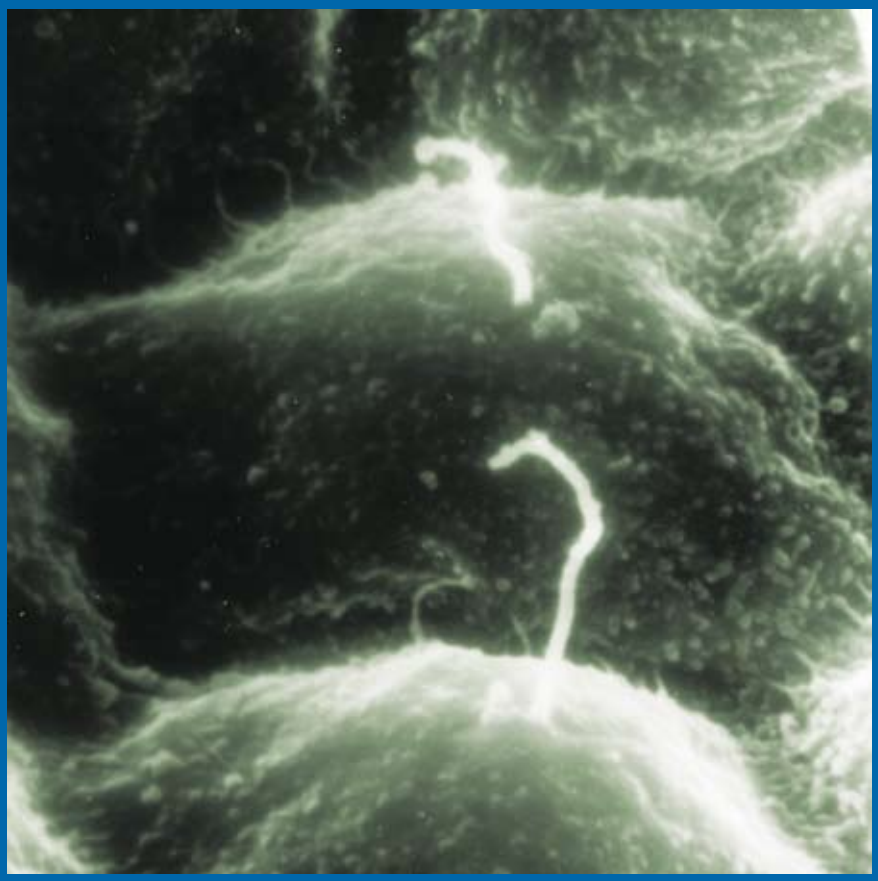


A scanning electron micrograph showing cilia present on kidney tubule cells. Cilia are hair-like structures that sense and process signals located outside the cell. Recent research, including research described in this chapter, has shown that defects in the cilia found on these kidney tubule cells may contribute to the development of cystic kidney diseases.

Kidney, Urologic, and Hematologic Diseases

Diseases of the kidneys, urologic system, and blood are among the most critical health problems in the U.S. They afflict millions of Americans, including children and young adults. The NIDDK supports basic and clinical research studies of the kidney and urinary tract and disorders of the blood and blood-forming organs. The goal is to increase understanding of kidney, urologic, and hematologic diseases to enhance prevention and treatment strategies.

Normal, healthy kidneys process about 200 quarts of blood a day to filter out about two quarts of waste products and extra water from the blood, excreting them as urine. In people with chronic kidney disease, the function of these life-sustaining organs is impaired. Kidney disease may progress to irreversible kidney failure, a condition known as end-stage renal disease (ESRD). People with ESRD require dialysis or a kidney transplant to live. At the close of 2005, more than 485,000 patients were receiving treatment for ESRD.[1] An estimated 26 million Americans suffer from chronic kidney disease.[2] The leading cause of kidney disease is diabetes, with hypertension (high blood pressure) the second-leading cause. If unchecked, the recent increases in obesity and type 2 diabetes in the U.S. will have grave implications in several years, as more people begin to develop kidney complications of diabetes.

Racial minorities, particularly African Americans, Hispanics, and American Indians, bear a disproportionate burden of chronic kidney disease. African Americans are four times more likely and American Indians are twice as likely to develop kidney failure as non-Hispanic whites. Hispanics have a significantly increased risk for kidney failure as well.

The NIDDK supports a significant body of research aimed at increased understanding of the biology underlying chronic kidney disease. The Institute's chronic renal diseases program supports basic and clinical research on kidney development and disease, including the causes of kidney disease; the underlying mechanisms leading to progression of kidney disease to ESRD; and the identification and testing of possible treatments to prevent development or halt progression of kidney disease. Areas of focus include diseases that collectively account for more than half of all cases of treated ESRD. Of special interest are studies of inherited diseases such as polycystic kidney disease, congenital kidney disorders, and immune-related glomerular diseases, including IgA nephropathy and the hemolytic uremic syndrome. The Institute's National Kidney Disease Education Program is designed to raise awareness about the problem of kidney disease and steps that should be taken to treat chronic kidney disease and prevent kidney failure. It represents a major educational outreach effort to patients, physicians, and the public.

Urologic diseases affect men and women of all ages, result in significant health care expenditures, and may lead to substantial disability and impaired quality of life. The NIDDK's urology research effort includes basic, clinical, and epidemiologic research on the genitourinary (GU) tract. The NIDDK has supported studies in benign and noncancerous urologic disorders and diseases, including benign prostatic hyperplasia, prostatitis, urinary tract infections, urinary tract stone disease, interstitial cystitis, urinary incontinence, pelvic floor disorders, congenital anomalies of the genitourinary tract, and sexual dysfunction.

Benign prostatic hyperplasia, or BPH, is a common, symptomatic condition that increases with age in men. Prostatitis—chronic inflammation of the prostate

---

[1] *U.S. Renal Data System, USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007.*

[2] *Coresh J, et al: Prevalence of chronic kidney disease in the United States. JAMA 298: 2038-2047, 2007.*

gland—is a painful condition that accounts for a significant percentage of all physician visits by young and middle-aged men for complaints involving the genital and urinary systems. To determine the greatest scientific opportunities for research in these areas, the NIDDK is nearing completion of a Prostate Basic and Clinical Science Strategic Planning effort, which will serve as a guide for future scientific inquiry. The NIDDK is committed to enhancing research to understand, treat, and prevent these common and troubling disorders.

Infections of the urinary tract are extremely common in women, and many women suffer repeated urinary tract infections (UTIs). NIDDK research includes both basic and clinical projects aimed at understanding UTIs and finding ways to prevent their recurrence. Interstitial cystitis/painful bladder syndrome (IC/PBS) is a debilitating, chronic, and painful bladder disease. The number of individuals suffering with IC/PBS is not known with certainty, but it has been estimated that 1.3 million adults in the U.S. may have the disorder, with more women affected (90 percent) than men.[3] NIDDK-supported basic and clinical research is focused on elucidating the cause(s) of IC/PBS, identifying "biomarkers" that will aid diagnosis, and improving treatment and interventions. Ongoing epidemiologic studies will help refine prevalence estimates and demographics. The NIDDK sponsors the Interstitial Cystitis Clinical Trials Group/Research Network to conduct clinical studies in IC/PBS. A new initiative, "Multi-disciplinary Approach to Chronic Pelvic Pain (MAPP)," is addressing many of the unanswered questions that impede research progress in both IC/PBS and chronic prostatitis, which share similar symptoms.

A conservative estimate is that approximately 12-13 million Americans, most of them women, suffer from urinary incontinence.[4,5] Many who have the disorder suffer in silence due to embarrassment and lack of knowledge about options available. The clinical field of urinary incontinence has changed dramatically in the last decade with the advent of new surgical procedures that have rapidly been introduced into the field. The NIDDK's Urinary Incontinence Treatment Network (UITN) has recently reported findings of the SISTEr trial (see research advances later in this section), which compared two surgical treatments for urinary incontinence. The Network is near completion of a second trial examining the effect of emptying the bladder on a regular schedule, along with Kegel exercises to strengthen pelvic muscles, to determine whether these practices will allow women to stop drug therapy and maintain the same level of bladder control. The third UITN study is recruiting patients to compare two minimally invasive surgeries for the treatment of stress urinary incontinence.

