kidney disease. We all have headaches from time to time, so longstanding “nagging” headache should not be a worry to patients with polycystic kidney disease. On the other hand, a PKD patient with a new type of headache that is unrelenting should seek medical attention. Aneurysms in the abdominal blood vessels usually occur in the aorta, the major blood vessel running through the body just in front of the spinal column. Patients will occasionally notice an “extra heartbeat” in the upper abdomen when an aneurysm is present. These types of aneurysms can also cause pain in the abdomen of a nonspecific nature. It is relatively easy to check for abdominal aneurysm with a sonogram test to exclude this as a cause for abdominal pain.

## **I am a PKD patient on dialysis. Two weeks before my kidneys failed, I had a stroke. The CT scan showed an intracerebral (brain) hemorrhage but no aneurysm. I know about PKD and cerebral aneurysms, but I wonder if there is a connection between PKD and intracerebral vessel weakness?**

Individuals with high blood pressure, whether they have PKD or not, have a higher incidence of intracerebral hemorrhage than those who do not have elevated blood pressure. Since more than one-half of polycystic kidney patients have elevated blood pressure, there may be an increased incidence of stroke due to intracerebral hemorrhage that is not related to aneurysm formation. There is no information to indicate that the blood vessels of polycystic kidney patients are inherently weaker than normal. Thus, intracerebral hemorrhage in a PKD patient with normal blood pressure should raise the question of an occult cerebral aneurysm.

## **Once an aneurysm has been found, how successful is surgical intervention?**

Not all intracranial aneurysms require surgery. While aneurysms causing symptoms should be treated immediately, the recommendation for surgery in the case of incidental, asymptomatic aneurysms will depend on the estimated risk of rupture if left untreated and the risk of surgery. These risks are determined by the number, size and location of the aneurysms, the age of the patient, and the expertise of the neurosurgeon. In good hands, the average incidental intracranial aneurysm can be repaired with a less-than 5 percent risk of dying or having major complications.

## **We have heard of patients with PKD who have ruptured cerebral aneurysms. My husband has PKD and is 65 years old and on dialysis. His sister died of a ruptured aneurysm at age 32. We have three children ages 24-33, and the oldest has PKD. What if anything, should we do?**

It does not appear necessary to look for aneurysms in every person with PKD, since it seems that aneurysms are not very common in PKD. There has been a suggestion that aneurysms may occur in some PKD families and not in others. Because of this, some doctors might suggest that only PKD patients in such families, or PKD patients who would cause a high risk to others if an aneurysm ruptured and they became unconscious (like an airplane pilot), should be studied for aneurysms. Ruptured aneurysms don't seem to happen very often in PKD patients on dialysis. The tests available to look for aneurysms include arteriography, computed tomography, and the new technique of magnetic resonance angiography. This last test appears to be the easiest and the best.

## **My 38-year-old sister has been diagnosed as having two fluid-filled arachnoid cysts in the lining of the brain. A CT scan and MRI were used to confirm the diagnosis. The doctors don't know if these cysts are associated with PKD. Do you have any information about this?**

Arachnoid cysts have indeed been detected by CT scan in several patients with polycystic kidney disease. Very little is known about how these cysts in the brain may affect patients. In the experience of a few nephrologists, these cysts have been asymptomatic, and no treatment was recommended. There is very little experience in the management of these cysts. Should a patient develop symptoms that neurologists and neurosurgeons agree may be caused by an arachnoid cyst, direct intervention may be indicated.

## **I am a 39-year-old man with polycystic kidney disease. My father and two brothers, also with PKD, had heart attacks before the age of 50. Is there any relation between PKD and an increased risk for heart attacks? What can I do to reduce my risk?**

The most common cause of death in all patients with renal failure, including ADPKD, is cardiovascular death. This is most likely due to a combination of the presence of hypertension, the pro-inflammatory state of renal insufficiency, and abnormalities in lipid metabolism found in patients with all types of renal disease. Hypertension occurs early in ADPKD, prior to the loss of renal function. It occurs, on average, a decade earlier than the hypertension found in the general population. Hypertension is an important risk factor for the progression of renal disease in ADPKD and is associated with the presence of left ventricular hypertrophy, which is an independent risk factor for cardiovascular death. Aggressive control of hypertension in ADPKD is helpful in reversing the presence of left ventricular hypertrophy, particularly with the use of angiotensin-converting enzyme inhibitors. One way to reduce cardiovascular risk if you have ADPKD is to monitor your blood pressure closely, and, if you have high blood pressure needing treatment, to have a blood pressure goal of less than 125/75 mm Hg. This monitoring will help prevent organ damage (left ventricular hypertrophy) related to hypertension and probably reduce the rate of progressive loss of renal function in ADPKD. If these goals are met, your cardiovascular risk will decline significantly.

**What happens to the adrenal glands, which sit on top of the kidneys, when the kidneys become enlarged in PKD? Do the kidneys push on the glands and make them excrete adrenaline?**

The adrenal glands do not appear large when viewed by computed tomography in ADPKD. Although they rest on top of the kidneys, the cystic expansion of the polycystic kidney does not interfere with the adrenal gland. However, of interest, one of the hormones, aldosterone, made in excess quantities, results in high blood pressure and protein in the urine. Some, but not all, studies suggest that aldosterone levels may be elevated in ADPKD patients.

**I have PKD, and my cysts are small. The only problem I have associated with my disease is high blood pressure. I take Benazepril (10 mg) for high blood pressure. I want to quit smoking, but can I take Zyban (bupropion) to help me stop smoking?**

There is no contraindication to taking Benazepril and Zyban together. In addition, Zyban is not contraindicated in patients with polycystic kidney disease. High doses of Zyban can increase blood pressure, so it is important to make sure that your doctor is involved as you use this medication. Most importantly, the health benefits of quitting smoking far outweigh the risks of polycystic kidney disease in someone like yourself, where the disease appears to be very mild.

**I am in the military, am 41 years old, and have PKD. I am taking Benazepril for high blood pressure. I am also taking the Depo-Provera shot for birth control. My doctor has told me that I should stop taking the shot, because it may raise blood pressure. I do not plan on having children, and he suggests that I have a tubal ligation since I don't want any other birth-control method. Does the Depo-Provera shot increase blood pressure? Will having the tubal ligation interfere with my PKD?**

Depo-Provera has been reported to be associated with increases in blood pressure as well as edema and swelling. However, high blood pressure is a relatively uncommon side effect of Depo-Provera. Depo-Provera is a long-acting progesterone that suppresses ovulation. The advantage of Depo-Provera is that one does not have to remember to take a pill every day. The other choices for birth control include diaphragm and spermicidal jelly, daily birth control pill use or tubal ligation. Tubal ligation has no special effect on women with ADPKD.

**Recently, I spent some time at a natural health farm. My blood pressure was up, my weight was up, and I felt terrible. I fasted on juices, raw vegetables and fruit, and water. I was able to keep my pressure at a normal level while I was there, without medication. I would like to return to the health farm for a water fast. Since I have polycystic kidneys, is there any harm involved? When I returned in October after a 10-day stay, I had a blood pressure test, which turned out to be the best of all tests in the past 9 or 10 years.**

We are what we eat. You provide a good example of what the National Institutes of Health and the Heart Lung and Blood Institute and the National Education Program for High Blood Pressure recommend for the initial treatment of high blood pressure: DIET AND LIFESTYLE MODIFICATION. Regular exercise, weight loss if necessary, and reduced sodium intake can help control hypertension in the majority of individuals with mild essential hypertension and help to control blood pressure in others with kidney disorders. Unfortunately, most patients have a difficult time successfully modifying their diet enough to reduce the amount of salt in their diet to a level that will reduce blood pressure. Part of the difficulty is related to the fact that 80% of our dietary salt intake comes from processing of food or preservatives. This is something that we as individuals cannot change without obtaining our foods from fresh, unprocessed sources.

One special feature of the health farm that you describe is the use of vegetables and fruits in the diet. These foods are rich in potassium. Although patients with kidney disease can have a difficult time with maintaining potassium balance, if kidney function is normal or near normal, increasing potassium intake is not a problem. Interestingly, if one increases potassium intake, particularly if he or she had a relatively low potassium intake to begin with, blood pressure will decrease significantly. Part of the benefit that you received from visiting this health farm is in part related to the increase in potassium in the diet you received. Clearly, if one is about to embark on a major change in their diet, it is important to review the potential changes with your dietician or doctor. One of the most important advances for patients with renal disease, with GFR below 50 ml/min, was instituted in January 2002 is that any Medicare or Medicaid beneficiary is eligible for a full consultation and regular follow-up with a dietician to obtain the correct information regarding dietary intake.

Water loading in people with normal renal function is usually safe, and most individuals can drink large amounts of water without a problem. However, if one has less than normal renal function, or if one is taking medicine(s) that affect water handling by the kidney, such as a diuretic or water pill, increasing water intake should be done with caution. No one should be drinking in excess of 10 liters of water a day.

### **I have PKD, am the mother of one child, and very much want another child. I read that more than three pregnancies could have a negative effect on a woman with PKD. Why is three the magic number? Are two pregnancies almost as bad?**

Increasing number of pregnancies has been associated with a very small negative effect on renal outcome in ADPKD. This effect is so small that it is only apparent by statistical analyses (analysis of a large number of ADPKD women, and not an individual patient) when a woman has had more than three pregnancies. There is no magical cutoff between two and three pregnancies. If you are otherwise healthy and do not have medical conditions related to ADPKD such as hypertension or renal insufficiency, the chances of your having a successful pregnancy and not causing damage to your kidneys is extremely good. Successful pregnancies occur in ADPKD women with the same rate of success as in the general population. However, new-onset hypertension, worsening hypertension and pre-eclampsia are frequent complications occurring in up to 30% of pregnancies. These complications are most common in women with hypertension or renal insufficiency prior to becoming pregnant. Should you become pregnant, it is important for you to see your obstetrician regularly and to see a nephrologist who has experience in taking care of women with renal disease.

### **I have PKD and have been taking Enalapril for three years with excellent blood pressure control. I recently read in *Worst Pill, Best Pills II* by Wolfe and Hope that Enalapril shouldn't be taken by people with kidney disease. My kidney function has always tested satisfactory. Should I be concerned?**

There is reasonable concern that individuals with advanced renal disease or serum creatinine concentrations greater than 3.0 mg/dl should be careful when taking angiotensin-converting enzyme inhibitors. When renal function is this low, ACE inhibitors can cause an acute, reversible change in renal function particularly when individuals are taking diuretics simultaneously or are on low protein diets. Importantly, potassium handling by the kidney can be affected in individuals with poor renal function and ACE inhibitors can exacerbate the poor handling of potassium. In other words, patients with poor renal function, taking ACE inhibitors can develop hyperkalemia or a high potassium concentration in the blood. This is dangerous, and, if potassium levels are too high, it can be a life-threatening problem. This is most likely why this book cautions against using these agents in patients with renal disease.

Given that ACE inhibitors appear to carry many beneficial effects in patients with renal disease, we try our best to be able to use them even in patients with markedly elevated creatinine levels. There are many ways to continue ACE inhibitor therapy in these situations and avoid high potassium levels. This includes modification of the diet to reduce potassium intake, the addition of diuretics to help the kidneys excrete potassium, the use of a potassium-binding called Kayexalate, and to maintain volume status or fluid intake to avoid dehydration and further elevations in serum creatinine concentration.

**My blood pressure is 145/100, and my doctor has recommended Enalapril, which may help preserve kidney function as well as lower blood pressure, as I understand it.**

It is very important to bring blood pressure under good control, as this will diminish scarring of the tiny blood vessels in the kidney. Enalapril has been used for blood pressure control in polycystic patients with reasonable success. It is usually prescribed together with a salt-restricted diet and weight control.

We do not know for sure if Enalapril or other related drugs that block the angiotensin-converting enzyme have any other special actions for polycystic kidneys, but one hypothesis suggests that, by lowering the blood pressure in the kidney filters (called glomeruli), we may prevent additional scarring of these important structures.

Confirmation of the hypotheses will not be known for several years, but, in the meantime, Enalapril and other equally good blood pressure-lowering drugs make good sense in the management of high blood pressure.