Urolithiasis and urinary tract stone disease are frequent causes of visits to health care providers. The NIDDK has a robust interest in this field, ranging from prevention to basic stone formation/dissolution and treatment with improvement of the current minimally invasive treatment modalities of laser or ultrasound lithotripsy or extracorporal shock wave lithotripsy (ESWL).

One of the most common causes of kidney failure in children is vesicoureteral reflux. In fact, abnormalities of the genitourinary tract are among the most common birth defects. The NIDDK is conducting a clinical trial to determine if the current practice of long-term antibiotics is necessary for the treatment of these children.

The NIDDK's hematology research program uses a broad approach to enhance understanding of the normal and abnormal function of blood cells and the blood-forming system. Research efforts include studies of a number of blood diseases, including sickle cell disease, the thalassemias, aplastic anemia, iron deficiency anemia, hemolytic anemias, and thrombocytopenia. The Institute is also keenly interested in the basic biology and genetic regulation of stem cells, especially adult hematopoietic stem cells, which are needed for bone marrow transplants and may have broader application in gene therapy research. An additional priority of the Institute's hematology research program is the development of improved iron chelating drugs to reduce

---

[3] *Clemins JQ, et al: Interstitial Cystitis and Painful Bladder Syndrome in* Urological Diseases in America *(pp. 125-154). NIDDK, NIH Publication Number 07-5512, 2007.*

[4] *Nygaard I, et al: Urinary Incontinence in Women in* Urological Diseases in America *(pp. 157-191). NIDDK, NIH Publication Number 07-5512, 2007.*

[5] *Stothers L, et al: Urinary Incontinence in Men in* Urological Diseases in America *(pp. 193-221). NIDDK, NIH Publication Number 07-5512, 2007.*

the toxic iron burden in people who receive multiple blood transfusions for the treatment of diseases.

PREVENTING URINARY TRACT INFECTIONS

Vaccination May Help Prevent Recurrent Urinary Tract Infections in Women: Urinary tract infections (UTIs) are extremely common and can interfere with work and daily activities. Women are highly susceptible to UTIs, and many women suffer from recurrent infections—sometimes three or more per year. Most are caused by the bacterium, *E. coli*. In a recent clinical trial, researchers found that a vaccine approach may be effective at preventing recurrent *E. coli* UTIs in women. In the trial, adult women with a history of frequent UTIs were randomly assigned to one of three treatment groups. One group received placebos only, one group received primary vaccinations, and one group received primary vaccinations plus additional monthly vaccine "boosters." The vaccine was designed to build up the body's immune defenses in the urogenital tract, where UTI pathogens take hold. The team found that vaccination was most effective against *E. coli* UTIs when vaccine boosters were provided. Almost 73 percent of vaccinated women who received boosters remained infection free 160 days after starting treatment, versus only 30 percent of those on placebos. The vaccine plus boosters regimen was especially effective at slowing the rate of *E. coli* UTI recurrence among sexually active women, and among women under the age of 52. Currently, women are prescribed antibiotics to prevent UTI recurrences, but drug-resistant UTI bacteria are increasingly making this approach less effective. The encouraging results of this trial suggest that a vaccination strategy targeting the urogenital tract may prove a good alternative approach to prevent recurrent UTIs in women.

Hopkins WJ, Elkahwaji J, Beierle LM, Leverson GE, and Uehling DT: Vaginal mucosal vaccine for recurrent urinary tract infections in women: results of a phase 2 clinical trial. J Urol 177: 1349-1353, 2007.

NEW TREATMENT FOR HYPEROXALURIA

Study Offers New Hope for Patients with Primary Hyperoxaluria Type 1: Intestinal bacteria show promise as a therapy for primary hyperoxaluria type 1, a rare condition characterized by the accumulation of oxalate due to deficiency of an enzyme that degrades this substance. In the kidneys, the excess oxalate combines with calcium to form calcium oxalate, a hard compound that is the main component of kidney stones. Deposits of calcium oxalate can lead to kidney damage and ultimately failure, and injury to other organs. Current therapeutic options for primary hyperoxaluria are few and not effective in a majority of patients. Researchers have now found that a number of intestinal bacteria, including *Oxalobacter formigenes (O. formigenes)*, can degrade oxalate. Building on this finding, a recent pilot study investigated whether oral administration of *O. formigenes* to primary hyperoxaluria patients for 4 weeks can reduce oxalate levels in blood and urine. The study demonstrated potential promise because three of five patients with normal kidney function showed decreased oxalate in their urine. In addition, two patients with kidney failure showed a significant drop in blood oxalate levels, as well as an improvement in their symptoms. The scientists found that this treatment strategy is safe and effective in reducing urine and plasma oxalate and thus, may be a useful therapeutic option for primary hyperoxaluria.

Hoppe B, Beck B, Gatter N, von Unruh G, Tischer A, Hesse A, Laube N, Kaul P, and Sidhu H: Oxalobacter formigenes: a potential tool for the treatment of primary hyperoxaluria type 1. Kidney Int 70: 1305-1311, 2006.

GENETICS OF KIDNEY DISEASE

Novel Gene Implicated in Early-Onset Kidney Disease: Scientists have recently identified a role for the phospholipase C epsilon gene (*PLCE1*) in early-onset nephrotic syndrome. Nephrotic syndrome is a kidney disease characterized by elevated levels of protein in the urine, diminished levels of protein in the blood, and fluid retention and tissue swelling. Abnormal function of podocytes, specialized cells within the kidneys' filtering units, appears to be at the center of nephrotic syndrome. Widespread scarring of the kidney in this syndrome can result in diminished kidney function and end-stage renal disease, in which case dialysis or a kidney transplant is required. There is no effective long-term treatment.

At least six genes have previously been implicated in nephrotic syndrome. Researchers performed genome-wide scans of several extended families with nephrotic syndrome who did not carry any of the previously described mutations, to search for additional genetic clues to this condition. Seven families or individuals were found to carry mutations in their *PLCE1* gene. In six, the mutations resulted in a truncated protein; in the seventh, it produced a full-length but defective protein.

In the kidney, PLCE1 protein initiates a cascade of intracellular signaling events resulting in changes in gene expression, cell growth, and differentiation. Using cultured cells and tissue analysis, the researchers demonstrated that PLCE1 protein is expressed in normal podocytes. When PLCE1 protein expression was experimentally reduced during development in zebrafish, the kidneys showed anatomic changes consistent with nephrotic syndrome.

Some of the children in the study had been treated previously with steroids or the drug cyclosporine A, two drugs used to suppress the immune system. Most were not responsive to therapy, as are most patients with nephrotic syndrome. Surprisingly, two of them—now 6 and 13 years of age—retained near-normal kidney function. To explain this exception, the researchers hypothesize that PLCE1 protein may be necessary for the kidneys to complete a particular developmental phase, and that drug therapy somehow compensated for the absence of PLCE1 signaling during this critical window. Future studies will examine additional individuals with nephrotic syndrome to test these intriguing hypotheses, as well as characterize a recently-described mouse that lacks the *PLCE1* gene as a potentially valuable model system to study this condition.

Hinkes B, Wiggins RC, Gbadegesin R, Vlangos CN, Seelow D, Nürnberg G, Garg P, Verma R, Chaib H, Hoskins BE, Ashraf S, Becker C, Hennies HC, Goyal M, Wharram BL, Schachter AD, Mudumana S, Drummond I, Kerjaschki D, Waldherr R, Dietrich A, Ozaltin F, Bakkaloglu A, Cleper R, Basel-Vanagaite L, Pohl M, Griebel M, Tsygin AN, Soylu A, Müller D, Sorli CS, Bunney TD, Katan M, Liu J, Attanasio M, O'Toole JF, Hasselbacher K, Mucha B, Otto EA, Airik R, Kispert A, Kelley GG, Smrcka AV, Gudermann T, Holzman LB, Nürnberg P, and Hildebrandt F: Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. Nat Genet 38: 1397-1405, 2006.

Identification of New Genetic Cause of Kidney Disease: Researchers have identified a gene that, when mutated, leads to an inherited form of kidney disease known as nephronophthisis (NPHP) and may explain why kidney size is significantly decreased in this disease. Characterized by kidney degeneration during childhood, NPHP leads to renal failure and ultimately the need for kidney transplantation. By conducting a genome-wide scan of three related children with early onset NPHP and their family members, researchers identified a single mutation in the gene encoding GLIS2 that is linked to the disease. To gain insight into its functional role, the scientists studied GLIS2 in normal mice and in mice containing a mutated form of the protein. The GLIS2 protein is expressed in normal adult mouse kidney, specifically in the cilia—microscopic hair-like projections on the cell surface. When the *GLIS2* gene is mutated in mice, researchers observed that the kidneys demonstrated several of the hallmarks of NPHP, including fibrosis, smaller kidney size, and loss of tissue organization.

To understand the mechanism by which the diseased kidneys are decreased in size in NPHP, the researchers looked for genes that were specifically switched on in the mice lacking functional GLIS2. The researchers examined genes with a specific DNA sequence to which GLIS2 is known to bind, indicating that these genes are directly regulated by GLIS2. They found that the absence of GLIS2 resulted in greater expression of genes involved in such processes as change in cell type, cell signaling, fibrosis, and cell death. Notably, the activated genes indicated a high level of cell death in the diseased kidney without the cell proliferation necessary to maintain organ size. By discovering how GLIS2 regulates genes involved in a change in kidney cell type to one that is typically involved in fibrosis, the researchers may have uncovered an explanation for the loss of normal kidney structure and progressive fibrosis that occur in NPHP. These results provide insight into the cause of the reduced kidney size seen in NPHP and may guide future approaches to treating and preventing this inherited form of kidney disease.

Attanasio M, Uhlenhaut NH, Sousa VH, O'Toole JF, Otto E, Anlag K, Klugmann C, Treier AC, Helou J, Sayer JA, Seelow D,

Nürnberg G, Becker C, Chudley AE, Nürnberg P, Hildebrandt F, and Treier M: Loss of GLIS2 causes nephronophthisis in humans and mice by increased apoptosis and fibrosis. Nat Genet 39: 1018-1024, 2007.

NEW INSIGHTS ON THE ROLE OF CILIA IN DISEASE

New Role of Cilia in Health and Disease: Recent research implicates the loss of cilia function in kidney disease and obesity. Cilia on many cell types are involved in cellular movement and, with stationary cells, as sensors that detect movement of fluids over the cells and detect molecules in the fluids. In the mouse kidney, this movement and its subsequent cellular signal are required for normal development of the organ. Researchers recently examined the effects of mutating two genes, *Tg737* and *Kif3a*, required for the formation and maintenance of cilia in adult mice. Surprisingly, loss of cilia throughout the body of the mouse did not lead to any immediate effects on the kidney, liver, or pancreas. Cysts eventually developed in the kidney and liver after 6 months, indicating that the cyst formation was not directly due to the inability of the cilia to convert sensory input into a cellular signal. While studying this mouse model of kidney disease, the scientists observed that these mutants exhibited a significant increase in their body weight that was not seen in control mice. This increase in body weight appeared to be primarily due to the fact that the mice ate a greater quantity of food than is optimal. The researchers also observed corresponding significant increases in fat mass and percentage of body fat, as well as elevated levels of molecules that act as satiety signals. To examine the underlying mechanisms of these effects, the researchers specifically deleted the cilia on neuronal cells in the hypothalamus section of the brain. These mice also became obese and demonstrated many of the same symptoms, suggesting that cilia on these cells are critical for regulating normal feeding behavior. Since the resulting obesity and related symptoms seen in mice resemble those seen in humans with insulin resistance and diabetes, this finding may not only provide significant insight into regulating feeding behavior and sensing "fullness," but may also provide a new target for therapeutic approaches for diabetes and obesity.

Davenport JR, Watts AJ, Roper VC, Croyle MJ, van Groen T, Wyss JM, Nagy TR, Kesterson RA, and Yoder BK: Disruption of intraflagellar transport in adult mice leads to obesity and slow-onset cystic kidney disease. Curr Biol 17: 1586-1594, 2007.

A Common Defect Links Multiple Disorders: Studies of families with two rare disorders have revealed the importance of genes that control the function of cilia. In a recent report, scientists conducted analyses to determine the variation across the human genome of families affected by cerebello-oculo-renal syndrome and Meckel syndrome. Individuals with these syndromes suffer from developmental problems, as well as from kidney cysts and liver fibrosis. In performing these scans, the researchers identified mutations in the gene *RPGRIP1L*, which codes for a protein component of the cilia. Additional experiments determined that *Rpgrip1l* is expressed in many organs during development. This finding is consistent with the multiple organs affected in patients with these two syndromes. Interestingly, *Rpgrip1l* is not the first cilia-associated gene to be associated with developmental problems. This observation suggests that disruption of cilia signaling can give rise to more generalized defects in development. While the precise biological function of *Rpgrip1l* is not known, its identification suggests that this signaling pathway may play a more central role in a number of diseases than previously realized.

Delous M, Baala L, Salomon R, Laclef C, Vierkotten J, Tory K, Golzio C, Lacoste T, Besse L, Ozilou C, Moutkine I, Hellman NE, Anselme I, Silbermann F, Vesque C, Gerhardt C, Rattenberry E, Wolf MTF, Gubler MC, Martinovic J, Encha-Razavi F, Boddaert N, Gonzales M, Macher MA, Nivet H, Champion G, Berthélémé JP, Niaudet P, McDonald F, Hildebrandt F, Johnson CA, Vekemans M, Antignac C, Rüther U, Schneider-Maunoury S, Attié-Bitach T, and Saunier S: The ciliary gene RPGRIP1L is mutated in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel syndrome. Nat Genet 39: 875-881, 2007.

DIETARY FACTORS AND THE RISK OF DEVELOPING KIDNEY STONES

Dietary Oxalate Is Not a Major Contributor to Kidney Stone Formation: Researchers have made the surprising discovery that increased intake of dietary oxalate does not substantially increase risk of kidney stones. A large percentage of kidney stones contain a compound called calcium oxalate. Since calcium and oxalate are both components of a normal diet, it

would be reasonable to propose that increased dietary intake of these compounds may increase the risk of developing kidney stones. To examine the link between oxalate intake and kidney stones, scientists analyzed historic dietary information from over 240,000 men and women participating in three major national long-term health studies. This information was compared to new patient complaints that were found to be associated with the presence of kidney stones. Quantifying dietary oxalate is difficult because of the lack of information about the oxalate content of most foods. Therefore, the researchers first examined oxalate intake using a measure of the 10 most common foods that contribute to dietary oxalate. They subsequently analyzed spinach intake alone as a measure of dietary oxalate, because raw or cooked spinach accounted for nearly half of the oxalate intake of the participants. The results of these analyses demonstrated that even those individuals who ate the highest levels of oxalate-containing foods or spinach had only a modestly increased risk of developing kidney stones compared to those individuals who ate little or no oxalate-containing foods or spinach. These results are quite surprising for patients, as well as for health care providers who treat kidney stones. Many physicians currently advise patients with kidney stones to decrease their intake of oxalate-containing foods. However, the results of this research suggest that decreasing oxalate intake in the diet may not be an effective strategy for preventing stone formation. For more information on the association between dietary factors and kidney stone formation, please see the "Scientific Presentation" in this chapter.

Taylor EN and Curhan GC: Oxalate intake and the risk for nephrolithiasis. J Am Soc Nephrol 18: 2198-2204, 2007.

SLOWING PROGRESSION OF POLYCYSTIC KIDNEY DISEASE

Targeting Cellular Pathway To Slow the Progression of Polycystic Kidney Disease: Using a rat model of autosomal dominant polycystic kidney disease (PKD), researchers have found that targeting vascular endothelial growth factor receptor 1 (VEGFR1) and VEGF receptor 2 (VEGFR2) may slow formation of cysts and preserve kidney function. VEGFR1 and VEGFR2 were first discovered on the surface of endothelial (blood vessel) cells and have been shown to enhance cell division when stimulated. These receptors also play a role in cancer, by promoting tumor-associated blood vessel formation. They also are found on the surface of cancer cells, where they can stimulate cell division. The discoveries in cancer have led to the development of multiple agents designed to block VEGFR1 and VEGFR2 pathways.