**I have ADPKD and was found to have hypertension in 1979. I have been treated with a combination of metoprolol and hydrochlorothiazide, which has kept my blood pressure stable at 120/90. I have never realized side effects. My lab values are completely normal. I would like to know whether an ACE inhibitor (Enalapril, Captopril) would have any advantages in relation to my present pharmacologic treatment in this stage of my hypertension.**

Hypertension can accelerate the progression of renal insufficiency in patients with polycystic kidney disease. There is reason to think that ACE inhibitors may have a theoretical advantage in the treatment of hypertension in patients with ADPKD. A controlled clinical study has not been done, however, and we would not be inclined to recommend a change in treatment if the blood pressure is well controlled with the current regimen. On the other hand, in patients with hypertension who have not been previously treated, ACE inhibitors are probably good choices for the initiation of antihypertensive therapy.

## Renal Manifestations

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**In December 1996, my polycystic 64-year-old husband, who is a peritoneal dialysis patient, had a fever and chills. Blood cultures showed an E. coli infection. The search was made for the infection site. All tests and scans of abdomen and gallbladder, and colonoscopy were negative. A urine specimen was unattainable because my husband no longer makes urine. He had one kidney removed four years ago due to discomfort and size. It is believed that E. coli came from the remaining kidney. I would like to know if this happens with PKD patients, or is this very unusual?**

This is not unusual. Escheri Ca Coli is a bacterium that typically comes from the gastrointestinal tract. It can make its way into the urinary system by fecal contamination or is due to the presence of stones, decreases in urinary flow or because the prostate glands in men get large. In a patient with polycystic kidney disease, an infection like this could easily come from a polycystic liver, the gallbladder, from diverticular disease that is often found in PKD patients, or from the urinary system (from the bladder up to the kidney). It is possible that it has come from his polycystic kidney; however, this should be considered as a diagnosis of exclusion until all other possible sites have been ruled out. Given that this is the first time that this infection has been present, it was appropriate that other tests that should be done before assuming that this has come from the patient's kidney.

## Can one have a kidney infection with a negative urinalysis and urine culture?

In patients without ADPKD, the urinalysis and the urine culture usually demonstrate evidence for infection when someone has a kidney infection. In ADPKD, the source of the infection is most often the cysts in the kidney that no longer communicate with the collecting system or the urinary tract. When these become infected, there is no place for the bacteria to travel to in the urinary system, so it is infrequent that the urine culture is positive in patients with ADPKD who have a cyst infection. It is more likely that the bloodstream will have a positive culture than will the urine. Even so, it is important to obtain a urine sample and test it for the presence of bacteria. If the bacteria is identified, it is most likely that the correct antibiotic will be chosen for the treatment of infection.

## Is aspiration of a single large cyst indicated for relief of recurrent urinary infection?

There are multiple types of cysts that are not part of the genetic disease, polycystic kidney disease. Oftentimes, cysts can be causing obstruction in the urinary tract, which predisposes to infection, or, alternatively, infections may have nothing to do with the cysts at all since solitary cysts are common in the general population. A physician should evaluate each case so as to decide whether autosomal dominant polycystic kidney disease is present. In ADPKD, aspiration of single cysts is not routinely recommended unless severe pain or refractory infection is present. If another kind of cystic disease is present, the physician will need to determine what relationship that cyst has to recurrent urinary tract infections. If a single cyst is causing obstruction, it can be aspirated under ultrasound guidance, and relief of pain symptoms may be obtained.

## Antibiotics help recurrent kidney infections for a few days, but the symptoms – nausea, fever, chills, pain, fatigue and weakness – recur when they are discontinued. My doctor is open to suggestions.

Recurrent kidney infections usually mean that one or more cysts have been infected. It is important for the physician to try to culture the bacteria from the bloodstream and the urine so that a specific treatment can be prescribed. Unfortunately, the bacteria “hide out” in the cysts and cannot be cultured in many cases, and antibiotics must be given blindly. We have known several patients who required continuous antibiotic treatment for several years in order to control the symptoms.

Research supported by the PKD Foundation has led to the discovery of two drugs that may be helpful in some patients with recurrent and resistant kidney cyst infections. One of them, chloramphenicol, is an old-time medicine that works well but has a reputation for causing serious anemia on rare occasions. Nevertheless, it can be used for treating difficult cyst infections if patients are willing to take the small risk. Gyrase inhibitors (norfloxacin and ciprofloxacin) are very good for treating infected cysts. Considerable experience has been gained with these drugs, and, so far, only a few problems have surfaced.

## I am a 26-year-old female who has had three urinary tract infections in the last two months. My back has really been bothering me.

Recurrent urinary tract infection is a very common problem for women, and especially difficult for PKD patients. Most often the bacteria (germs) that cause these infections enter the urinary tract through the urethra, the opening to the bladder just below the pelvic bone. Many women can relate the infections to recent sexual intercourse. For patients with PKD, it is very important that a urine culture be obtained each time you have symptoms of infection (burning on urination, a feeling of urgency to pass urine, fever, chills, and back pain that develops with these other symptoms). Your doctor should do the culture before you receive antibiotic treatment. Very often the infecting bacteria can be identified and specific treatment prescribed. The germ may be different with each infection, suggesting that the bacteria are invading from outside the body. If the same germ is found each time, it is possible that the antibiotics are not destroying a stubborn focus of infection in the urinary tract.

Recurrent infection with the same germ can be seen in patients with infected cysts or kidney stones. All urinary tract infections in PKD patients should be treated aggressively and usually for longer periods than in persons with normal kidneys. Women patients with recurrent infections (who have reasonably normal kidney function) are advised to drink six to eight cups of fluid every day (preferably plain water), urinate every two hours during the day and within 30 minutes after intercourse. Evaluation by a nephrologist or urologist is also advisable.

## **Can persons with PKD have kidney stones removed with the new shock-wave machines?**

PKD patients have a high incidence of kidney stones, and these can cause serious problems. A recent review of the use, in a number of medical centers, of extra corporeal shock-wave lithotripsy on PKD patients with stones suggests that it can be used with few complications.

**I am male, 38 years old, and was diagnosed with PKD in 1987. I have recurrent calcium oxalate stones for which I take hydrochlorothiazide twice daily, potassium citrate (12 tablets daily) and magnesium oxide. I pass three to five stones per week, all less than 3mm in diameter. I have normal amounts of oxalate in my urine and drink three to four quarts of water a day. Nothing seems to work. Will anything stop kidney stone formation?**

Stone formation can be stopped in most patients, including those with PKD, with simple measures such as drinking enough fluid and, when the chemical composition of the urine is abnormal, with dietary changes or medications such as those you are taking. You should realize that passage of stones does not always indicate that a particular treatment is not working. X-rays are needed to confirm that the stones that are passed are new and not stones formed before starting the treatment. The patients who fail the conventional types of treatment and continue to form stones may benefit from evaluation in centers specializing in renal stone disease.

## **I have been told that my kidneys measure 38 and 28 centimeters in length. What is the record kidney size in PKD?**

There is no Ripley's Believe it or Not for kidney size in PKD. However, 38 and 28 cm are large for a polycystic kidney. Most end stage PKD kidneys weigh approximately 20-25 lbs or 10 kg each. This accounts for the pain, fatigue and decreased energy, difficulty with sports and an active lifestyle that many PKD patients feel. As well, when kidneys get to be this size, eating regular quantities of food can be difficult.

**I have polycystic kidney disease and have been treated for hypertension for a number of years. At the last visit with my nephrologist, I was informed that my urine contains protein. Is this abnormal, and is this cause for concern?**

Protein in the urine is not a common manifestation of ADPKD. Less than 20% of all ADPKD patients have detectable levels of proteinuria by urinary dipstick. There are many renal diseases that have large amounts of proteinuria associated with them, and this is not one of those conditions. The proteinuria that is found in ADPKD is low grade and usually less than one gram/day. If there is more protein in the urine than that, it is possible that another process is taking place in your kidneys. When found in ADPKD, proteinuria is usually associated with more severe disease including higher blood pressure levels, bigger kidneys, higher serum creatinine concentrations or lower levels of renal function. This means that proteinuria in ADPKD is probably a marker for worse renal function and may also predict those individuals who are more likely to progress to ESRD.

## **My wife has PKD and would like to know why she has so much renal bleeding. What causes it, and what, if anything, can be done to control it?**

Renal bleeding can be due to a number of causes. Bleeding can be spontaneous from a ruptured cyst. This can be painful or painless, depending on where the cyst lies and how much stretch to the cyst occurs. The cause of bleeding from a ruptured cyst is not always clear, but recent trauma can be important; use of anti-platelet drugs such as adult aspirin or Coumadin can be important. The larger the kidney or cyst, the greater the chance that bleeding will occur. Therefore, those individuals with bigger kidneys are at increased risk for bleeding from their kidneys.

Bleeding can also come from a stone in the kidney or collecting system of an ADPKD kidney. Infection, from either the bladder or kidney, can also be a source of blood in the urine. Given that some of these conditions need early medical treatment, whenever bleeding occurs, it is important to see your physician right away or at least contact her/his office. The bleeding, if due to a hemorrhagic cyst, should be limited to as short a time period as possible. The way to help this happen is to drink plenty of fluids, keep your blood pressure controlled, and, if bleeding does not disappear in 24-48 hours, to go to bed or the recumbent position. All of these maneuvers should help to limit the duration of bleeding from the kidney.

## **Pregnancy, Birth Control, and Menopause**

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### **I'm 18 years old – diagnosed with PKD at birth. My creatinine level is 3.3. How might I go about having children without a complicated pregnancy?**

Assuming you are of normal adult height and weight, the creatinine level suggests that kidney function is between one-fourth and one-third of normal. If high blood pressure is present, both of the factors of a low kidney filtration rate and high blood pressure make pregnancy complicated and sometimes extremely difficult. Not only may there be complications that endanger health, but there may be complications that endanger the baby's health. Prior to pregnancy, it is very important to seek the advice and counsel of a "high risk" obstetrician—that is, someone who takes care of pregnant women who have complicated health problems. One should ask specific questions about the risks to the mother and to the baby. In autosomal dominant PKD, the child will have one out of two chances of having the disease; if the disease is autosomal recessive, the disease will not be passed on unless the father should have one recessive gene. At the moment, there is no way to know about this in advance.

### **I had a large ovarian cyst and one ovary removed when I was 21 years old. My gynecologist has recommended staying on low-dose birth control pills until I am ready to have children to prevent the formation of more ovarian cysts. I have been taking these pills for seven years, and my blood pressure and kidney function are normal. Could birth control pills speed up the growth of my kidney cysts?**

There is no information to show that birth control pills increase the growth of kidney cysts. Computed tomographic studies have shown that hormone replacement therapy has no effect on renal volume or renal cyst volume in a small group of ADPKD women. The relationship between birth control pill use and progression of cystic disease is strongest in cystic disease of the liver as opposed to cystic disease of the kidney.

## Is estrogen replacement therapy after menopause contraindicated in patients with ADPKD?

Even though it has been shown that hormone replacement therapy affects the rate of growth of liver cysts in ADPKD, cysts in the liver do not appear to affect liver function. Even in individuals with massive polycystic liver disease, liver-function tests remain normal, and liver mass unaffected by cystic disease remains unchanged. So, if there is good indication to receive estrogen replacement therapy and the liver cystic disease is mild, it is reasonable to consider the estrogen patch for hormone replacement therapy.

## I saw my gynecologist because of irregular menstrual cycles and was diagnosed with polycystic ovary syndrome. Is this related to polycystic kidney disease? Are patients with PKD more likely to have polycystic ovaries?

Polycystic ovaries are a separate clinical entity associated with facial hair, acne, and infertility. This form of polycystic ovaries is not associated with ADPKD. However, in women with ADPKD, cysts in the ovaries can develop. They are not related to polycystic ovary syndrome. The treatment of polycystic ovaries unrelated to ADPKD usually includes the use of birth control pills. As well, the polycystic ovaries can be treated by taking a small piece of tissue out of the polycystic ovary. If birth control pills are used, it is wise to undergo imaging of the liver to determine if significant polycystic liver disease is present. If so, one might consider wedge resection of the polycystic ovary instead of birth control pill use. Currently, polycystic ovaries in PKD have no known associated abnormalities and are not treated unless large enough to cause pain. If this occurs, removal of the ovary is often considered.