Scientists interested in PKD took advantage of the recent discovery of VEGFR1 and VEGFR2 on the surface of renal tubular epithelial cells, as well as the agents designed to target these receptors to explore the role of VEGFR1 and VEGFR2 in the development of cysts and in kidney function. Using methods to decrease the levels of VEGFR1 and VEGFR2 on the surface of the renal tubular epithelial cells, the researchers showed that the division of epithelial cells in existing cysts was decreased, leading to delayed growth of cysts. Blocking VEGFR1 and VEGFR2 also decreased serum creatine and blood urea nitrogen—two important indicators of kidney function—indicating that this treatment may improve kidney function. Furthermore, the specific methods used to block VEGFR1 and VEGFR2 did not lead to measurable negative consequences for kidney function, complications that have been seen with other agents used to target this pathway. The report of the VEGFR1 and VEGFR2 studies is exciting for patients with PKD because it provides the impetus for further exploration of the contribution of these receptors to PKD, which could have significant implications for how this disease is treated in the future. Current treatment of PKD focuses mainly on detecting and monitoring cysts and managing patients' blood pressure. The VEGFR1 and VEGFR2 results suggest that effective targeted therapies could be developed to treat PKD.

Tao Y, Kim J, Yin Y, Zafar I, Falk S, He Z, Faubel S, Schrier RW, and Edelstein CL: VEGF receptor inhibition slows the progression of polycystic kidney disease. Kidney Int 72: 1358-1366, 2007.

NOVEL CAUSE OF IRON OVERLOAD IN THALASSEMIA DISORDERS

Study Identifies Protein That Contributes to Iron Overload in Thalassemias: NIDDK intramural scientists have discovered a novel cause of iron

overload in patients with thalassemia. This inherited blood disease is characterized by impaired production of hemoglobin—the oxygen-carrying protein in red blood cells—and by anemia. The scientists found that thalassemia patients had unusually high levels of the protein growth differentiation factor 15 (GDF15) in their blood when compared to normal volunteers. From subsequent experiments, it appears that GDF15 suppresses the production of the liver protein hepcidin, an important regulator of iron metabolism in the body. A drop in hepcidin levels leads to an increase in the uptake of dietary iron in the gut. The body lacks a mechanism to excrete excess iron. Too much iron can cause damage to many organs, including the heart and liver. The identification of GDF15 as an important contributor to the regulation of normal iron levels has implications for the management of iron metabolism in patients with thalassemia and other diseases. It may also be a valuable tool in the development of future therapies for these health problems.

Tanno T, Bhanu NV, Oneal PA, Goh S-H, Staker P, Lee YT, Moroney JW, Reed CH, Luban NLC, Wang R-H, Eling TE, Childs R, Ganz T, Leitman SF, Fucharoen S, and Miller JL: High levels of GDF15 in thalassemia suppress expression of the iron regulatory protein hepcidin. Nat Med 13: 1096-1101, 2007.

New Insights on Bladder Control in Women

Loss of bladder control, or urinary incontinence, can be embarrassing and difficult to deal with. It is also a common and costly condition that reduces quality of life for many Americans, especially women. According to the NIDDK's *Urologic Diseases in America* project, up to three-fourths of women have some degree of incontinence. It is estimated that, in 2000, the direct cost of incontinence for women—including hospital stays and visits to office-based physicians, hospital outpatient clinics, and emergency rooms—was $453 million.[1] These women usually have stress or urge urinary incontinence—the most common forms of incontinence—and sometimes a combination of both.

Now, in the largest and most rigorous U.S. trial comparing two traditional operations for stress urinary incontinence in women, a team of urologists and urogynecologists supported by the NIDDK, the National Institute of Child Health and Human Development, and the NIH Office of Research on Women's Health, has found that a sling procedure helps more women achieve dryness than the Burch technique. The results of the trial will help women with stress incontinence and their doctors make better-informed choices based on clear benefits, risks and personal preferences.

SISTEr Results

Stress urinary incontinence, in which coughing, laughing, sneezing, running or lifting heavy objects causes urine to leak, is sometimes treated with surgery designed to provide additional support to the bladder neck and urethra during increases in abdominal pressure that occur with these kinds of activities. Many different surgical procedures exist to treat stress urinary incontinence. However, randomized, controlled trials comparing these operations for safety and efficacy are rare.

The Stress Incontinence Surgical Treatment Efficacy Trial (SISTEr) randomly assigned 655 women with either pure stress urinary incontinence or a combination of stress and urge incontinence to receive the sling or Burch procedures. Complete information on measures used to assess urinary incontinence was available for 520 participants 24 months after surgery. Quality of life, patient satisfaction and side effects were also studied. SISTEr found that significantly more women with a sling made from the patient's own tissue and placed around the urethra for additional support were dry, compared to women with a Burch colposuspension, in which sutures are attached to a pelvic ligament to support the urethra. Two years after surgery, 47 percent of women who had the sling procedure and 38 percent who had a Burch were dry overall, including leakage that could have been caused by urge incontinence. Considering only stress-specific leakage, 66 percent of women with a sling and 49 percent with a Burch procedure were dry.

While most women in the study were satisfied with the results of treatment, those with a sling were significantly more satisfied. Eighty-six percent with a sling were satisfied, compared to 78 percent of the Burch group. However, side effects were more common among women with slings, tempering the positive results of the procedure. The most common side effect was urinary tract infections, which occurred in 63 percent of women with a sling and 47 percent of the Burch group. Women with a sling also had more voiding problems (14 percent versus 2 percent) and persistent urge incontinence, the loss of urine just before feeling a strong, sudden urge to empty the bladder (27 percent versus 20 percent). Nineteen women with slings who had difficulty voiding after treatment needed surgery to correct the problem; none in the Burch group needed corrective surgery for voiding problems.

Studies predating SISTEr were small, short-term, or less stringent about diagnostic criteria and outcome measures, producing inconsistent results across studies. SISTEr set a higher bar by standardizing definitions, clinical evaluations, and surgical procedures at all sites and by using "composite outcome measures and a more rigid definition of success compared to other studies," according to the study.

SISTEr defined two levels of treatment success. Success specific to stress incontinence required that women have no symptoms of leakage during physical activities, no leakage during a relevant stress-test, and no re-treatment for the problem. Overall success required that women

meet stress-incontinence-specific treatment goals, have a negative pad test and have no leakage episodes recorded on a 3-day voiding diary. This higher bar may account for lower success rates observed in SISTEr than in earlier trials. However, this carefully conducted trial will inform the planning of future trials of surgical therapies for urinary incontinence and other urological health problems.

The Urinary Incontinence Treatment Network

SISTEr is the first trial completed by the Urinary Incontinence Treatment Network (UITN), a multi-center research network supported by the NIDDK. Beginning in 2000, the NIDDK, the National Institute of Child Health and Human Development, and the NIH Office of Research on Women's Health established this Network to conduct a series of rigorous, long-term trials of common incontinence therapies in women. The UITN is also collecting data on body weight and diabetes, which could serve as a resource for ancillary studies to investigate the association of urinary incontinence with obesity and diabetes. In addition to SISTEr, two other UITN studies are in the wings:

- *BE-DRI:* Behavior Enhances Drug Reduction of Incontinence (BE-DRI) is a trial of therapies for urge incontinence. BE-DRI asked 307 women to make changes such as emptying the bladder on a regular schedule and to practice Kegel exercises to strengthen pelvic muscles to learn if these common treatments would allow women to stop drug therapy and maintain the same degree of bladder control. The BE-DRI trial has been completed and as this document goes to press, trial results are expected to be published shortly.

- *TOMUS:* The third UITN study, the Trial of Mid-Urethral Slings (TOMUS), is recruiting patients to compare two minimally invasive surgeries for the treatment of stress urinary incontinence. Both procedures include placement of a synthetic mesh sling (rather than a sling made from the patient's own tissue, as was used in SISTEr), and have been approved by the Food and Drug Administration for treatment of stress incontinence. For a list of centers enrolling patients for TOMUS, visit *http://www.uitn.net* or search for TOMUS at *http://www.clinicaltrials.gov*

---

[1] *Litwin MS and Saigal CS: Introduction in* Urologic Diseases in America *(pp. 1-7). NIDDK, NIH Publication Number 07–5512, 2007.*

Urologic Diseases in America

Urologic Diseases in America, released in Spring 2007, was developed by a team of epidemiologists, health economists, statisticians, programmers, and urologists—with NIDDK funding. According to the report, bladder, prostate and other urinary tract diseases cost Americans nearly $11 billion a year and Medicare's share of these expenses exceeds $5.4 billion. The report describes more than a dozen diseases of children and adults, among them congenital abnormalities, erectile dysfunction, chronic prostatitis, interstitial cystitis, urinary incontinence and a chapter on the topic of sexually transmitted diseases, contributed by the Centers for Disease Control and Prevention. The findings include:

- *Urinary Tract Infections:* Medical care for almost 12.8 million urinary tract infections in women alone costs nearly $2.5 billion annually. Adding the cost for men raises the total to $3.5 billion; Medicare's share was $1.4 billion. Another $96.4 million was spent on 3.3 million prescriptions. More than half of all women will have an infection during their lifetimes. While only 20 percent of infections are in men, they are more often hospitalized, and are out of work about twice as long as women due to this health problem.

- *Kidney Stones:* While hospitalizations, length of stay and the need for open surgery are declining for kidney stones, medical care still costs $2.1 billion annually, with another $4 million to $14 million spent on prescription drugs. Men are two-to-three times more likely than women to develop a stone, but more people of all ages and races are now getting them: an estimated 5 percent of adults between 1988 and 1994, up from nearly 4 percent between 1976 and 1980. Compared to Caucasians, African Americans and Mexican Americans have a 70 percent and 35 percent lower risk, respectively, of developing a stone.

- *Childhood Urologic Diseases:* Although data for childhood urologic diseases are scarce, urinary problems in children cost at least $75 million dollars a year. Vesicoureteral reflux, the abnormal flow of urine from the bladder up toward the kidneys, affects about 10 percent of all children and makes them prone to urinary tract infections and kidney damage. The cost of hospitalizations for reflux alone rose from $10 million in 1997 to $47 million in 2000; Southern states, defined using U.S. Census Bureau regions, saw the highest rise—56 percent—attributable to a doubling in the number of cases.

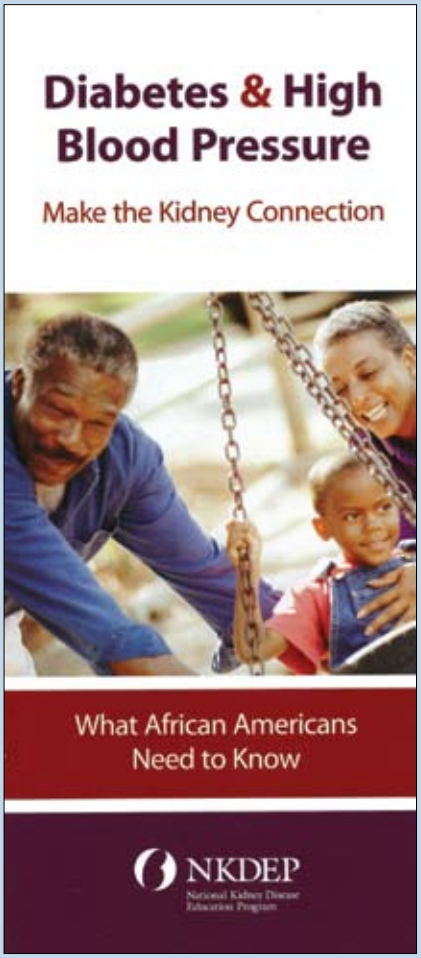
Urologic Diseases in America—printed books and CDs—may be ordered from the National Kidney and Urologic Diseases Information Clearinghouse at 1–800–891–5390, *nkudic@info.niddk.nih.gov*, and at *www.catalog.niddk.nih.gov*

National Kidney Disease Education Program: New Publication Helps African Americans "Make the Kidney Connection"

An estimated 26 million Americans suffer from chronic kidney disease (CKD)[1] and, according to the NIDDK-supported United States Renal Data System (USRDS), more than 340,000 patients are on dialysis.[2] Patients with CKD are at increased risk for kidney failure. It is estimated that treating the number of people with kidney failure, also called end-stage renal disease (ESRD), through dialysis or kidney transplantation costs the U.S. health care system more than $30 billion every year.[2] ESRD is an enormous public health problem that disproportionately affects minority populations.

Helping address these issues is the NIDDK's National Kidney Disease Education Program (NKDEP). This educational program seeks to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk—those with diabetes, high blood pressure, cardiovascular disease, or a family history of kidney disease—and the availability of treatment to prevent or slow kidney failure. The progression from CKD to kidney failure can be prevented or delayed if it is detected and treated early enough. The NKDEP underscores that effective treatments and management strategies for kidney disease exist, yet are being underutilized.

Recently, the NKDEP created an educational brochure tailored specifically for African Americans at risk for kidney disease. The brochure explains the connection between diabetes, high blood pressure, and kidney disease. The brochure also encourages those at risk to talk to their health care providers about getting tested.



This new NKDEP brochure tailored for African Americans at risk for kidney disease explains the connection between diabetes, high blood pressure, and kidney disease.

African Americans are disproportionately affected by kidney failure due in part to higher rates of diabetes and high blood pressure—the two leading causes of kidney failure. In a press release announcing the new publication, Dr. Griffin Rodgers, NIDDK Director, noted that, "Diabetes and high blood pressure are all too common among African Americans, yet many are unaware of their risk factors and the importance of getting tested. NKDEP recognizes the importance of promoting key messages about kidney disease risk factors to this audience." Dr. Andrew Narva, NKDEP Director, added, "Unlike many diseases, kidney disease often has no symptoms until it is very advanced. For this reason and others, it is important for African Americans to not only become aware of their risk, but also to learn about the steps they can take to keep their kidneys healthier longer. An important step is to get tested."

The brochure explains the blood and urine tests used to detect kidney disease in simple, easy-to-read language. It also outlines several steps that African Americans can take to protect their kidneys. These steps include:

- Keeping kidneys healthy by managing diabetes and high blood pressure;
- Asking health care providers to test blood and urine for kidney disease; and
- Talking to health care providers about treatment options if already diagnosed with kidney disease.

In developing the brochure, the NKDEP worked with health care professionals who routinely care for African American patients at risk for kidney disease. Reviewers included NKDEP Coordinating Panel members and representatives from the Association of Minority Nephrologists. By partnering with national, state, and local organizations, including government agencies, NKDEP hopes to reach a large number of African Americans with this information.

For more information about the brochure and other NKDEP materials, visit *www.nkdep.nih.gov* or call 1-866-4 KIDNEY (1-866-454-3639).

---

[1] Coresh J, et al: Prevalence of chronic kidney disease in the United States. JAMA 298: 2038-2047, 2007.

[2] www.usrds.org/2007/pdf/00a_precis_07.pdf

STORY OF DISCOVERY

Polycystic Kidney Disease

Polycystic kidney disease, or PKD, is the fourth leading cause of kidney failure in the U.S.[1] Fluid-filled cysts form in the kidneys and other organs and can, as they grow over time, compromise kidney function. Patients with the disease typically have high blood pressure, urinary tract infections, and chronic pain. There is no primary treatment for PKD, and patients generally receive drugs to control their blood pressure and manage their pain. However, knowledge of the causes of PKD has increased dramatically in the past 20 years due to NIDDK-supported research. Scientists have a better understanding of the genetic causes of PKD, and are studying the use of new technologies to improve disease detection and monitoring. Because of the efforts of many dedicated scientists, there is hope for the future for people with PKD and their families.

What is Polycystic Kidney Disease?

Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous fluid-filled cysts. These cysts develop primarily in the kidneys, but also can appear in organs such as the liver, pancreas, spleen, and thyroid. In the kidneys, these cysts can slowly replace much of the mass of the kidneys, reducing kidney function and leading to kidney failure. About half of people with the most common form of PKD progress to irreversible kidney failure, also called end-stage renal disease (ESRD). When this occurs, usually in the fifth or sixth decade of life, patients require either a kidney transplant or dialysis to survive. In the United States, an estimated 600,000 people have PKD, and it is the fourth leading cause of kidney failure. While there is no effective treatment for the underlying causes of PKD, patients are usually prescribed pain-relieving drugs, antibiotics to treat infections, as well as medications to control blood pressure that are aimed at preserving or slowing the decline in kidney function.

There are two major inherited forms of PKD, called autosomal dominant and autosomal recessive. Autosomal Dominant PKD, or ADPKD, accounts for about 90 percent of all cases. People with ADPKD usually develop symptoms between the ages of 30 and 40, but symptoms can appear earlier, even in childhood. The genetically recessive form of PKD, Autosomal Recessive PKD, or ARPKD, is a rare inherited form of the disease that displays symptoms in the earliest months of life, even in the womb.