## Kidney Failure, Dialysis, Transplantation

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### I am contemplating a kidney transplant after being on CAPD for a year. Since we now know that PKD is genetically transmitted, I am wondering whether there is a genetic tendency for rejection of cadaver organs. My father had three kidney transplants, and all failed. Does that mean that I have a genetic predisposition to experience a rejection?

There are risk factors for the loss of a transplanted kidney. Transplanted kidneys will reject if immunosuppressive regimens are not properly administered. They will also reject if the match between the donor and the recipient is not good. Importantly some antigens are more rejectable than others, and, some people, unfortunately, can inherit these. However, the role of these inherited antigens becomes quite small when appropriate immunosuppression is given. The immunosuppressive medication's available today are more effective than medication used only 5-10 years ago. Regardless of someone's genetic makeup, as the number of transplants in an individual increases, the chance of rejection increase markedly.

### What is the normal serum creatinine in adults, and how do you interpret it?

Serum creatinine is a marker of kidney function or glomerular filtration rate that all doctors and health care providers use. It has many advantages and is easy to measure. However, there is a wide range of "normal" for serum creatinine that can depend on the race of the patient, the body weight or muscle mass, the gender and the age. All of these factors mean that a serum creatinine concentration of 1.0 mg/dl (considered normal) in a six-foot-two inch man who works out in the gymnasium gives a higher level of function than a serum creatinine of 1.0 mg/dl in an elderly woman who is five foot two inches. The National Institutes of Health is trying to help laboratories incorporate most of these variables into a formula so that doctors and their patients can get an estimate of kidney function from their serum creatinine.

For people with kidney disease of any type, it is important to note that a large amount of kidney function is lost while the serum creatinine concentration is within the normal range. What this means is that if an individual usually has a serum creatinine concentration of 0.8 mg/dl (considered normal), which stays the same for many years, and then, all of a sudden, the serum creatinine concentration is 1.2 mg/dl (still considered normal), that person has lost 50% of their kidney function. This is why it is so important to know what your serum creatinine is, not just that it is normal.

### **I have PKD and have lost some renal function. At what hematocrit level do most people start taking erythropoietin?**

The kidney makes a hormone called erythropoietin. This hormone stimulates the bone marrow to produce red cells. Erythropoietin levels are increased when red cell number declines (anemia) to help maintain an appropriate red cell number. Erythropoietin levels decrease as kidney tissue is damaged or destroyed and usually results in anemia due to renal disease. It was once thought that ADPKD patients did not have anemia or suffer from a loss of erythropoietin as much as patients with other renal diseases. We now know that this is not true and that ADPKD patients are just as likely as any other patient to have anemia related to renal disease. Erythropoietin is a protein and cannot be taken as a pill. Erythropoietin therapy should be started when the hematocrit is below 30% or when the patient is symptomatic. Erythropoietin will only be effective if all other causes of anemia or a low blood count such as iron deficiency are corrected. Given that erythropoietin is a protein, it must be given as an injection under the skin or through the vein. These injections are usually given once a week.

### **I am 62 years old, and I have polycystic kidney disease. My physician has told me that my renal function is beginning to decline, but that it may still be a few years before I need dialysis. Is there an age limit for renal transplantation?**

In the United States, there is no formal age limit to renal transplantation. There is some concern that as people get older, there are more illnesses or medical conditions present that make the possibility of a successful transplant less likely. During the transplantation evaluation performed on every applicant, there is a greater likelihood that there will be a medical or surgical contraindication to transplantation (such as cancer, significant heart disease, etc.).

### **What are some of the signs and symptoms of PKD patients on dialysis, and how are they handled? How long can a patient remain on dialysis?**

Patients who are on hemodialysis typically dialyze three times a week. Hemodialysis or cleaning the blood is performed in three to four hours at each session. This process performs the work of the kidneys that usually takes place 24 hours a day, 7 days a week. Because of the massive changes in blood chemistries and the volume of fluid that is removed during the short time of dialysis, patients feel tired and drawn out after their dialysis session. Often patients will take a nap or rest for the rest of the day following dialysis.

Another biochemical abnormality that occurs in renal failure in patients who receive dialysis is anemia or a low blood cell count. The kidney is a source of a hormone called erythropoietin. This hormone stimulates the bone marrow to make red cells and correct the anemia. Very little erythropoietin is made in patients in renal failure, and this results in anemia. This accounts in part for the fatigue, tiredness, lack of concentration, shortness of breath and depression that a lot of renal failure patients experience. Erythropoietin is now given to patients on dialysis regularly along with iron supplementation to correct the anemia. This process has allowed for higher hemoglobin levels and renal failure patients who are much more functional.

Hyperparathyroidism is another condition associated with renal failure. The parathyroid glands are next to the thyroid in the neck (PARA-thyroid). These glands respond to changes in calcium concentration in the blood. When calcium levels go lower than normal (which happens quite often in patients with renal insufficiency or in renal failure), the parathyroid

glands work extra to try and bring the low calcium levels back to the normal range. Even though calcium levels improve, other problems arise because the parathyroid hormone levels are maintained at too high a level. These problems include itchy skin or pruritis, loss of matrix or bone from the skeleton, and deposits of crystallized calcium into soft tissues of the body. The best way to correct this process is to maintain calcium levels in the normal range. This is typically done by restricting the amount of phosphorus in the diet (see DIET) as well as by supplementing vitamin D sources that help absorb calcium from the diet.

Specific to ADPKD, these patients do very well on dialysis compared to the rest of the renal failure population. There are complications that occasionally arise related to ADPKD that include diverticular disease and rupture or infection of cysts in the kidneys or liver. It is important for patients with ADPKD who develop fevers and abdominal pain to let their physicians know immediately so that these potential complications can be investigated further.

### **Can peritoneal dialysis patients return to peritoneal dialysis after severe peritonitis?**

Peritoneal dialysis can be resumed after severe peritonitis. One of the problems that patients can face is that the surface area available for dialysis may diminish with an episode of peritonitis related to scarring of the peritoneal surface during the infection. If the reduction in surface area is significant enough, then there may not be adequate surface for dialysis, and patients can then be under-dialyzed. Given this, although most patients can return to dialysis after an episode of peritonitis, sometimes there is membrane failure.

### **Is there anything a polycystic kidney patient being treated with chronic ambulatory peritoneal dialysis can take to increase the blood pressure?**

Patients with all types of kidney diseases who are treated with dialysis, peritoneal or hemodialysis for chronic kidney failure, occasionally experience periods of low blood pressure. Polycystic kidney patients do not seem to be singled out in this respect. Most commonly, low blood pressure is caused by the loss of body fluids due to aggressive dialysis or because of intercurrent problems such as vomiting or diarrhea. In a few individuals, the blood pressure may be persistently decreased despite adequate attention to body fluid status and the elimination of medications that might lower the blood pressure. Nephrologists will usually test for heart failure, nerve damage (neuropathy) or the interposition of other diseases such as amyloidosis or Addison's disease in the search for the cause of hypotension. Unfortunately, there are a few individuals in whom no cause can be found, and the nephrologist must resort to a trial of different medications that may be of benefit.

### **What advice can you give on the care of arteriovenous grafts used for hemodialysis?**

Grafts are tricky things. Some become clotted early and repeatedly. Others remain open for years. They become clotted for a number of reasons – too much pressure on them (particularly if you lie on that arm at night), decreased blood pressure, abnormal clotting mechanisms, and strictures that develop in the veins at the end of the grafts, to name a few. Many of these things are beyond control. Individuals should not allow prolonged pressure on the graft or too tight clothing on that arm, for example. Blood pressure should not be taken in that arm, unless the person taking it knows a lot about grafts and has no other option but to take it in that arm. Very importantly, it helps to adhere to the fluid-management plan between dialysis treatments to avoid gaining a great deal of fluid weight. The fluid ingested between dialysis treatments gradually seeps into the tissues. During dialysis, the fluid must come out of the blood vessels before any can move from the tissues. The blood volume then becomes very low, and may lead to clotting. Sometimes blood-thinning agents are prescribed for those who have repeated clotting, especially when no strictures are found in the graft.

## **I am a PKD dialysis patient. I have incessant nausea, which my doctor feels is caused by the liver and kidney cysts. Is there anything to relieve the nausea?**

Patients on dialysis may have nausea for a variety of reasons, such as insufficient dialysis, too much acid production by the lining of the stomach, or neuropathy caused by renal failure. A markedly enlarged polycystic kidney or liver can press on the stomach. As a result, patients may feel full with small meals, have frequent heartburn, and vomit easily. These organs can compress the inferior vena cava (the vein returning the blood to the heart), which can cause low blood pressure during dialysis and may be associated with nausea. Without having a better idea about the cause of your nausea, we cannot give you more specific recommendations. Sometimes physicians cannot find or solve the cause of the nausea, and anti-nauseant medications are prescribed.

## **How do polycystic kidney disease patients do on various forms of dialysis as compared to transplantation?**

ADPKD patients tend to do better on dialysis than other patients with other kidney diseases. For example, patients with diabetes do not survive as long on dialysis as patients with ADPKD. The leading cause of death in ADPKD patients, whether they are receiving hemodialysis, peritoneal dialysis or a transplant, is cardiovascular or cerebrovascular. Even though ADPKD patients do better than other types of patients on dialysis, their survival is improved with a kidney transplant. There are complications in dialysis that are specific to ADPKD patients. Importantly, as ADPKD individuals survive longer, complications of liver cystic disease become more common. Complications include liver cyst hemorrhage, liver cyst infection and biliary stone disease. As well, in ADPKD individuals who undergo peritoneal dialysis, the development of inguinal or ventral hernias becomes more common. If the ventral hernia becomes big enough, it may be impossible to undergo peritoneal dialysis.

ADPKD patients tolerate transplantation very well. The complications that they endure are the same as other renal patients, with the exception that post-transplant lympho-coeles are more common in ADPKD patients.

## **Will polycystic kidney disease attack a newly transplanted kidney, and what is the survival rate of transplants in patients with polycystic kidney disease?**

There is no evidence that polycystic kidney disease occurs in a transplanted kidney. This is expected, since ADPKD is inherited and a transplanted kidney would not be likely to contain the genetic abnormality. Survival rates following kidney transplantation in patients with polycystic kidney disease are similar to all other patients undergoing transplantation. In fact, 80 percent to 85 percent of kidney recipients can expect a one-year survival of the kidney transplant from a cadaver donor.

## **Should a cadaver kidney transplant be performed in a patient with ADPKD prior to the need for dialysis?**

Transplantation with kidneys from recently deceased, unrelated persons is frequently performed on PKD patients and is as successful or more successful than cadaveric transplants in general. Many transplant centers do not like to perform transplants or put patients on the cadaveric transplant waiting list until their renal disease is advanced enough to require dialysis. This policy has multiple reasons, not the least of which is the shortage of cadaver donor organs for people who are already waiting on dialysis. Also, it is often a good idea to have a trial of dialysis, since many patients feel much improved and thus go into transplantation psychologically better prepared to face the 15 percent to 20 percent rejection rate of cadaver organs.

A PKD gene has been located on chromosome 16. Can you tell me why that gene would not affect a transplanted kidney? We do not know how the abnormal gene on chromosome 16 causes cysts to form in patients with polycystic kidney

disease, but if polycystic kidney disease is caused by an abnormal substance in the blood, one might expect that cysts would form in a kidney transplanted from a non-related person. The experience of many transplant surgeons and nephrologists indicates that cystic disease does not recur in kidneys transplanted into polycystic patients from individuals who do not have polycystic kidney disease. This “experiment in nature” shows that polycystic kidney disease does not recur in a non-related transplanted kidney and that polycystic kidney disease is probably not due to an abnormal factor circulating in the blood.