Past Treatment for PKD

About 30 years ago, knowledge about the causes and progression of PKD was limited. The details of the genetics of the dominant form of PKD were unknown. Doctors knew that, on average, half of children born to an affected parent would develop the disease, and that it could be transmitted by either the mother or the father. The mechanism by which the disease caused cysts to form and grow in the kidneys was not known. Diagnosis of well-established disease in adults was relatively straightforward using the imaging techniques that were available at the time, such as ultrasound. However, diagnosis of earlier stages of disease in children and young adults was much more difficult. By the time most people were diagnosed, their kidneys were so damaged that kidney function had begun to decline.

Treatment options for people with chronic kidney disease in general, and ADPKD in particular, were also inadequate. No specific therapy was available. The importance of controlling blood pressure and dietary protein intake in patients with chronic kidney disease was not recognized. Two life-saving kidney function replacement therapies—hemodialysis and kidney transplantation—were developed through fundamental NIH research in the 1960s. Although they were increasingly available, neither was ideal.

STORY OF DISCOVERY

Genetic Underpinnings of PKD and Insights from Animal Models

The emergence of molecular biology and modern biotechnology in the late 1970s and early 1980s permitted researchers for the first time to examine in detail the genetic underpinnings of a number of diseases. Scientists have identified two genes associated with ADPKD. The first was found in 1985 on chromosome 16 and was named *PKD1*. The second gene, *PKD2*, was localized to chromosome 4 in 1993. Within 3 years, scientists had isolated the proteins these two genes produce—polycystin-1 and polycystin-2. Most cases of the dominant form of PKD can be traced back to mutations in one of these two genes. However, evidence suggests that the disease development also requires other factors. Normally, polycystin-1 and polycystin-2 form an ion channel on the surface of kidney cells. This channel regulates the flow of calcium into and out of the cell. Mutation of either gene inhibits the activity of the channel, thus disrupting calcium-dependent intracellular signaling pathways.

This ion channel is part of a complex of proteins located on the cell surface at the site where tiny, hair-like projections called cilia emerge from the cell into the renal tubule, where waste products are filtered into what will become urine. Under normal conditions, the cilia on the surface of these renal tubule cells detect changes in urine flow, and transmit this information inside the cell through the activation of various molecular signaling pathways. One signaling mechanism is the opening of the ion channel formed by polycystin-1 and -2. The opening allows calcium ions to enter the cell, setting off a cascade of signaling events. However, when one or both are mutated, the channel does not function properly. As a result, calcium does not enter the cell, and the metabolic response to changes in urine flow is disrupted. This abnormality in calcium signaling may result in cells that grow abnormally and retain fluid, ultimately giving rise to multiple, fluid-filled cysts characteristic of PKD.

Disruptions in cilia signaling have been found to underlie a number of diseases of the kidney, as well as other organs. Many genes encode proteins that localize to the cilia, and mutations in these genes often produce similar clinical manifestations. These observations have given rise to the hypothesis that many cystic kidney diseases may arise from defects in primary cilia signaling. Future efforts will be devoted to improved understanding of cilia signaling and identifying potential new therapeutic targets. Because cilia are found on the surface of almost all cells in the body, insights gained from these studies may also benefit people suffering from a number of diseases in which cilia signaling is impaired.

Researchers have also identified the gene associated with ARPKD, called *PKHD1*. The protein encoded by this gene, known as fibrocystin or polyductin, is present in fetal and adult kidney cells, and is also present at low levels in the liver and pancreas. Its precise biological function is unknown.

Current Clinical Management and Research Studies of PKD

Advances in knowledge about cyst formation and disease progression have been complemented by improvements in the early detection and treatment of the most common form of PKD. The NIDDK supports a number of clinical studies aimed at furthering our knowledge about the origins, progression, and optimal treatment of this disease.

The NIDDK-supported Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments for the common form of the disease. Importantly, the CRISP study demonstrated that magnetic resonance imaging (MRI) could accurately track structural changes in the kidneys, and that such methods may be able to predict functional changes earlier than standard blood and urine tests in people with the common form of PKD.

STORY OF DISCOVERY

The respective roles of *PKD1* and *PKD2* in disease progression, as indicated by ultrasound analysis, have remained unclear. The CRISP investigators, using a more sensitive MRI method, reported that patients with the *PKD1* gene have more cysts and significantly larger kidneys than those with the *PKD2* gene. Data from the CRISP study suggest that this difference results from earlier development of cysts, not from a faster growth of cysts, in patients with *PKD1* mutations. These clinically important results will inform the development of targeted therapies for patients with this form of the disease.

To expand and follow-up on the important insights gained in the CRISP study, the NIDDK has funded an extension, CRISP II, to continue to monitor this valuable cohort of patients. The extension will enable researchers to determine the extent to which changes in kidney volume do in fact predict changes in kidney function.

The NIDDK, with co-funding from the PKD Foundation, is also conducting two clinical trials of people with the most common form of PKD—one in patients with early kidney disease and another in patients with more advanced disease. These two trials are the largest multi-center studies of PKD conducted to date, and are collectively termed HALT-PKD. These studies are testing whether optimum blood pressure management, in combination with drugs—either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers—will slow the progression of this disease. The NIDDK is also funding an investigator-initiated interventional trial of optimum blood pressure therapy in children and young adults. These interventional studies are the first clinical trials to implement and formally validate the imaging surrogate marker of PKD progression that was developed by the CRISP study.

Hope for the Future

Investigators are continuing to pursue basic biologic studies of the causes of PKD, as well as new avenues for therapies, in the hope that diagnosis and treatment can be improved. As scientists' understanding of the genetics and progression increases, it is hoped that there will be a decrease in the number of patients with the disease who progress to ESRD. Because PKD can affect patients very differently, even within the same family, the NIH is assembling a large genetic sample collection for future investigations. Studies of these samples may help to identify genetic markers that might predict who will develop more rapidly progressive kidney disease. These genetic studies could also provide new information on identifying key disease pathways and aid in the design of new drug treatment strategies. The studies also could yield clues about how to intervene earlier, more precisely, and more effectively in these patients. Earlier intervention, more intensive management of high blood pressure, and use of drugs that target kidney fibrosis may delay progression to ESRD and give patients additional years of life without the need for dialysis or a kidney transplant. For patients who eventually do need dialysis, the NIH is conducting a trial to determine whether more frequent dialysis improves their quality of life.

Although there have been advances in the knowledge base about dialysis and improvements in technology, a functioning kidney transplant remains a patient's best hope of living a more normal life. However, normal life expectancy and health-related quality of life are rarely, if ever, restored by organ transplantation. Furthermore, despite the best immunosuppressive therapies, many patients with kidney transplants still lose their transplanted kidneys due to rejection of the transplant by the body's immune system. Better strategies to maintain the

STORY OF DISCOVERY

function of transplanted kidneys and prevent chronic scarring are likely to emerge from ongoing basic research and improved imaging methods. The NIDDK and NIH will continue to support research into kidney disease in general, and PKD in particular, working across Institutes and joining with other partners to better understand, monitor, and treat this disease.

[1] *U.S. Renal Data System, USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007.*

Kidney Stones as a Systemic Disease

Dr. Gary Curhan

Dr. Gary Curhan is an Associate Professor of Medicine at Harvard Medical School and an Associate Professor of Epidemiology at the Harvard School of Public Health. He is a leading researcher in the field of kidney disease, as well as a number of other chronic diseases, including interstitial cystitis and high blood pressure. The following represents highlights of a scientific presentation by Dr. Curhan at the September 2007 meeting of the NIDDK National Advisory Council. Dr. Curhan shared with the Council his view of kidney stone disease as an organ-specific manifestation of a more generalized systemic disorder, rather than simply a disease of the kidneys.

Kidney stone disease is a common and painful health problem in the U.S. It is also a growing problem: the number of people in the U.S. with kidney stones has increased significantly over the past 30 years. White Americans are more prone to develop kidney stones than African Americans, and men are more likely to develop stones than women. For unknown reasons, some individuals are prone to repeatedly developing stones. Each year, people make almost three million visits to health care providers and more than half a million people go to emergency rooms for kidney stone problems.[1]

The first symptom of a kidney stone typically appears when the stone moves from the kidney into the ureter, causing irritation or blockage and resulting in extreme pain. Most kidney stones can pass harmlessly—though not painlessly—through the urinary system. In such cases, medication to alleviate the pain may be the only medical intervention needed. Stones that cause lasting symptoms or other complications may be treated by various techniques, most of which do not involve major surgery. In severe cases, however, surgery may be required to remove the stone.

In addition to being extremely painful, kidney stones also are costly to treat. According to the 2007 edition of *Urologic Diseases in America*, kidney stones are the second-costliest urologic disease, accounting for over $2 billion spent on medical care,[2] with another $4 million to $14 million spent on prescription drugs.[3] These numbers do not include costs not associated with direct medical expenditures, such as time lost from work.

Composition of Kidney Stones

Kidney stones can consist of a number of different components. The most common type of stone, accounting for two-thirds of all stones, is a combination of calcium and oxalate. Less common types of stones include stones caused by urinary tract infections, and stones made of uric acid or the amino acid cystine. "Nephrolithiasis" is the medical term used to describe stones occurring in the kidney, while stones in the urinary tract are formally designated as "urolithiasis." For the sake of simplicity, "kidney stone" is often used to designate stones regardless of their location in the kidney or urinary tract.

Urine is a liquid with various substances dissolved in it, and there is a finite amount of material that can be dissolved in a given quantity of water. If this limit is exceeded, material will fall out of solution and crystallize. Once this process starts, the nascent crystals attract other dissolved elements in the water, and the crystal grows in size. Although the precise steps that lead to kidney stone formation are not known, one way to think about crystal formation is as a problem of too much material trying to remain dissolved in too little water.

SCIENTIFIC PRESENTATION

Risk factors for kidney stones encompass gastrointestinal, skeletal, and metabolic factors, as well as obesity. At first glance, the connection of most of these factors to the kidney may not be obvious. However, closer examination reveals clues that implicate kidney stone disease as an organ-specific manifestation of more general systemic disturbances.

Risk Factors: Gastrointestinal

Because the most common type of kidney stone, the calcium oxalate stone, consists of two components found in a normal diet, it might stand to reason that increasing consumption of these factors would increase the risk of stone formation. Indeed, patients prone to developing stones are often counseled to limit their dietary intake of calcium and oxalate. However, studies reveal that increased dietary intake of calcium does not increase the risk of stone formation and may in fact reduce the risk. Increased dietary intake of oxalate has, at best, a modest impact on stone risk. Surprisingly, however, increased dietary intake of fructose correlates with a dramatic increase in risk of developing a kidney stone. Fructose is one of the two sugar molecules that comprise ordinary table sugar and is a major component of high fructose corn syrup, which is used in a large number of food products. It seems that, in some individuals, fructose can be metabolized into oxalate. This observation underscores the complexity in using diet modification in people prone to developing kidney stones, because traditional advice to limit intake of oxalate-containing foods may not be sufficient to reduce risk of stone development (for more details regarding the assessment of dietary oxalate and its role in stone formation, see the accompanying research advance, "Dietary Oxalate Is Not a Major Contributor to Kidney Stone Formation").

Risk Factors: Bone

In addition to providing structural support and protecting internal organs, the skeleton represents a large repository for calcium. The skeleton is an active site of tissue breakdown and regeneration throughout life. In diseases such as osteoporosis, more calcium is lost from bone than is deposited, resulting in a net negative calcium balance. Researchers have known for years that patients with elevated calcium levels in their urine are likely to have lower bone mineral density, emphasizing that there are metabolic sources for urinary calcium, as well as dietary sources.

Of course, skeletal remodeling is not the only source of circulating calcium, as this mineral is an important component of the diet. Does increased calcium in the diet increase one's risk of developing kidney stones? Quite the opposite: several large epidemiologic studies and one randomized trial suggest that high dietary calcium intake is associated with a decreased risk of kidney stones, and that people with the lowest dietary calcium intake had an increased risk of kidney stones. The reason for this is unclear, but it is possible that higher levels of dietary calcium bind to oxalate in the digestive tract and prevent it from being absorbed and eventually moving to the kidneys where it might form stones.

Risk Factors: Obesity

It has been know for years that increasing body weight puts individuals at risk for high blood pressure, diabetes, and a host of other health problems. Recent research has also uncovered a role for obesity in the formation of kidney stones. Studies have shown that the risk of stone formation can be almost twice as great in women who weigh more than 220 pounds compared to those who weigh less than 150 pounds; overweight men are also at higher risk. The increase in relative risk is also seen if one looks at body mass index, which takes both height and weight into account. The reason for this correlation is unclear, but it is the subject of ongoing research.

As rates of obesity in the U.S. continue to rise, more people are turning to bariatric surgery as a way to address the problem. In this surgery, doctors alter the digestive tract in order to restrict food intake and, in some cases, interrupt the digestive process. When

researchers examined urine oxalate levels in patients who had undergone this procedure, they found levels were two to three times higher than normal, and elevation in oxalate seems to result in a higher risk of stone formation. This finding underscores the complex metabolic pathways that regulate oxalate absorption and excretion and how changes to the digestive tract may have unexpected results on overall metabolism.

Risk Factors: Endocrine and Metabolic Pathways

Diabetes significantly increases an individual's risk of kidney disease, blindness, amputation, and cardiovascular disease. Scientists have recently shown that diabetes also increases the risk of developing kidney stones between 20 and 50 percent, and that this increase is especially apparent in younger women. There is also evidence that people with diabetes have a lower than normal urine pH—meaning that their urine is more acidic. This change in urine composition, sometimes accompanied by a decrease in urine volume, may also contribute to stone formation in these individuals. This observation further emphasizes that kidney stones may arise as much from generalized metabolic derangement as from kidney-specific factors.

Risk Factors: Genetics

As is the case with many diseases, it is likely that kidney stones arise from both environmental and genetic causes. Much of what is known about stone formation concerns dietary and metabolic factors, but it is likely that genetics plays an important role in determining an individual's likelihood of developing kidney stones. Currently, a number of potential candidate genes have been identified, including the calcium sensing receptor, the vitamin D receptor, and the oxalate transporter protein in the intestine. Large genome-wide association scans that might identify other candidates have only recently begun, but hold great promise for the future (for more information about genome-wide association scans, see the chapter on Cross-Cutting Science.)

Conclusion

Kidney stone disease should be thought of as a systemic disorder and not just a disease of the kidneys. In the past several years, significant progress has been made in understanding the causes of the disease, but much work remains to be done. Moving forward, new paradigms regarding the underlying causes of the disease will shape the research agenda, especially regarding the origins of stones and the risk factors that contribute to their formation. Future large studies of genetics and gene-environment interactions will further our understanding of this complex disorder.

---

[1] *Kidney Stones in Adults, National Kidney and Urologic Diseases Information Clearinghouse, National Institute of Diabetes and Digestive and Kidney Diseases. http://kidney.niddk.nih.gov/kudiseases/pubs/stonesadults/index.htm*

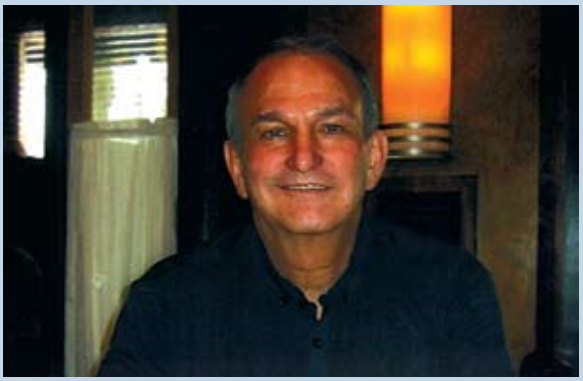
[2] *Litwin MS and Saigal CS: Introduction in* Urologic Diseases in America *(pp. 1-7). NIDDK, NIH Publication Number 07–5512, 2007.*

[3] *Pearle MS, Calhoun E, and Curhan GC: Urolithiasis in* Urologic Diseases in America *(pp. 281-319). NIDDK, NIH Publication Number 07-5512, 2007.*

PATIENT PROFILE

Richard Gordon

Study Finds Benign Prostatic Hyperplasia (BPH) in Older Men Effectively Treated with Drugs



Richard Gordon

"I couldn't get a good night's sleep," said 64-year-old corporate executive and grandfather of two, Richard Gordon. "I'd get up five to eight times a night to urinate. Also, I'd be sitting with friends at a Chicago Bulls basketball game with 2 minutes left in a close contest, the ball in Michael Jordan's hands—and I'd have to head to the men's room because of a sudden urge to urinate!" he said, adding that he's a big fan of spectator sports.