**A patient with advanced polycystic kidney disease requires a kidney transplant. Her 39-year-old sister has only two small cysts in the liver and none in the kidney (shown by contrast-enhanced CT). Would she be an acceptable donor of a kidney for her sister?**

This is a difficult question. It is most common to find kidney cysts develop, before liver cysts. Liver cysts do occur, although infrequently, in the general population. If this individual’s liver cysts were numerous and large, one would be hesitant to recommend that she donate a kidney. If this family had other affected members and could be tested for PKD-1 by gene-linkage analysis that would be the first step to try. If gene testing is not a possibility, one could look for other markers of PKD in the potential donor’s sister, such as inability of the sister to concentrate her urine when she does not have access to water, looking for other extra-renal signs of PKD such as mitral valve prolapse and the presence of hypertension. If the sister who is a potential donor has high blood pressure, inability to concentrate her urine, or mitral valve prolapse, that would increase the likelihood that she has the gene and makes her a less-likely donor.

**My dad has PKD, and I also have the disease. I am the only child of four who has been diagnosed as having the disease. Can I have a kidney from one of my sisters or brothers if needed?**

Each of your sisters and brothers has a 50/50 chance of having inherited PKD as you did. Patients older than 20 years of age will exhibit PKD when examined by computed tomography scanning (CT scanning), when the test is done with contrast enhancement. This is the most sensitive diagnostic test we know of with the exception of genetic-linkage test. In a family with PKD, the genetic-linkage test can determine whether asymptomatic individuals have the gene, irrespective of whether the X-ray tests show positive. Unfortunately, this gene test is only available in a few genetic-counseling centers in the United States.

**Do the immunosuppressive drugs used to treat transplant rejection, specifically prednisone and cyclosporine, have any effect on the underlying polycystic kidney disease?**

Prednisone and cyclosporine both increase blood pressure. Increased blood pressure can have deleterious effects on the transplanted kidney. Importantly, cyclosporine is toxic to the kidney when given in too great amounts. This can result in renal failure if excessive dosing is prolonged. In ADPKD individuals, transplantation occurs once their polycystic kidneys have stopped functioning. Any effects of the immunosuppression on kidney function at this point are not of significance. However, there have been reports of rapid growth of the polycystic kidney post-transplantation.

Rarely, ADPKD individuals with intact kidney function will undergo liver transplantation. As well, autosomal recessive polycystic kidney disease patients (ARPKD) will undergo liver transplantation in the setting of relatively normal renal function. Prednisone and cyclosporine (or cyclosporine-like drugs) are used for immunosuppression for other organ transplants such as the liver or heart. This could hypothetically impact disease progression in the polycystic kidney. Prednisone will increase blood pressure by increasing the kidney’s avidity for salt as well as increasing appetite and weight. Cyclosporine, by acting directly on the blood vessels to the kidneys, causes a decrease in blood flow and increases blood pressure. Increased blood pressure is associated with disease progression in ADPKD. In the experimental animal models of ADPKD, prednisone therapy has been associated with disease progression and renal cyst growth. In humans this has not been reported.

**If a PKD patient had cancer, underwent treatment and was cancer-free for two years, would this eliminate the patients from being a transplant candidate due to the use of anti-rejection drugs?**

The reason for the required time delay after treatment for cancer before being eligible for transplantation is that immunosuppressive medicines used to prevent the transplant kidney from being rejected allow cancer cells to multiply more rapidly and for cancer to grow and spread more quickly. It is very important to make sure that there is no cancer in the body prior to receiving an organ transplant that requires immunosuppressive therapy. The required cancer-free time prior to being eligible for a kidney transplant is the same for someone with ADPKD as it is with any other renal disease. Depending on the type of cancer, the minimum time required prior to being eligible for transplantation is two years. For example, for a successfully treated case of lymphoma, 2 years is the minimum time required. Renal cell cancer survivors require 4-5 years prior to being eligible, those with colon cancer 5-10 years. Non-invasive squamous or basal cell carcinoma can be considered eligible almost immediately after removal; however, melanoma, regardless of the degree of invasion or the stage of disease, requires 10 years prior to eligibility. These time requirements vary somewhat between transplantation centers.

**While renal transplantation has become a highly successful treatment for renal failure, the number of persons waiting and the time they have to wait for a kidney from a cadaver has been increasing because too few human organs are available. How close are transplant surgeons to being able to use pig kidneys for transplantation?**

Transplanting an organ from one species to another is called xeno-transplantation. There are body components used from other species that are implanted into humans; for example, pig or porcine valves are placed in the heart for valve replacement procedures, and brain cells from pigs are injected into the human brain for the treatment of Parkinson's disease. At the present, there is no immediate plan for the use of other species' kidneys for transplantation into humans.

**I am looking for help and information concerning a kidney transplant in the case of an antithrombin-3 deficiency. At first, my doctor gave me all the indications that a transplant would be a good bet. Then, he said he would not place me on the waiting list, because the transplant doctor would not consider doing the surgery. I am not going to lose hope, and that is why I am asking for information.**

Antithrombin-3 deficiency is a condition that leads to clotting of the blood. Often, medications are used to prevent the clotting from occurring that make any type of surgery more difficult. Currently there is no contraindication to transplanting a kidney in someone with this deficiency, as long as the surgeons can prepare properly for the procedure. Kidney transplantation is not a curative procedure for this illness, however.

**Is it possible to be placed on multiple cadaver transplant lists in several geographic locations? If a kidney came up at a site remote from the patient, would the patient go to the kidney, or the kidney come to the patient?**

Most often the patient, goes to the kidney. There are transplant centers that are linked together that determine which center the kidney should go to. However, it is still required to go to the transplant center. It is possible to be placed on multiple transplant lists in several geographical locations to improve the chances of receiving a kidney transplant. Each transplant center has its own rules with regard to the maximum distance away that a patient can be. This is based on the time that it takes for the patient to get to the transplant center to receive the kidney once contacted. Usually the maximum time allowed from the center is seven hours. The longer that a kidney waits to be placed into a recipient, the more likely it is that there will be a longer phase of non-function at the time of transplantation or that the kidney could fail.

## Diet, Drugs, Surgery, Exercise

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### **Some herbs are said to be dangerous to patients with PKD. Can you provide a list of herbs and other substances used as foods that might be harmful to polycystic kidneys?**

Slimming preparations can cause kidney damage, as can various compound mixtures with multiple ingredients, which include toxic, non-steroidal, anti-inflammatory drugs. Some slimming medications include water pills or diuretic-like substances. These can cause electrolyte abnormalities as well as dehydration. Some slimming medications will drive the sympathetic nervous system. These can be dangerous and should only be taken under the supervision of a physician. Licorice root in chronic use can cause sodium and water retention and potassium loss, which can result in hypertension, edema and hypokalemia. Chinese herbs such as aristolochic acid are toxic to kidneys and should be avoided. The best course to follow is to know the ingredients of anything you take medicinally and to clear the preparation with your physician.

### **What is the proper diet for a patient with ADPKD to prevent the progression to end-stage renal failure?**

Protein restriction started at an early stage of the disease has clearly shown to have a protective effect on cyst development and renal function in two animal models of polycystic kidney disease: the Han:SPRD rats and the pcy mouse. However, the evidence for a protective effect in humans is less convincing. The largest study, Modification of Diet in Renal Disease or MDRD trial, showed that a diet containing 0.58 gm/kg/body weight (bw) had no beneficial effect, as compared to 1.3 gm/kg/bw in 220 ADPKD patients with moderately advanced renal insufficiency for approximately 24 months. This result, however, is not conclusive because of the short period of observation and the fact that patients seen in this study already had moderately advanced renal insufficiency. Until more information becomes available, it seems prudent that patients with ADPKD avoid protein in excess of the RDA for normal adults (0.8 gm/kg/bw). While protein intake should not be greater than the 1 gm/kg/bw, severe restriction with consequent protein malnutrition is also not desirable. For all patients, particularly children, adequate amounts of fruits, vegetables, and minerals are desirable. The DASH Diet (Dietary Approaches to Stop Hypertension) is currently being advocated for ADPKD. This diet can be found at the NIH (National Institute of Health) website.

### **How much protein does my body need?**

Most Americans eat much more protein than they need. Many Americans eat 2 or 3 times the protein that their body needs to stay healthy. Any excess protein from the diet is not stored in the body like other nutrients such as fat or carbohydrate but excreted by the kidneys in the form of urea. Minimum dietary protein needs for healthy adults to avoid protein malnutrition vary between 0.45 to 0.6 gm/kg/bw. The current recommendation for dietary protein intake in the general adult population is 0.8 gm/kg/bw. The recommendation for ADPKD patients is 0.6-0.8 gm protein/kg/bw, which is an appropriate goal for the general population. The recommendation for children is much higher to allow for appropriate growth and ranges from 1.8-2.2 gm/kg/day.

### **Recent research in ADPKD animal models suggests soy protein may have a beneficial effect on delaying the progress of renal disease. Does this mean I should eat a lot of soy?**

The statement “eating a lot of soy” only means that you can eat as much soy as you wish as long as you stay within the guidelines for total protein intake. Soy protein should be counted as part of your protein allowance. At this point, the safe recommendation is to substitute soy products for animal protein (meat and dairy products). Soy protein has been shown to have increased benefit over other forms of protein in animal models of polycystic kidney disease. The effect

was moderate. Research is being conducted to delineate the specific beneficial components in the soy proteins that retard PKD. Phytoestrogens were once thought to be the beneficial compound, but research has determined that this is not the case. Currently, saponin B is being investigated, and if found to be beneficial, will be certainly tested further in humans with ADPKD.

## How do I figure out the amount of protein I should eat?

First, convert your weight to kilograms (kg) by dividing your weight in pounds (lb) by 2.2. (Example: if you weigh 154 lb, and divide by 2.2, you get 70 kg)

Next, multiply your weight in kg. by 0.8 to find the upper range of protein that you should eat/day. (Example: 70 kg multiplied by 0.8 = 56 gm of protein)

To find the lower range, multiply your weight in kg by 0.6. (Example: 70 kg multiplied by 0.6 = 42 gm protein/day at a minimum)

## Does the quality of protein we eat matter?

The whole idea of eating protein of high quality means you can eat all of the essential amino acids your body needs without eating excess amounts of non-usable protein that put stress on your kidneys to eliminate additional waste. The quality of the protein you eat is important especially if you are planning to reduce the amount of protein in your diet. Highest quality protein (high-biological-value protein) can be found in animal products such as eggs, chicken, fish, turkey and dairy products. While red meat such as beef and pork (also considered the other white meat!) also have high-quality protein, they should be consumed to a lesser extent because of their higher saturated fat content. The portion size of meat eaten at a meal should also be small, around 2 to 3 ounces per serving. This will put less bolus stress on the kidney. Whole eggs contain high-quality protein, but the yolk contains high levels of cholesterol. Therefore, if your cholesterol level is high, it would be important to check with your physician or dietician first before eating eggs every day. Dairy products should be low fat or skim (a better alternative would be to substitute soy for dairy). Animal sources are not the only foods containing high-biological-value protein soybean products, potatoes, mushrooms and broccoli are plant sources of high-biological-value protein and have the added benefit of fiber and of being “heart healthy” (low in fat, cholesterol and saturated fat).

## **My wife has been treated over the past 15 years or so for polycystic kidney disease. Lately, she has been, with the consent of her nephrologist, using fish oil supplements as well as flax seed. Do you know of any research showing benefits to patients who use flax seed or fish oil?**

Investigators in Canada have demonstrated the value of dietary fish and flax oils in a number of renal diseases in experimental animals. Fish oil and flax oil are excellent sources of a type of fatty acids (omega-3-fatty acids) which are thought to have anti-hypertensive, lipid-lowering and anti-inflammatory effects. Fish oil, however, did not have a beneficial effect on early disease progression in a strain of mice with polycystic kidney disease (pcy mice). Histologic studies revealed that flaxseed feeding in the Han:SPRD-cy rat was associated with a modest reduction in cyst change.

## **What is the proper amount of phosphate in the diet, and what is the thinking about calcium supplementation, vitamins, and water intake?**

This type of dietary prescription needs to be highly individualized among patients. Phosphate in the diet usually comes in the form of protein and dairy products; therefore, if you reduce protein and dairy products, you will be reducing the

dietary phosphorus. A certain amount of these minerals is necessary to prevent protein malnutrition. With kidney dysfunction, phosphate may be retained because of the failure of the kidney to excrete it. Under these circumstances, it needs to be restricted in the diet. In some patients, as kidney dysfunction advances, they may need to take phosphate binders in the form of calcium salts.

Calcium is a necessary ingredient for our bone health and life. It is best obtained in proper amounts of dairy products. The recommended daily allowance of calcium is approximately 1 gm (1000 mg) of elemental calcium per day. For dialysis patients, calcium supplements (1-1.5 gm/day) should be taken between meals. If your dietary prescription avoids dairy products, calcium supplements are a convenient way to get the calcium that you need. There is no evidence that calcium supplements cause increased kidney stones. As a matter of fact, calcium in the diet may bind certain ingredients that are more important in causing stones.

Vitamins should be taken in moderation. Vitamins ingested beyond the body's metabolic needs must be excreted by the kidney. High doses of vitamin C should not be used by patients who are stone-formers or have renal insufficiency. Patients with recurrent kidney stones are advised to limit their daily vitamin C intake to 100-200 mg, because subsets of these patients may be more susceptible to increased oxalate production due to metabolic defects. Patients with chronic renal insufficiency should also avoid large doses of vitamin C because deposition of calcium oxalate crystals in the kidneys and other tissues occurs commonly in patients with chronic renal failure.

Water intake needs to be varied, depending on the patient's urine output and body needs in general. A higher water intake protects against kidney stones.

For all of these ingredients, it is best to individualize. These are issues to be discussed with your nephrologist or renal dietitian so the diet is tailored to your particular needs. A good general rule, though, is moderation in everything.

## **What is the role of sodium restriction in the management of patients with polycystic kidney disease?**

When kidney function is compromised, restriction of dietary sodium can help in the management of elevated blood pressure. However, there is no simple statement that can be made, because some patients with polycystic kidney disease actually waste sodium. If a diuretic is part of the blood pressure treatment plan for an individual patient, it makes sense to follow modest sodium restriction (3000 mg of sodium/day, which is also the RDA for the general population). However, many patients do not need sodium restriction and, in fact, do better without it. It is best to check with your nephrologist or a renal dietitian about your individual requirement.

## **My nephrologist sent me to a nutritionist. I was provided with a renal diet and instructed to eat 60 gm of protein daily. I was also told to restrict phosphorus, because phosphorus and calcium levels become out of balance and cause bone disease. Do the restrictions change as the disease progresses?**

Your nutritionist is correct in recommending a moderate restriction of phosphorus early, even when the renal function is only slightly reduced and the level of phosphorus in the blood is still normal. An abnormal accumulation of phosphorus may result in the deposit of solid particles of calcium phosphate in tissues and damage to a variety of organs, including the kidney.

The parathyroid hormone (PTH) controls how much phosphorus is excreted in the urine. If phosphorus intake is high, the parathyroid glands must secrete increased amounts of the hormone to keep the serum phosphorus normal. Unfortunately, excess levels of PTH stimulate bone destruction. When the renal function has declined to less than 25 percent of normal, PTH cannot adequately clear the phosphorus, and serum phosphorus rises. So you can see that the process of bone demineralization is a long process that can be delayed by a moderate reduction in dietary phosphorus early on.

The control of the intestinal absorption of phosphorus as the renal function declines can be accomplished by restricting the dietary phosphorus and by the use of agents, known as “phosphate binders,” which bind the phosphorus in the diet and prevent its absorption. Both aluminum and calcium are phosphate binders, which form insoluble complexes with phosphorus and limit absorption. Calcium salts are the most commonly used phosphate binders, because aluminum accumulates in renal failure and is toxic to many organs, including the brain and bone.

### **When I was first diagnosed with PKD, I was told not to eat licorice. Would you please explain why?**

Licorice root in chronic use can cause sodium and water retention. Potassium loss may also occur. These can result in hypertension, edema and hypokalemia (a low potassium concentration). In addition to licorice sticks, a number of other products contain considerable amounts of glycyrrhetic acid, the active ingredient in licorice. These include certain health products (herbal cough mixture, licorice tea) and chewing gums, chewing tobacco, and certain alcoholic drinks (Belgium beers and anisette).

### **I am a patient with a very mild case of PKD. I have no complications, so far, and the cysts were discovered by accident. We live in a city with very hard water, and I am considering installing a water softener in my new house. Will the added sodium in the softened water have negative long-term effects? Is potassium an option to soften the water instead of sodium?**

Small amounts of sodium added in the softened water probably are safe in your case if, as you have indicated, your polycystic kidney disease is very mild and your blood pressure is normal. Nevertheless, the situation may be different in other patients with PKD. An excellent source of information related to your question is an article published in Archives of Internal Medicine of 1997 (vol. 157, pages 218-222). The following is a summary of useful information mainly derived from that article.

Water softening is used to remove the “hardness” in the water, which is mainly caused by calcium and magnesium salt. The main reasons for “softening” water are to prevent mineral buildup in pipes and appliances, to improve water taste, and prevent iron stains in toilets and sinks. In the softening process, sodium chloride or potassium chloride is exchanged for the undesirable calcium and magnesium, thereby increasing the sodium or potassium content of the water (sodium chloride is more commonly used). In one study, the sodium content in multiple samples of softened water averaged 278 mg/L. Most of the sodium consumed in the diet derives from the salt used in food processing. While non-softened water contains very little sodium, softened water may contain significant amounts. Assuming a daily consumption of 2.5 liters of water, the sodium contained in softened water may add up to a significant amount. The recommended total daily intake of sodium is 2300-3000 mg. Alternatives to avoid the softened water for dietary purposes are to bypass the softener for a drinking water faucet, installing a reverse osmosis (RO) to remove sodium, using potassium chloride (KCl) instead of sodium chloride (NaCl) in the softener or using bottled water for cooking and drinking.

While the increased intake of sodium from softened water may be of little importance to healthy individuals, the same may not be true in patients with hypertension, renal or cardiac disease.

### **My husband has PKD. He feels fine, and I would like to keep it that way for as long as possible. He eats right and exercises. I would like him to start taking a multivitamin, but he has been told to stay away from vitamin C due to PKD. I've heard so many good things about vitamin C, as well as other antioxidants. Please advise whether it is true that he should avoid vitamin C.**

A number of studies have suggested that oxidative stress may play a role in the pathogenesis of polycystic kidney disease, but, for now, there are no data to support the use of antioxidants in the treatment of human ADPKD. In regard to the use

of vitamin C in patients with ADPKD, a number of issues have to be considered. Vitamin C, or ascorbic acid, is essential for many metabolic processes. The recommended daily allowance of ascorbic acid is 60 mg daily. Higher doses of vitamin C have been recommended by some investigators for its antioxidant effect. This is usually safe, but not always.

A small fraction of vitamin C is metabolized into oxalate. In addition, oxalate is formed during the metabolism of certain amino acids and is absorbed from certain foods in the diet. The only way the human body can get rid of the oxalate is by elimination into the urine. Precipitation of calcium oxalate in the urine can cause kidney stones. In addition, when the absorption and/or production of oxalate exceeds the renal capacity for excretion into the urine, the oxalate accumulates and precipitates in the tissues in the form of calcium oxalate salts. This can result in damage to the kidneys and other vital tissues such as the heart.

Concerns that high doses of vitamin C could result in the development of kidney stones in otherwise healthy individuals, as a result of its metabolism into oxalate, have not been substantiated. The reason why this does not occur is that both the absorption of vitamin C from the gut and its metabolic transformation into oxalate are both saturable processes. As the dose of vitamin C is increased, the fraction of the dose that is absorbed and the fraction of absorbed vitamin C that is metabolized into oxalate decrease. As a result, even high doses of vitamin C cause only minor increases in the urinary excretion of oxalate in healthy individuals.

High doses of vitamin C should not be used by patients who are stone-formers or have renal insufficiency. Patients with recurrent kidney stones are advised to limit their daily vitamin C intake to 100-200 mg, because subsets of these patients may be more susceptible to increased oxalate production due to metabolic defects. Patients with chronic renal insufficiency should also avoid large doses of vitamin C because deposition of calcium oxalate crystals in the kidneys and other tissues occurs commonly in patients with chronic renal failure.

### **My nephrologist told me that major breakthroughs in PKD research have occurred in the last few years. What will it take to go from these research breakthroughs to new effective therapies?**

This is a very important question. Although scientific breakthroughs come along, translating these findings into patient care or curative therapy can often take a long time. The most exciting scientific breakthroughs in PKD research are related to the identification, location and understanding of the PKD and ARPKD genes. This is the first step in getting closer to a cure for these diseases. With this information, investigators are now beginning to understand how these genes and other related genes work within and between cells. This information will then be translated to determine how to manipulate PKD and ARPKD gene function to either bypass an ineffectual gene product, override a mutated gene product or some sort of combination of the two. Biopharmaceutical research is involved in identifying or creating compounds that could potentially provide the function that a mutated ADPKD or ARPKD gene cannot. These compounds will need to go through extensive testing in the test tube, then in experimental animal models and finally in humans prior to being available for clinical use by practicing physicians and health care providers. The magnitude of this process is obvious.

### **I have just been diagnosed with breast cancer, and must take cytoxan, methotrexate, and 5-fluorouracil. What effect on my polycystic kidneys should I expect? What should be monitored?**

The medications that you are about to take for breast cancer have many toxicities, including hair, liver, skin, bone marrow, brain and kidney. Only the cytoxan is directly toxic to the urinary system and can result in bleeding from the bladder. This bleeding is called hemorrhagic cystitis. This condition can be avoided by assuring excellent hydration prior to being given the cytoxan. The kidney is an important terminal eliminator of many drugs. Therefore, if there is a decrease in kidney function below normal, it is very important that your oncologist or physician dose your medications appropriately to avoid toxicity to other organs in the body.

## What has happened to the drug taxol?

Taxol is a chemotherapeutic medication that functions by changing how cells maintain their internal skeleton or infrastructure. Taxol showed tremendous promise in a mouse model of polycystic kidney disease, with a reduction in cyst size, kidney size and prolongation of life. However, when the drug was tested further in other animal models, no benefit was found. As well, the toxicities of the drug were common and made this agent less ideal for chronic therapy in PKD patients who are otherwise healthy. However, understanding the effects of taxol has helped investigators try similar directions for therapy in PKD and has been very helpful in understanding the pathogenesis of disease.

## I have polycystic kidney disease. My serum creatinine is 4.3 mg/dL. Because of a history of chest pain and the results of noninvasive studies, my doctor recommends that I have a coronary angiogram and possible angioplasty. I have been told that the contrast agent needed for this study may damage my kidneys. Is there an effective substitute for the contrast material?

This is an important question. The contrast that is used to perform a coronary angiogram includes iodinated contrast. This contrast agent is filtered by the kidneys and is toxic to the tubules in the kidney. Patients with poor renal function are particularly at risk for renal toxicity after receiving iodinated contrast because more contrast comes into the remaining nephrons. However, there are times when patients with renal insufficiency need to have a contrast study performed. There are many ways to minimize the risk of toxicity to the kidney after receiving a contrast agent. First, the physician performing the test (usually the cardiologist) needs to know that the patient has renal insufficiency so that she/he can limit the amount of contrast that you receive. Next, the nephrologist needs to be involved prior to the procedure. Usually when patients are given intravenous fluids and medications that could contribute to the toxicity of the contrast (non-steroidal anti-inflammatory agents and diuretics) are stopped for 3-4 days prior to the procedure, the chance of kidney damage occurring is very small.

A recent study has demonstrated that a medication called mucomyst (acetyl cystein) given for 3 days (beginning one day prior to the administration of contrast) is protective against kidney toxicity from contrast. Your nephrologist and cardiologist can decide whether this medication would be beneficial in your case.

There are ways to obtain the information needed that the contrast study would provide by using other agents. This includes doing a CO angiogram with carbon monoxide. This is more difficult for the cardiologist to perform, and the images are not clear; however, it can be done. Alternatively, there have been other radio-opaque agents developed that have been preliminarily reported not to be toxic to the kidneys that could be used; however, they are very expensive and have not always shown improvement in the occurrence of damage to the kidneys after a contrast study.

## At age 45, my PKD kidneys failed. I understand that this is a little early. I've never had children, don't eat junk food or drink coffee or tea. I was even a vegetarian for two years. My sin is chocolate. Did chocolate do me in?

LONG LIVE CHOCOLATE!!! The chocolate that you have been enjoying did nothing to damage your kidneys. The average age of entry into dialysis in ADPKD is 52-57 years of age, but the range is broad. ADPKD patients have occasionally begun dialysis in their 20s and some individuals live into their 80s or 90s without requiring dialysis at all. Although you are young with regard to starting dialysis, 45 years of age is not uncommon in ADPKD. This broad range of age is seen within families as well as between families with ADPKD. Why the broad spectrum for age of initiating dialysis exists is hard to explain but may in part be related to the fact that mutations in the PKD genes also occur in the good copy of the gene in the cells that line cysts in the kidney.

## **My husband's sister had general surgery on her polycystic kidneys four years ago to drain some cysts. Now the cysts are back, and she is contemplating the same surgical procedure. Can you provide some information on this surgical procedure?**

There are a number of different surgical techniques that are available for patients who have enlarged painful cysts either in the kidney or the liver. The least invasive way to drain cysts is to use a needle, place it in the cyst, and withdraw fluid. This requires a local anesthetic and no incision. This procedure is usually done by an interventional radiologist. This procedure is limited to a few cysts that should locally be causing symptoms. Usually patients have more diffuse pain problems, including bilateral flank pain or abdominal pain. Two surgical approaches are currently available. One is a laparoscopic approach in which the surgeon makes two small incisions and can see the kidney and cysts through a camera and selectively drain the cysts. The other approach is open surgery, in which an incision is made and the cysts drained. The laparoscopic approach is different, from the open surgical approach in that fewer cysts can be drained. However, the operating time is shorter, and recovery time is much quicker. In both approaches, the cysts are destroyed permanently. However, new cysts typically form and replace the previous cysts. Usually the majority of individuals gain much in the way of pain relief with both of these procedures. The pain disappears permanently or for approximately two years. A minority of patients (approximately 30%) develop recurrence of symptoms. When these individuals undergo cyst reduction procedures a second time, pain disappears or improves in the majority of patients. The surgical approaches become more difficult because of the scar tissue. This means that more often a laparoscopic approach may not be successful, and open procedures may need to be used.

## **I have ADPKD and want to know if there is a safe weight gainer (or protein) I could take for weight training, to gain more muscle and body mass?**

There are few additives that should be taken by individuals with renal diseases that do not either affect the kidney or make it difficult to interpret measures of renal function. Creatine is an additive taken to increase muscle stores in individuals who weight lift. This substance, however, interferes with the blood tests that are done to measure serum creatinine concentrations in the bloodstream. This makes it difficult to determine renal function accurately in an individual. Other additives typically taken include stimulants to muscle growth or hormones. These compounds can be dangerous to other organ systems in the body, including the liver, and may have cyst-growth-promoting effects as well. Any additive or over-the-counter medicine should be reviewed with your physician before embarking on long-term intake.

## **What is the proper type of exercise that an ADPKD patient can do?**

Exercise is an important health benefit that all ADPKD patients should undertake. However there are some exercises that put an ADPKD individual at increased health risk. These include contact sports, in which the kidney may be hit or knocked. A good example of this is karate, football, or boxing. As well, there are exercises that have repetitive jarring or impact. A good example of this is horseback riding. Although there is no evidence that these exercises will result in worse renal function, there are many anecdotal reports of blood in the urine appearing in young individuals after being hit in the kidneys or after an otherwise uneventful horseback ride. Given that blood in the urine appears to be a risk factor for progression to renal failure in ADPKD, if other sporting activities are of interest, they should be considered as an alternative source of exercise.

Always, regardless of the exercise chosen, hydration is an important component to the exercises performed by ADPKD individuals. There is a mild concentrating defect present in the kidneys of individuals with ADPKD that will exacerbate dehydration if fluids are not available on a regular basis. The concentration defect becomes more severe as renal function declines. Therefore, it is important to make sure that fluids are available during all exercise programs.

## What is the proper diet for a patient with ADPKD to prevent the progression to end-stage renal failure?

One of the simplest dietary changes to make that can help reduce loss of function in ADPKD is to reduce sodium intake. Dietary protein restriction has demonstrated a significant impact on cystic disease in rodent models of cystic disease. Lowering protein intake will reduce cyst burden by more than 20% in most animal models. The benefits of protein restriction are improved even more when the type of protein intake is controlled. For example, soy-based protein intake in animal models reduces cyst burden compared to casein-based protein diets. In humans, reduced protein intake in ADPKD has not been demonstrated to be beneficial in slowing progression to renal failure. Studies in human ADPKD have only been done in advanced disease, i.e., those with less than 50% normal renal function, with massive cystic involvement. Does this mean that it is not worth restricting protein in ADPKD in individuals with renal insufficiency? No. Protein restriction in all individuals with renal insufficiency, whether they have ADPKD or not, is beneficial in reducing the symptoms of uremia. Reducing protein intake to between 0.6 and 0.8 gm/kg/day will allow for adequate protein intake and minimize the production of uremic toxins that the kidney is ultimately going to excrete from the body. Reducing protein intake also reduces the amount of acid and phosphorus that is taken in and will help reduce the acidosis and hyperparathyroidism that occurs in chronic renal insufficiency.

## What is the relationship between a primary care physician and a nephrologist?

The relationship between a primary care physician and a nephrologist is a very important one. Clearly all relationships depend on the individuals involved. Often the primary care physician for renal patients is a nephrologist. The nephrologist is important in providing treatment for anemia, acidosis, dietary protein restriction, blood pressure control and to counsel the patient in preparation for dialysis. These are all conditions that require continued, long-term follow-up. The patients with ADPKD who are in the early stages of their disease need a primary care doctor to continuously monitor them with regard to their renal function, blood pressure control and level of proteinuria. The patient needs to have a consistent and direct physician relationship with both physicians. Both physicians play important roles in different stages of the renal disease process. In addition, it is expected and hoped for that the nephrologist and primary care doctor work well together.

## How often should a patient with PKD visit a nephrologist? How often should the creatinine level be checked?

ADPKD patients should have a check-up with a physician no less than once a year. This will guarantee at least an annual check on blood pressure and screening for the presence of proteinuria by urine dipstick. Serum creatinine concentrations should be checked at each of these visits as well. This is the minimum that a patient with polycystic kidney disease should do with regard to regular follow-up. This includes individuals with normal renal function and those with more advanced disease. If other conditions such as hypertension or abnormal renal function are also present, then it is important to be seen more than once a year. For all patients with hypertension, it is worth obtaining a home blood pressure monitoring device so that blood pressures can be checked at regular intervals. Individuals with renal function that is less than normal (clearance < 70 ml/min) most likely should be seen at least twice a year to include a review of their dietary intake as well as an assessment of their adherence to a diet and their creatinine level.

## What medications are damaging to kidneys?

There are certain over-the-counter medications that need to be avoided in individuals with renal disease. These include the non-steroidal anti-inflammatory medications such as indomethacin, naprosyn and clinoril. These medications reduce the amount of blood flow to the kidneys, which may be important in ADPKD patients. Other medications such as Tylenol or Ultram (by prescription only) can be used for pain control instead. There are newer classes of anti-inflammatory agents, the COX-2 inhibitors, such as Celebrex, that may also potentially diminish blood flow to the kidneys and should be

avoided in ADPKD patients. Sometimes either non-steroidals or the COX inhibitors are the most effective pain-reducing agent. In that situation, with limited intake and supervision, they can be used with patients. These patients should be encouraged to increase their liquid intake.

Other medications that are important and prescribed by doctors can have potential deleterious effects on kidney function. Iodinated contrast, used in computed tomographic scans, is potentially damaging to the kidneys. Also, Bactrim, a helpful drug for urinary tract infections, will selectively increase serum creatinine concentrations temporarily without changing the kidney disease itself. This makes it difficult to determine what a patient's renal function really is and has to be taken into consideration when assessing someone's level of renal function.

### **In view of the finding from the MDRD study that a low-protein diet does not slow the progression of PKD, are these diets still recommended for individuals who have not reached the dialysis stage of the disease?**

While the low-protein diet study has failed to show clear benefit, dietary management can still be recommended to reduce symptoms in patients approaching end-stage renal disease, or in managing potassium and phosphate retention. For the purpose of slowing the progression of renal disease, certain individuals do seem to have a beneficial change in their rate of decline, although the overall study is negative. The best course of action is to work with your individual nephrologist and dietician to find out what might be reasonable for you while still maintaining good nutritional status.

### **Do we know what causes kidney cysts to enlarge, and are there any dietary or lifestyle modifications that can be made to prevent this from occurring?**

We know that, for cysts to enlarge, they need to make more cells and secrete more fluid into the inside of the cyst. Although we know some of the factors that can cause this in a "test tube," we do not know what causes this in people. Because a drug like caffeine can cause cysts to grow in a "test tube," it may be advisable to avoid large amounts of food and beverages high in caffeine.

My friend with PKD has been told to reduce the amount of protein in her diet, but she also has hypoglycemia (low blood sugar), which is treated by increasing dietary protein. Which condition should take priority in respect to dietary protein? Protein restriction has been used in an attempt to prolong the course of patients with established chronic kidney disease, including PKD. While the low-protein diet study has failed to show clear benefit, dietary management can still be recommended to reduce symptoms in patients approaching end-stage renal disease.

Hypoglycemia is very rarely due to organic causes, but a skilled renal dietician could give the best advice about the exact proportion of protein and carbohydrate, which must be in any individual's diet so that such coexisting conditions can be accommodated.

### **It is my understanding that there is a drug in the experimental stage for use on patients with polycystic kidney disease. I also understand that its use on some animals has proven to eliminate the cysts in those affected with the disease, but that the amount of the drug needed to do this is far too great for any human to tolerate. What can you tell us about this type of research?**

Research is being conducted to find drugs that will slow the progression of renal cysts in patients with polycystic kidney disease. This kind of research is done in a multistep process. The first step in the sequence is to use test tube models of cysts to screen potential drugs for the effect of slowing the growth of the cysts. Several candidate drugs have been found in the test tube experiments to have an effect of slowing the rate at which cysts grow. Some of these are being tested in

experimental animals, but there are no results to report. These types of studies often take several years to clearly validate whether a drug may be worthwhile. When one or more candidate drugs are found, they will be tested in individuals with polycystic kidney disease in a strict research protocol, and they will not be offered to the general public for treatment until efficacy and safety have been clearly established. In summary, there are currently agents in the “pipeline” that are promising, but the use of these drugs in human beings is several years in the future.

### **I have arthritis in my thumb joints, and my doctor advises me to take only acetaminophen. Will aspirin hurt my polycystic kidneys?**

Acetaminophen or aspirin in usual doses for short-term indications has no major impact on kidney function. Long-term use of combination analgesics can produce kidney damage, which would be in addition to that already present in polycystic kidney disease. The best advice is to limit the amount of analgesic that is used. If the need is prolonged, these drugs should be prescribed under the direct supervision of a physician who can carefully monitor the patient for adverse effects and who can maintain excellent blood pressure control.

### **Is there any known effect of lead exposure on a person with PKD, such as earlier onset or more severe illness?**

Lead exposure, particularly in childhood, can lead to kidney disease in the absence of polycystic disease. If a patient has underlying abnormalities, obviously any lead-induced kidney damage would be additive. There are ways to test whether a patient’s total body lead burden is increased. If this is proven to be the case, it might make sense to use chelating drugs to lower the lead content of the body. The possibility of lead exposure should be evaluated by a competent specialist in nephrology or occupational medicine.

### **I’ve heard that with laparoscopy, a technique that enables surgeons to operate on internal organs through tiny incisions, kidneys can be removed. How does that affect the viability of the tissue for research? Is there any room for the use of this technique in the management of PKD?**

Laparoscopy has been used on an experimental basis in the management of polycystic kidney disease. Under a grant from the Polycystic Kidney Research Foundation, investigators at Oregon Health Sciences University are reducing the volume of cyst fluid through the laparoscope in patients with refractory pain and discomfort from their polycystic kidneys. Should this technique prove feasible and safe, wider indications for active intervention in established cystic disease could be possible. It would be difficult to completely remove large polycystic kidneys through a laparoscope. For this, standard surgical techniques are probably necessary.

### **I am 36-years-old, and I have very painful polycystic kidneys. Doctors say the kidney function is normal. I have a stone in one kidney. I feel constantly tired and ill. A surgeon removed some of the larger cysts, but that did not help. Now he is considering cutting the sympathetic nerves to the kidneys. Can you tell me if this is normal for PKD patients and if there is anything else that can be done?**

Your situation is shared by others with PKD, but, fortunately, pain of this severity is limited to fewer than 10 percent. It is very difficult to pinpoint the exact cause of severe chronic pain in most cases, but occasionally kidney stones, kidney infections, kidney bleeding, blockage of the drainage tubes or kidney tumor may be found and corrected. We do not know the cause of pain in those individuals without obvious cause. We suspect that there may be inflammation in the kidneys caused by the cysts, but this is only a theory at the present time. Some patients get relief from an operation that removes

hundreds of cysts from the kidneys, but this treatment has not been widely applied in the United States. Others have been helped by clinics that specialize in the management of chronic pain by injection, biofeedback, transcutaneous stimulators and local injections of pain-killing drugs. If these measures fail, it may be necessary to resort to analgesics, but many of these may potentially damage polycystic kidneys (acetaminophen, aspirin, and ibuprofen). This is an area of PKD management that continues to frustrate patients and physicians.

## Pain

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### Is the amount of pain in polycystic kidney disease related to the stage of the disease?

Pain in polycystic kidneys occurs for a number of reasons. Many acute pain syndromes occur when there is bleeding into a cyst or the development of a new cyst or kidney infection. Typically, the pain in these situations is rapid in onset and localized to the area where bleeding or infection is occurring. Treatment of the problem in these situations usually takes care of the pain.

Chronic pain in ADPKD is usually due to the size of the kidneys or liver. Kidney size can increase up to 20 lbs in an ADPKD individual. The pain in these individuals is due to multiple reasons. Sheer weight of the kidney is one obvious cause. The weight can pull back muscles out of alignment and change the usual support patterns that these muscles provide to the spinal column. This can result in changes in the pathways that nerves take as they come out of the spinal column and result in compression or aggravation of the nerve root. Importantly, back pain in ADPKD may be musculoskeletal, but the original cause of the pain may be kidney size. There are individuals who tolerate the increased size of the kidney very well. It is not clear why some and not others can be so severely affected with pain.

### How can one tell if pain is from polycystic kidneys or liver, and what are the symptoms of a cyst rupture?

Pain from cyst rupture is usually localized to the area where the cyst lies. Therefore, liver cyst rupture usually results in pain over the front of the abdominal wall, with localization more often to the right upper quadrant. These events are stressful, and a low-grade temperature may accompany this. Blood is not usually detected in the urine of an individual who has a ruptured liver cyst. However, this often does occur in individuals who have a ruptured kidney cyst. Ruptured kidney cysts usually produce pain in areas lower than the liver and often in the flank or lateral area. Blood in the urine can accompany these events, often visible to the eye (macroscopic hematuria) or just seen under the microscope and not visible to the eye (microscopic hematuria). Pain is often present and can be difficult to control. When a cyst ruptures, there are a number of things that you can do to limit the time of discomfort or bleeding. This includes adequate hydration, blood pressure control, and if bleeding persists after 48 hours, bed rest is also helpful in limiting the duration of pain. Clearly your physician needs to know if this occurs.

### Is there an analgesic (pain killer) of choice for the PKD patient?

This is a difficult problem for PKD patients that has been made even more problematic by a report in the New England Journal of Medicine that suggests that acetaminophen may injure the kidneys if taken for long periods of time. It appears, therefore, that no analgesics can be used with impunity. Codeine and other narcotics can lead to dependency or addiction. Non-steroidals (aspirin, ibuprofen, naproxyn and several more) can reduce the flow of blood through the kidneys and aggravate high blood pressure. Acetaminophen can probably be used in small doses for short periods of time without injuring the kidneys, but patients with chronic, severe pain may have to consult a specialized pain clinic in order to consider alternative types of treatment.

## **I have been on dialysis four years and am doing well except for unrelenting kidney pain. I am interested in having a transplant, but I want a better quality of life if I go to the trouble. Would it be best to have my diseased kidneys taken out before the transplant?**

This is one of the most common issues facing PKD patients who are awaiting transplants. Opinions vary among transplant physicians and surgeons regarding the need to remove all polycystic kidneys before transplantation. Some surgeons insist that all kidneys be removed before the transplant, whereas other equally successful surgeons remove the kidneys only if there is evidence of infection, persistent bleeding, tumors, stones, excessive size or debilitating pain. Until recently, one reason to leave the old, non-functional kidneys in place was their capacity to make a hormone that keeps the red blood count relatively high.

Erythropoietin has been approved by the FDA for use in anemic dialysis patients. This hormone will improve blood counts in anemic dialysis patients and improve the way they feel. Thus, PKD patients can have their kidneys removed without fear of developing debilitating anemia. On the other hand, if the old PKD kidneys have continued to make significant amounts of urine (more than 500 cc per day), dialysis patients will lose this amount of extra water they can drink if the kidneys are removed. Thorough discussion among members of the transplant team and the patient is indicated in each case before pretransplant nephrectomy is done.

## **General Information**

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### **If one kidney is removed from an individual with PKD, will the cysts in the other kidney grow faster?**

Many patients with PKD have had one of their kidneys removed because of infection, stone, tumor or accidental injury. Experience has not indicated that the remaining polycystic kidney grows any faster than it might were the other kidney left in place. As indicated previously in PKD Progress, it is difficult to judge just how fast the polycystic disease will progress in an individual. Only about one-half of those with PKD will develop kidney failure in their lifetime; the remainder may have few complications of the disease. Thus, when a kidney is removed from an individual, one does not know whether that person was destined to develop renal failure or not. Nephrologists are very reluctant to remove polycystic kidneys from individuals with good-to-moderate levels of renal function. On the other hand, for those already enrolled in a chronic dialysis program or who have received a successful renal transplant, nephrologists are more likely to recommend removal of polycystic kidneys that are causing discomfort or other medical complications.

### **Are there any dangers to a PKD patient flying in an unpressurized airplane?**

The dangers to a PKD patient from flying in an unpressurized airplane as a passenger are not different from those to an individual without PKD. Because of the increased risk for intracranial aneurysms, it has been recommended that PKD patients fly an airplane with a copilot or as a copilot.

### **What is the average life expectancy for an individual with the adult form of PKD?**

The life expectancy of individuals with the adult form of PKD is much better than thought years ago. In general, this is due partially to milder forms of the disease being diagnosed more frequently, better preventive medicine and medical care, and to the success of dialysis and renal transplantation. For these reasons, the estimated mean life expectancy of PKD patients in a recent study approaches that of the general population, while it was 15 years shorter in older studies.

## Why do some PKD patients develop distended abdomens and others don't? Does it have anything to do with the location of the kidneys (lower/higher)?

The distention of the abdomen in some patients with polycystic kidney disease is caused by extremely large polycystic kidneys, polycystic liver, or both. The reason why some patients develop more severe enlargement of these organs than others is not known. Of interest is that polycystic liver disease tends to be more severe in women than in men, while polycystic kidney disease is slightly more severe in men than in women. Certain body configurations, obesity, and rarely, fluid accumulation can also contribute to abdominal distention in some patients with large polycystic kidneys or polycystic liver.

## ADPKD/ARPKD

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**Our youngest child was born with ARPKD last year and lived for only 3 weeks. Two older children (ages 3 and 2) appear healthy. We have received conflicting advice regarding the need to test our older children for ARPKD symptoms. What advice can you give a parent regarding the care of children who have lost a sibling to the infantile form of PKD (ARPKD)? At what age would the risk of developing ARPKD symptoms disappear (i.e. is it safe to say that a child has not inherited the disease if he has survived past two years-of-age?)**

Autosomal recessive polycystic kidney disease is a rare disorder, occurring in approximately 1:20,000 individuals. This disease results from the mutated gene being inherited from both mother and father who are carriers for the gene but are not affected with the disease. The gene responsible for ARPKD has been identified, and mutations are now being determined in ARPKD individuals. This means that it is soon going to be possible to screen for the presence of ARPKD in individuals at risk for the disease. The gene responsible for ARPKD is on chromosome 6, and no other genes responsible for ARPKD have been identified. Given that you and your husband are carriers for ARPKD, it is certainly possible to screen your children genetically for the disease. However, as with ADPKD, a genetic diagnosis does not provide prognostic information.

ARPKD affects both kidneys and the liver. Affected individuals may have significant kidney involvement at the time of birth, meaning very enlarged kidneys and decreased urine production. This results in difficulty with breathing that ultimately is responsible for the death of these infants. How often ARPKD infants die at the time of birth is not known; however, it does not happen in all ARPKD babies. Importantly, for those children who survive the first month of life, survival rates are very good, in fact much greater than 80%. When ARPKD infants survive, they have a number of medical problems that require attention. Most commonly these children have hypertension that requires medication. As well, the liver involvement in ARPKD is slowly progressive and can become symptomatic any time in childhood. The liver involvement in ARPKD is due to congenital hepatic fibrosis. This process results in dilation of the intra-hepatic bile ducts associated with periportal fibrosis. This process continues until the liver ultimately develops portal hypertension. The complications encountered related to the intra-hepatic bile duct dilation include biliary stones and infection. These complications are serious and can be life threatening, and, should symptoms of fever or abdominal pain develop in someone with ARPKD, he or she should see their doctor immediately. Other complications of congenital hepatic fibrosis include esophageal varices. The veins lining the esophagus (the tube that carries food from your mouth to your stomach) enlarge and tend to burst and bleed when portal hypertension in the liver is present. This results in massive bleeding into the stomach, which is also dangerous and life threatening. For children at risk for ARPKD who either have not or do not wish to undergo ultrasound examinations or genetic screening for ARPKD, it is wise to make sure that their physicians know that they are at risk for ARPKD so that, should complications develop, they can act quickly.

## **Our children are at risk for ADPKD. Given the potential problems with medical insurance, we are reluctant to have them undergo screening for ADPKD. What do you suggest?**

This is a difficult question without a straightforward answer. There are treatable complications that are undetected in almost 60% of patients due to ADPKD. Complications include hypertension, urinary tract infections and hematuria or blood in the urine. These conditions contribute to disease progression in ADPKD. However, a diagnosis of an inherited kidney disease can limit access to life and health insurance coverage, and for those whose employment provides excellent health insurance coverage, a diagnosis can alter a decision regarding change of employment. These issues have tremendous impact with regard to undergoing screening for a diagnosis of ADPKD.

An alternative to undergoing screening for a diagnosis of ADPKD is that at-risk individuals can practice universal precautions, i.e., assume that everyone at risk has ADPKD and treat accordingly. This would include having a home blood pressure measuring device, having a physician obtain blood pressure measurements and check urinalyses regularly, and having blood work done to measure kidney function. Should symptoms develop, such as flank pain, back pain, pain with urination, or blood in the urine, a fast referral to a nephrologist could then be made available. Importantly, the field of scientific investigation in ADPKD is making tremendous progress, and, with the current pace and an increased understanding of the PKD genes and their protein products, specific therapy may soon be available. Those diagnosed early with ADPKD would benefit the most from such therapies. All of these issues make this decision a case-by-case and year-by-year consideration. It is worthwhile to discuss all questions and concerns with your health care provider before proceeding with a screening test for the presence of ADPKD.

## **I have PKD and am a 37-year-old woman. Last week, my 11-year-old daughter was found to have elevated blood pressure and kidney cysts by ultrasound test. She is receiving Enalapril. Isn't this a little early for PKD to show up? Does this early diagnosis mean more than the usual trouble ahead for her?**

Her results indicate that she has inherited ADPKD. The fact that she has elevated blood pressure is unfortunate but not unusual. Approximately 15% of ADPKD children have hypertension. High blood pressure is important to identify and treat, as it is accompanied by disease progression in ADPKD children marked by increases in renal size and cyst number. Importantly, the majority of ADPKD children have high blood pressure and are not aware of their condition. If she controls her blood pressure and takes her medications regularly, she may be able to slow down progression of her renal disease.

## **What kind of cystic diseases do children have?**

There are four major kinds of cystic disease that can be seen in infancy and childhood. The most common kind is called "multicystic dysplasia." It may occur in only one kidney or both and is frequently associated with an obstruction or absence of the ureter (the tube leading from the kidney to the bladder). It may be seen in children with some kinds of congenital malformation syndromes or may be an isolated entity. It is rarely inherited.

## **What are the qualifications of a pediatric nephrologist, and does the pediatric nephrologist differ from a regular pediatrician?**

The word "nephros" means kidney in Greek. Hence, the pediatric nephrologist cares for children with kidney diseases. This is in contrast to the pediatric urologist, who is a surgeon who deals with operable conditions of the genitourinary tract, including congenital anatomical abnormalities and obstructions to urine flow.

A general pediatrician receives three years of training in pediatrics following medical school. In general, they have one to several months, but they must rotate through all other subspecialties (such as neurology [nervous system diseases] and

neonatology [newborn medicine]) as well as spend time caring for children with routine pediatric problems. The pediatric nephrologist spends those three years in the same way, but then has an additional two to three years in which he/she cares only for children with kidney diseases in order to learn extensively and intensively about the diagnosis and management of such diseases. General pediatrics has a “board” exam following the first three years. Passing that exam qualifies the doctor to be a “board-certified pediatrician.” Pediatric nephrology also has a certifying examination that may be taken after the two- to three-year fellowship. The doctor then becomes a “board-certified pediatric nephrologist.”

### **Should my child with PKD go to a pediatric nephrologist?**

PKD in children is an uncommon disease. Pediatric nephrologists have trained in major pediatric centers that have large referral areas, so the pediatric nephrologist sees several children with PKD during training. On the other hand, the pediatrician-in-training might see only one or no such patients. Obviously, then, the pediatric nephrologist knows far better how to care for such children. If there is no pediatric nephrologist in your area, it is perfectly appropriate to ask your pediatrician to send your child for a consultation with a pediatric nephrologist in a university center. The consultant will then help the pediatrician plan an appropriate management strategy and educate the pediatrician on the ways to observe your child.

### **Why does polycystic disease affect a fetus so quickly and fatally, while it takes years in an adult?**

The quick answer is, we don't know. Medical research has revealed recently, however, that in the rapidly fatal type of recessive PKD, nearly all of the kidney tubules are altered by cyst formation. By contrast, in the autosomal dominant form, only a small percentage of the tubules are affected with cysts. It may be that each cyst must grow to a much larger extent to cause damage when they are few in number, thus delaying kidney malfunction in the adult.

### **My daughter was born with adult PKD, and I carry it. (I am under no treatment at this time.) She just turned six months, and it breaks my heart that this happened to her. She is the only one of 13 offspring in our family to whom this happened at birth. Why?**

The autosomal dominant (adult) type of PKD is present at birth in the kidneys of individuals who have inherited the gene, but the degree to which the cysts are expressed varies greatly from person to person. With the almost routine use of sonography (sound wave testing) during pregnancy, many more cases of PKD are being discovered in unborn children. If the cysts are discovered in the fetus or newborn baby as an incidental finding (that is, no symptoms directed the physician to look for the disease), the outlook is no different than for anyone with the autosomal dominant type of PKD. However, recent studies of children in the University of Colorado polycystic kidney research program have indicated that, early in life, some children with ADPKD may develop problems. If a child with PKD develops signs or symptoms, treatment should be started immediately and followed with regular health checks. Affected children without signs or symptoms of PKD should have regular checks for high blood pressure and urinary tract infections.

### **I have PKD, as did my mother. My 8-year-old daughter was born with only one kidney, but the remaining one is of normal shape, size and function. We have not had any kidney tests done to look for PKD. Could the missing kidney be due to PKD, and should we be taking any special precautions?**

Although dominantly inherited PKD (ADPKD) can often be detected in childhood, this condition is not ordinarily associated with congenital abnormalities such as solitary kidney, so finding only one kidney has no special significance. A solitary kidney is relatively common in the populations at large and does not usually lead to serious problems of renal function. Occasionally, the kidney will excrete more protein in the urine than normal, and some researchers have

suggested there may be a predilection to high blood pressure in individuals with only one kidney. ADPKD does not appear to progress at an unusual rate in individuals with only one kidney, but this information is based on studies of older individuals rather than children. It would seem reasonable to have a child with a solitary kidney examined by a pediatric nephrologist at periodic intervals to check the level of kidney function and to monitor blood pressure.

Two of my grandchildren died shortly after birth due to infantile PKD. A third child is a bright, sociable 4 year-old, but she has cysts on her kidneys and liver, and has high blood pressure. I wonder if it would be possible, in this age of genetic engineering, to have one of the parents' genes altered to produce a pregnancy free of this disease?

Despite the advances in genetic engineering, we are not yet at the point where we can correct genetic defects. The first experimental trials of these techniques are underway, and intensive efforts are being made toward the goal of "gene therapy." Nevertheless, it will be some time before these techniques can be applied in inherited kidney disease – many technical hurdles need to be overcome. In the meantime, a genetic counselor will be able to help your son/daughter-in-law evaluate the risk of PKD in a future pregnancy.

### **My six-month-old daughter died of a virus that affected her heart. An autopsy disclosed autosomal recessive PKD. We want to have other children. What is the life span of this disease? Is there any treatment, surgery, medication or diet that would have helped?**

The viral disease that your daughter had was a separate disease from the autosomal recessive polycystic kidney disease (ARPKD). ARPKD results in death in early infancy in about 60 percent of those who have it. Usually, these babies die from lung problems, but some of them may have kidney failure. The remaining children may do well for a number of years. Some develop kidney failure fairly early and require dialysis or transplantation, and most children need that kind of treatment by or during adolescence. One of the most common problems associated with ARPKD in the child who survives is high blood pressure. We believe that prompt and careful treatment of the blood pressure will help maintain kidney function longer. There is no specific treatment for ARPKD, so we are careful to treat all the symptoms of the disease as it progresses.

Since you are hoping to have more children, you may wish to talk to a geneticist about the disease. The likelihood that each future child might have the disease is one in four, or 25 percent. Prenatal ultrasound examinations can sometimes, but not always, detect the disease before birth, and ultrasounds done sequentially after birth will also help with early diagnosis.

### **I just lost my first baby to "bilateral cystic renal dysplasia, polycystic kidneys." The doctor told me that this type is not a genetic disorder, just a mechanical fault. Are there really forms of PKD that aren't genetic or recessive?**

Unlike the genetically transmitted polycystic kidney diseases (autosomal dominant and autosomal recessive), bilateral cystic renal dysplasia is a sporadic condition caused by abnormal development of the kidneys early in embryonic life. The cause of multicystic dysplasia is unknown and, in many instances, this kidney malformation may be associated with malformations in other parts of the body. The bilateral cystic dysplastic kidney is considered to be nonhereditary. However, there are documented cases of familial recurrence of bilateral cystic dysplasia, particularly if there is a family history of other urologic abnormalities present. In families without a history of renal disease, there appears to be a small (1 percent to 3 percent) risk of recurrence of this problem in subsequent children.

### **We understand that there are some projects underway to study autosomal recessive polycystic kidney disease, the type that affects infants. Where do these stand, and what has been learned so far? What can we do to help?**

The road to understanding the abnormalities in ARPKD requires several approaches. If one could start at the beginning, one would look for the genetic abnormality that produces a disease, determine whether that genetic abnormality was a single one or one of several abnormal genes that produced several abnormal gene products, determine what the gene

products were (the proteins made by the genes that caused the abnormality), then determine whether there were some environmental factors that contributed to formation of the cysts, and, finally, how to alter the one of many processes that were abnormal. Needless to say, such a stepwise approach would take a very long time. For that reason, it is important that several processes be studied simultaneously, a procedure that requires the expertise of several different investigators with several kinds of expertise.

For those who have children with ARPKD, researchers are starting a registry and relatively soon will need blood samples from your affected child/children as well as other family members. You may want to notify PKD Foundation of your willingness to be involved in research so that we will be able to contact you as appropriate needs arise.

A family wrote to ask if it were true that there were four types of autosomal recessive or infantile polycystic kidney disease and whether all affected children from one family would have the same type. This is a particularly worrisome question for those families who have a baby severely affected at birth who quickly succumbs.

In 1971, two geneticists named Blyth and Ockenden (*J. Med Genet.* 8:257, 1971) described ARPKD in children seen in London. They separated the children into four groups. A “perinatal” group presented at birth with huge abdominal masses that were the enlarged kidneys. These babies died within the first six months of life. Microscopic examination of their kidneys showed that 90 percent of the kidney tubules were cystic, whereas the fibrosis of the liver was minimal. A second “neonatal” group presented from one day to one month of age with large kidneys. The majority of these babies had also died within the first six weeks of life. Sixty percent of the tubules were cystic, and the liver scarring was a little more obvious. A third “infantile” group presented from three months to six months of age and had both enlarged kidneys and an enlarged liver. The majority of these children developed kidney failure but not until several years of age. In addition, they had very increased pressures in the liver blood vessels (called portal hypertension). In these children, only about 25 percent of the kidney tubules were cystic. Finally, a group called “juvenile” presented in childhood under the age of 5. The predominant symptom in them was the enlarged liver, and portal hypertension was severe. Less than 10 percent of the kidney tubules were cystic.

Several other reports of children with ARPKD have suggested this separation, and several authors have suggested that the affected children from a single family will always present the same way—that is, if one child has the perinatal type, any future child in that family who has ARPKD will fit in that same group.

More recent information says that this is not always true. Two recent reports have made a point of noting that one child can present with the severe, perinatal form, and another will not develop severe disease until several years of age. Among our patients are several families whose presentations fit different types. On the other hand, there are some families in which the group seems to “breed true.” That is, the affected children fit in the same group. Unfortunately, there is no way to predict in advance whether affected children will fall in the same or different groups. One needs to remember, however, that each child in an affected family has only a 25 percent chance of having the disease at all and a 75 percent chance of not having the disease.

# Index

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- ADPKD (autosomal dominant polycystic kidney disease)
  - Aneurysms
  - Children
  - Diagnosis
  - Diet
  - Drugs for
  - Hypertension
  - Imaging studies
  - Incidence
  - Mitral valve prolapse
  - Physical fitness
  - Pregnancy
  - Tests for
  - Urinary tract infection
- Alcohol
- Aneurysms
  - Brain
  - Abdominal
- ARPKD (autosomal recessive polycystic kidney disease)
  - Congenital hepatic fibrosis
  - Hypertension
  - Incidence of
  - Liver
  - Underdeveloped lungs
- Caffeine
- Computed tomogram
- Creatinine
- Cysts
  - Arachnoid
  - Aspiration of
  - Draining of
  - Enlarged
  - Infection in
  - Growth in
  - Surgery for
- Dialysis
  - Diarrhea
  - Grafts for
  - Hemodialysis
  - Hypotension
  - Nephrectomy
  - Nausea
  - Peritoneal dialysis
- Drugs
  - Acetaminophen
  - Aspirin
  - Chloramphenicol
  - Ciprofloxacin
  - Captopril
  - Enalapril
  - Erythropoietin
  - Ibuprofen
  - Norfloxacin
  - Phenacetin
  - Propoxyphene
  - Sulfamethoxazole
  - Theophylline
  - Trimethoprim
- Fluid intake
- Genes
  - ADPKD-1 chromosome 16
  - ADPKD-2 chromosome 4
  - ARPKD chromosome 6
- Therapy
- Hypertension
  - Blood pressure
  - Portal
- IVP
- Infection
  - Bladder
  - Cyst
  - Kidney
  - Urinary tract
- Kidneys
  - Bleeding in
  - Cadaver
  - Cysts in
  - Enlarged
  - Failure of
  - Infection in
  - Stones in
  - Transplants
- Laparoscopy
- Liver
  - Cysts, drainage
  - Enlarged
  - Laparoscopic surgery
  - Pregnancy
- Magnetic resonance angiography (MRI)
- Mitral valve prolapse
- Pain
- Polycystic kidney disease; see ADPKD (autosomal dominant polycystic kidney disease) or ARPKD (autosomal recessive polycystic kidney disease)
- Pregnancy
  - Kidney function
  - Liver cysts
- Protein
- Sports
- Stones
  - Extra corporeal shock-wave lithotripsy (ESWL)
- Testing
- Transplantation
- Treatment
- Ultrasound