That was 15 years ago. Richard was suffering from a condition called benign prostatic hyperplasia, or BPH, which can manifest symptoms in men as young as 50. BPH is a condition in which the prostate gland enlarges, compressing the urethra and interfering with the normal flow of urine. Richard was experiencing frequent urination, a typical BPH symptom (see sidebar), and it was adversely affecting his sleep pattern and lifestyle.

Although surgical removal of the enlarged part of the prostate was considered an effective long-term solution for many patients with BPH, researchers continued to search for a way to shrink, slow, or stop the growth of the prostate without the use of invasive surgery, risks of which include possible incontinence and impotence.

Today, as a result of participating in a study called the Medical Therapy of Prostatic Symptoms (MTOPS) trial, sponsored by the NIDDK, Richard said that the drug regimen he was put on has his BPH under control. "I'd definitely recommend others take part in such studies," said Richard. "It has improved the quality of my life, and I feel I'm in a much better position to make informed decisions about how to treat BPH."

Medical Therapy of Prostatic Symptoms (MTOPS)

The MTOPS trial enrolled over 3,000 participants with symptomatic BPH from 1993 to 1998 and was conducted at 17 clinical sites in the U.S. The trial was designed to test whether two FDA-approved drugs—finasteride and doxazosin, alone or together—could prevent or reduce the progression of the symptoms of BPH. Finasteride is a 5-alpha reductase inhibitor, so named because it inhibits the action of the enzyme that converts the male hormone testosterone to its more potent derivative dihydrotestosterone (DHT). DHT is a key regulator of prostate growth. Doxazosin is an alpha-blocker, a drug that relaxes smooth muscle and, in the context of BPH, can allow urine to flow more freely through the urethra, and reduce the symptoms of urinary frequency and urgency. Both classes of drugs had been previously approved for treatment of BPH, but they had not been compared head-to-head in a long-term clinical trial, and they had not been formally tested as combination therapy.

PATIENT PROFILE

After learning of the MTOPS study from a friend, Richard contacted one of the trial sites directly. Richard participated in the 3-year trial as well as a 2-year follow-up study, and said, "I was very pleased to be a part of it."

Today, as a result of participating in a study... sponsored by the NIDDK, Richard said that the drug regimen he was put on has his BPH under control. "I'd definitely recommend others take part in such studies," said Richard. "It has improved the quality of my life, and I feel I'm in a much better position to make informed decisions about how to treat BPH."

As part of the study protocol, he was given a digital rectal exam to determine whether he actually had BPH, as well as a prostate-specific antigen (PSA) blood test and rectal ultrasound to rule out cancer. Participants were randomized to one of four treatment groups: double-placebo; finasteride alone; doxazosin alone; or the combination of the two drugs. Because it was a "double-blind" study, neither Richard nor his doctor was told of his assigned group until the study was over.

"I was required to take my pills every night and to have a digital rectal exam once a year," he said. He appreciated the fact that, while taking part in the study, the drugs were provided free of charge.

At its conclusion, the MTOPS study demonstrated that, compared to placebo, finasteride and doxazosin, in combination, reduced the risk of BPH progression 67 percent. In contrast, the risk of progression was reduced by 39 percent with doxazosin alone and by 34 percent with finasteride alone.

"Combination therapy not only provides better long-lasting [BPH] symptom relief," said MTOPS trial leader John McConnell, M.D., professor of urology and executive vice president of the University of Texas Medical Center in Dallas, "but because finasteride reduces prostate size, patients have fewer episodes of urinary retention and invasive treatments," including surgery. He added that the study also clearly demonstrated which patients are at increased risk of progression and thus most likely to benefit from treatment.

Richard continues to see his urologist once a year, has an annual digital rectal exam, takes his medications as prescribed, and instead of having to rouse himself from bed five to eight times to urinate, as he once did, he now averages only once a night. He reports experiencing no sexual dysfunction or other side effects, and said, "I couldn't be happier."

What is BPH?

The cause of BPH is not yet well understood. What is known is that it is common for the prostate to become enlarged as a man ages. The prostate is a walnut-sized gland that forms part of the male reproductive system. It is located in front of the rectum just below the bladder, where urine is stored. One of its main roles is to squeeze fluid into the urethra as sperm moves through during sexual climax. As the prostate enlarges, however, it may affect the function of the bladder. Consequently, typical BPH symptoms include:

- A slow, interrupted, weak urine stream;
- Urgency of the need to urinate;
- Leaking or dribbling of urine; and
- More frequent urination, especially at night.

Because the prostate gland plays a role in both sex and urination, many people feel uncomfortable talking about BPH. Nonetheless, more than half of men in their 60s and as many as 90 percent in their 70s have some symptoms of BPH. BPH rarely causes symptoms before age 40. Richard was in his late 40s when he first started to manifest symptoms of the condition, and he was wise to seek help.

PATIENT PROFILE

Studies show that in 8 out of 10 cases, the symptoms mentioned previously are indicative of BPH, which is common and treatable. However, these symptoms also can signal other, more serious conditions that require prompt treatment, including prostate cancer. Richard said he knows several men around his age whose symptoms were similar to his, but, after seeing their physicians, they learned they had prostate cancer.

"I'm grateful that my BPH was treated early; this is a problem that men should take seriously," said Richard.

Not to be discounted, severe BPH itself can cause serious problems over time. Urine retention and strain on the bladder can lead to urinary tract infections, bladder or kidney damage, bladder stones, and incontinence—the inability to control urination. If the bladder is permanently damaged, treatment for BPH may be ineffective. However, when BPH is detected in its early and moderate stages, there is a lower risk of developing such complications.

"I'm grateful that my BPH was treated early; this is a problem that men should take seriously," said Richard.

Improving Health Through Medical Research

Richard's improved quality of life results from the Nation's investment in biomedical research. There is much more that needs to be learned about BPH. To address this, the NIDDK continues to support research including studies to elucidate factors which contribute to onset, natural history, and alternative therapies.

In addition to clinical research, the NIDDK's Division of Kidney, Urologic, and Hematologic Diseases supports a robust Basic Cell Biology Program that supports a diverse array of projects with a primary emphasis on basic research in the bladder, prostate, urinary tract, kidney, and the lower reproductive system. This Program promotes scientific investigations aimed at understanding the fundamental cellular and molecular mechanisms operating under normal and diseased states. Supported work includes studies in human cells as well as in animal model organisms. Additionally, the Developmental Biology of the Kidney and Urogenital Tract Program encompasses studies that focus on fundamental cellular biology of the kidney and urogenital tract (bladder and prostate) and on mechanisms through which they develop.

PATIENT PROFILE

Diagnosis of BPH

Diagnosis of BPH usually occurs when a patient reports symptoms to his physician or when the physician, during a routine check-up, finds that the patient's prostate is enlarging.

Several tests help the doctor identify the problem and decide the appropriate form of treatment, including:

Digital Rectal Exam (DRE)—the physician inserts a gloved finger into the rectum to help determine the size and condition of the prostate.

Prostate-Specific Antigen, or PSA, Blood Test—helps to rule out cancer as a cause of urinary symptoms. Note: Much remains unknown about the interpretation of PSA levels, the test's ability to discriminate cancer from benign conditions of the prostate, and the best course of action following a finding of elevated PSA.

Rectal Ultrasound and Prostate Biopsy—a procedure whereby a probe inserted in the rectum directs sound waves at the prostate to help determine whether an abnormal-looking area is indeed a tumor. The doctor can use the probe and the ultrasound images to guide a biopsy needle to the suspected tumor to collect tissue specimens for further study under a microscope.

Urine Flow Study—the physician asks the patient to urinate into a special device that measures how quickly urine is flowing. A reduced flow often suggests BPH.

Cystoscopy—a small tube called a cystoscope, containing a light and a lens is inserted through the opening of the urethra in the penis to help determine the size of the gland and identify the location and degree of the obstruction.

Very seldom are all of the above tests necessary to make a diagnosis.

NIDDK | NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES