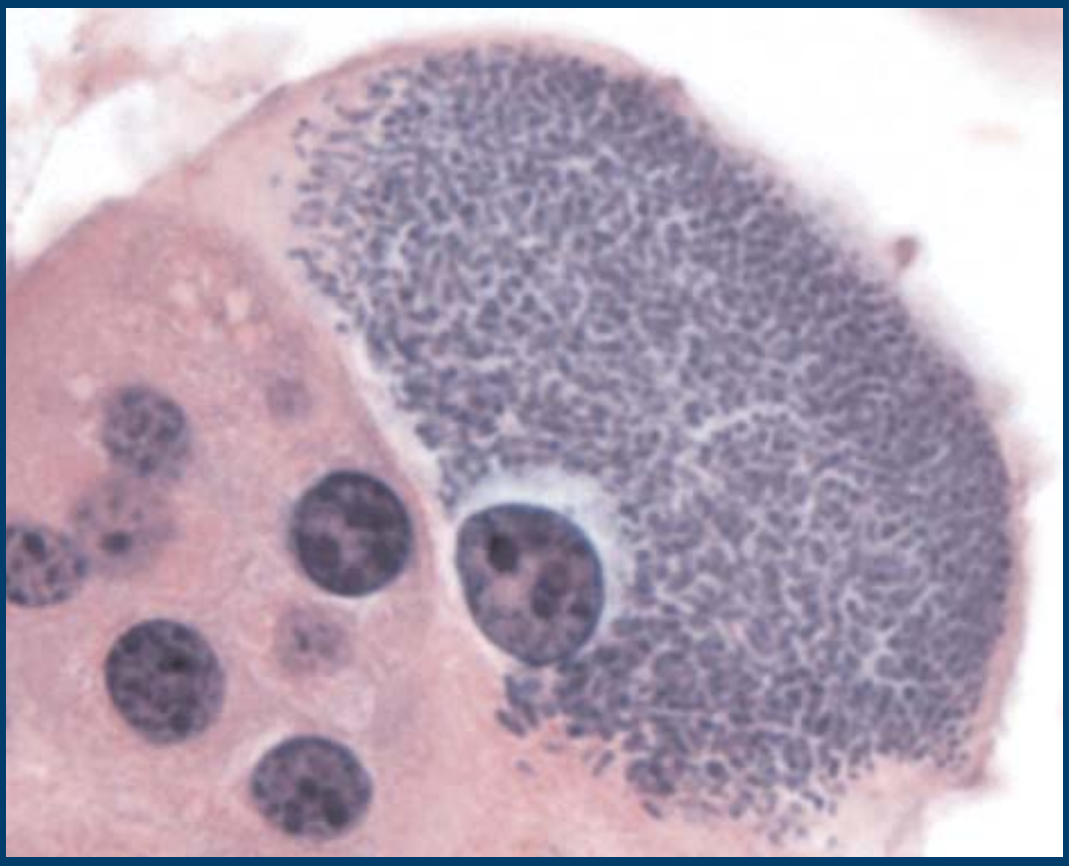

In mouse bladder tissue, a dense "biofilm" of bacteria (at right side, stained dark blue) completely fills a cell. Forming biofilm-like pods within cells may be a way for infection-causing bacteria in the urinary tract to survive antibiotic treatments and cause recurrent infections. Unaffected bladder cells (stained pink, with dark purple nuclei) are visible at left. Photo: Dr. Joseph Palermo and Dr. Scott Hultgren, Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO. Reprinted with permission from Anderson GG *et al, Science* 301:105-7, 2003. © 2003 AAAS.

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 is committed to enhancing research to understand, treat, and prevent these diseases.

Normal, healthy kidneys filter toxins from the blood so that they may be excreted. In people with chronic kidney disease, these organs are less able to perform this life-sustaining function. Persons whose disease progresses to irreversible kidney failure, also known as end-stage renal disease (ESRD), require dialysis or kidney transplantation to live. Conservative estimates find that 4.5 percent of American adults 20 years of age and older–about 7.4 million adults–have substantially impaired kidney function. The leading cause of kidney disease is diabetes, with hypertension (high blood pressure) the second-leading cause. The recent increases in obesity and type 2 diabetes in the U.S., if left unchecked, will have grave implications in several years, as more people begin to develop renal complications of diabetes.

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

The U.S. has seen an enormous increase in people with ESRD. The NIDDK-supported United States Renal Data System, a nationwide database covering kidney disease, reports that nearly 100,000 people developed ESRD in 2001 and a total of nearly 400,000 patients were living with the disease at the end of that year. These numbers have doubled since 1990 and are expected to nearly double again by 2010. The cost of ESRD is high–nearly $23 billion in public and private spending for healthcare alone in 2001.

The NIDDK devotes significant resources to understanding the basic mechanisms underlying chronic kidney disease. The 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. Research areas 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. A major new, pilot educational outreach effort is the National Kidney Disease Education Program.

Urologic diseases affect persons of all ages, result in significant health care expenditures, and, if mis-diagnosed or improperly treated, may lead to irreversible kidney and/or bladder damage and possibly death. The NIDDK's urology research portfolio includes basic and clinical research on the normal and abnormal development, structure, and function of the genitourinary tract. Nonmalignant

urologic diseases include benign prostatic hyperplasia, prostatitis, urinary tract infections, urinary tract stone disease, interstitial cystitis, urinary incontinence, and congenital anomalies of the genitourinary tract.

Benign prostatic hyperplasia, or BPH, is a condition that affects an estimated 9 percent of men 30 years of age and older, with men 55 and older accounting for most cases. Prostatitis is inflammation of the prostate gland that accounts for a significant percentage of all office visits by young and middle-aged men for complaints involving the genital and urinary systems. The NIDDK is committed to enhancing research to understand, treat, and prevent these diseases.

Infections of the urinary tract are extremely common in women, and many women suffer repeated urinary tract infections (UTIs); according to one recent national health survey, over half of women 20 years of age or older report they have had at least one UTI or related bladder infection (cystitis). In 2000, UTIs and cystitis accounted for over 9 million physician visits. Interstitial cystitis (IC) is a debilitating, chronic, painful bladder disease that has been estimated to affect as many as 847,000 Americans adults, over 90 percent of whom are women. Millions of Americans, most of them women, suffer from urinary incontinence. For both men and women, kidney stones, formally known as urinary tract stone disease, accounted for over 2.2 million physician visits in 2000. In children, one of the most common causes of kidney failure, vesicoureteral reflux, occurs in an estimated 1-to-2 percent of newborns. In fact, abnormalities of the genitourinary tract are the most common birth defects.

To address these and other urologic problems, the NIDDK's urology research efforts support basic, applied, and clinical research in prostate and prostate diseases; diseases and disorders of the bladder; male sexual dysfunction; urinary tract infections; urinary tract stone disease; and pediatric urology, including developmental biology of the urinary tract. A research emphasis of the urology program is the study of chronic inflammatory disorders of the lower urinary tract.

The NIDDK's hematology research program uses a broad approach to understanding the normal and abnormal function of blood cells and the blood-forming system. Research areas include a number of blood diseases, such as 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 have broader application in gene therapy research. An additional priority of the Institute's hematology research programs is the development of improved iron chelating drugs to reduce the toxic iron burden in people who receive multiple blood transfusions for the treatment of diseases such as Cooley's anemia (thalassemia major).

BUILDING INSIGHTS IN PKD AND OTHER CYSTIC KIDNEY DISEASES

Polycystic kidney disease (PKD) affects people of all ages and is the fourth leading cause of kidney failure in the U.S. PKD causes massive enlargement of the kidneys due to the progressive development of fluid-filled cysts. Mutations in the PKD1 and PKD2 genes are responsible for the most common forms of the disease. The proteins encoded by *PKD1* and *PKD2*, polycystin-1 (PC1) and -2 (PC2), respectively, form a functional complex implicated in cell signaling in kidney epithelial cells, but the precise mechanism by which PKD mutations interfere with kidney tubule development is still unclear. Fascinating new studies in model organisms have led PKD researchers to focus on a single hair-like structure on kidney epithelial cells called the primary cilium. An emerging scientific model suggests that structural or functional defects in this single cilium interfere with normal kidney tissue development, and may be at the root of PKD and other cystic diseases of the kidney. Scientists are rapidly building this picture of PKD mechanisms.

Cilia and Cystic Kidney Disease: A recent study strengthens the link between ciliary defects and PKD, and reinforces the importance of the cilium to normal kidney development. Previously, researchers had shown that PC1 and PC2 co-localize to the cilium, and that loss of functional PC1 and PC2 disables a cell signaling mechanism normally triggered by mechanical stress on the cilium. Loss of this pathway may abrogate the cells' ability to sense and respond to environmental cues regulating kidney tissue development and function. In related work, researchers have now found that proteins implicated in another cystic kidney disease, nephronopthisis (NPHP), also co-localize to the cilium. NPHP is the most frequent inherited cause of ESRD in children and young adults. Researchers recently identified the causative gene for a particular form of the disease that attacks in infancy. This gene encodes a protein called inversin. Inversin is important for determining left-right body axis symmetry, or "patterning," during development, but appears to have other developmental tasks as well. In experiments using a common, simple model of animal development, the zebrafish, the investigators found that if they reduced expression of this animal's inversin gene, it not only disrupted normal development, but caused PKD-like renal cyst formation. In other experiments, they found that inversin interacts with another NPHP disease protein (nephrocystin)–findings which culminated in the discovery that inversin and nephrocystin can be observed together in the cilium of cultured kidney epithelial cells. These results suggest that inversin is important in animal kidney development and that NPHP proteins, like PKD proteins, may fulfill some of their functions through their presence in the cilium.

The roles of the cilium in normal development or maintenance of kidney epithelial cells–and hence, its possible role in cyst formation–are still under investigation. In particular, because PC1, PC2, and other PKD and cystic kidney disease-related proteins are found in other parts of the cell in addition to the cilium, it is unknown whether ciliary dysfunction alone is sufficient to cause disease. However, the results of this recent research bolster the significance of cilia and ciliary proteins in cystic kidney diseases. Continued investigation of both cilia themselves and the PKD-related proteins is required to determine exactly how defects in the kidney epithelial cell cilium may contribute to the pathogenesis of PKD and other cystic kidney diseases.

Potential Therapeutic Target for PKD and NPHP: Another team of researchers has uncovered a promising therapeutic approach for PKD and other cystic kidney diseases. Basic research studies have shown that levels of an important intracellular molecule, cAMP, are increased in kidney cells from PKD animals, and the expression of genes that are responsive to cAMP levels is also altered. This "upregulation" of cAMP levels thus has a multitude of downstream effects on kidney cell growth and function that may influence PKD pathogenesis. Building upon these studies, the researchers found that, in two rodent models of childhood cystic kidney disease, levels of VPV2R are increased. VPV2R is a cell receptor for vasopressin, an anti-diuretic hormone secreted by the pituitary gland in the brain. When vasopressin interacts with VPV2R, it increases levels of cAMP in kidney cells. Using their two animal models, the researchers tested whether a drug that could block this vasopressin receptor could specifically reduce renal accumulation of cAMP and influence the course of PKD. They found that, indeed, early administration of the drug prevented the accumulation of cAMP and inhibited cystic kidney disease development in both models, with an estimated protective effect of up to 75 percent in a rat model of autosomal recessive polycystic kidney disease (ARPKD). Excitingly, they also observed disease regression in the other rodent model, a model of nephronopthisis (NPHP3), when the drug was administered later in life, to adolescent animals–the first interventional study in an animal model of cystic kidney disease to show such an effect. Vasopressin receptor-blocking drugs that have been or are being tested in pre-clinical and clinical studies

are apparently safe, with minimal adverse effects. Importantly, although the researchers worked with models of ARPKD and NPHP3, not ADPKD (the most common form of PKD), the tissues affected by kidney cysts are similar in all three diseases. Thus, such VPV2R blocking drugs may be well-worth studying in future prevention and treatment trials for cystic kidney disease.

In addition to these important fundamental investigations of PKD pathology and treatments, the NIDDK is supporting several clinical initiatives in PKD. The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease, or CRISP, is an NIDDK-sponsored study designed to find ways through imaging techniques to monitor changes in the kidneys and kidney cyst size in patients with PKD. The goal is to improve clinicians' ability to monitor the progression of kidney disease in these patients, in order to assess possible strategies for clinical intervention. Furthermore, the Polycystic Kidney Disease Clinical Trials Network has been established to design and implement clinical trials of treatments that will slow the progressive loss of renal function in PKD. The first large interventional clinical trial conducted by this network, the HALT-PKD trial, will be a randomized, controlled trial of the efficacy of blocking the renin-angiotensin system on slowing the rate of decline of kidney function in patients with PKD. The commonly used "ACE inhibitors" target this system, and an ACE inhibitor will be one of the drugs tested in this trial. It is expected that patient recruitment will be initiated in the Spring of 2004. Finally, investigation of PKD and other kidney diseases will benefit from the NIDDK-supported Kidney Disease Clinical Studies Initiative (KDCSI), a new paradigm for kidney disease clinical research. This initiative aims to improve the quality and quantity of clinical studies by maximizing outcomes and reducing costs through sharing of resources obtained in previous studies, such as samples, specimens, and data, and through innovative funding mechanisms.

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FUNDAMENTAL INSIGHTS INTO KIDNEY DISEASE

Each day, the kidneys cleanse the blood by passing it through millions of tiny filtering units called glomeruli. The glomeruli permit waste molecules to move out of the blood to form urine, while holding back other molecules, such as albumin and other critical blood proteins. Diseases that injure the glomeruli–including systemic diseases such as diabetes, and kidney-specific diseases such as focal segmental glomerulosclerosis (FSGS)–lead to excess protein in the urine (proteinuria), edema, hypertension, reduced waste clearance, and other symptoms of kidney dysfunction. Recent research on both systemic molecules and kidney cell proteins is providing new insights into glomerular disease susceptibility and injury.

sFlt1 Antagonism of Angiogenic Factors May Underlie Symptoms of Preeclampsia: Preeclampsia affects approximately 3 to 4 percent of pregnancies and is the leading cause of maternal and fetal death in the U.S. Mothers with preeclampsia develop hypertension, proteinuria, and edema–all resulting from widespread endothelial dysfunction. Abnormal endothelial growth in the glomeruli is the typical kidney lesion of preeclampsia. Although the symp-

toms are known, the cause of preeclampsia has remained elusive. One hypothesis is that a soluble factor(s) secreted by the placenta triggers maternal endothelial dysfunction and subsequent clinical disease. Identifying that factor(s) could be key to developing a treatment or preventive therapy for preeclampsia.

In an important new advance, researchers have found that a soluble protein, sFlt1, is strongly associated with the symptoms and lesions of preeclampsia. Following a screen to identify candidate factors, the researchers found that serum levels of this protein–which are normally elevated during pregnancy–are nearly five-fold higher in patients with severe preeclampsia than in pregnant women with normal blood pressure. This is significant because the protein is a known antagonist of two promoters of new blood vessel development (angiogenesis)–VEGF (vascular endothelium growth factor) and PlGF (placental growth factor). Loss of VEGF activity has also been implicated in the development of hypertension and excess levels of protein in the urine, which are indicative of kidney damage. Consistent with their initial finding, the research team observed that serum levels of free VEGF and free PlGF were significantly decreased in preeclampsic mothers. Using an *in vitro* model system, they also found that that both serum from preeclampsic mothers and control serum supplemented with sFlt1 could disrupt angiogenesis–an effect that could be overcome by adding back VEGF and PlGF. Furthermore, sFlt1 blocked the ability of VEGF and PlGF to relax blood vessels in another experimental system, suggesting that excess levels could induce hypertension. Most significantly, the team was able to reproduce human preeclampsia symptoms and lesions in a rat model by the addition of the sFlt1 protein. Notably, pregnancy was not required for the induction of these symptoms in rats, suggesting that this protein is interfering directly with the maternal endothelium, rather than through a second pregnancy-related factor. The effects were seen in rats with both a high dose of the protein and with lower dosages more closely resembling levels in human preeclampsia patients, differing only in severity of symptoms.

Currently, there is no specific treatment for preeclampsia, and severe cases often require premature delivery of the infant. These results from work done with humans, animal models, and *in vitro* suggest that overproduction of the sFlt1 protein, possibly by the placenta, tips the balance between proangiogenic and antiangiogenic factors in the body, thereby causing generalized endothelial dysfunction. This new knowledge is encouraging, for if abnormalities in levels of this protein are the primary cause for some or all of preeclampsia symptoms in pregnant women, then treatments to overcome its effects may ameliorate symptoms. Furthermore, if this protein is overexpressed early in pregnancy, it may serve as a diagnostic marker for patients at high risk of developing the condition.

Deficiency in Podocyte Protein May Increase Susceptibility to Kidney Disease: How well a person's glomeruli function normally may determine how well they can resist certain types of injury. In each glomerulus, specialized epithelial cells (podocytes) and their associated thin cell junctions (slit diaphragms) are the ultimate filtration barrier preventing loss of crucial blood components to the urine. Several proteins necessary for podocyte function have been identified, including CD2 adaptor protein (CD2AP). Scientists have now uncovered a possible link between CD2AP deficiency and susceptibility to glomerular kidney disease. The CD2AP protein is a component of podocyte slit diaphragms, where it is thought to play an important structural role. In mice, lack of this protein leads to massive proteinuria and early death from kidney failure. Investigators recently examined the kidneys of mice which had some, but much less than normal, CD2AP, and compared them with normal siblings. They found that while none of the mutant mice developed proteinuria during a 1 year study, older CD2AP-deficient mice developed lesions in the glomeruli–including protein deposits similar to those observed in human glomerular disease. Furthermore, the mutant mice were more susceptible than normal mice to experimentally-induced glomerular damage. Finally, electron microscopy studies revealed that the podocytes of the mutant mice had certain defects in an important cellular

activity–targeting endocytosed proteins for intracellular degradation. This finding is consistent with other studies implicating the CD2AP podocyte protein in regulation of protein trafficking. From these results, it appears that this protein fulfills more than one role in mouse podocytes, and that its insufficient expression may increase vulnerability to glomerular injury over time.

Extending these observations to human glomerular disease, the investigators screened 45 persons suffering from idiopathic or HIV-associated focal segmental glomerulosclerosis (FSGS) for mutations in the human CD2AP gene that might alter protein levels. Among ten individuals, they identified six gene sequence variants that were not found in a control group. Two patients had a specific mutation in one of their two chromosomal copies of the CD2AP gene. This mutation was predicted to cause these patients to produce less of the normal protein. In fact, an easily grown test tissue from these individuals (B cells) showed reduced levels of CD2AP protein. These results suggest that variation in CD2AP levels may indeed contribute to human glomerular disease.

Collectively, glomerular diseases are a leading cause of kidney disease and kidney failure. These findings have provided researchers with new hypotheses to test regarding underlying mechanisms of glomerular injury. Furthermore, identifying factors such as CD2AP gene variants that may predispose individuals to glomerular injury could help clinicians develop tests to identify patients at higher risk for kidney disease.

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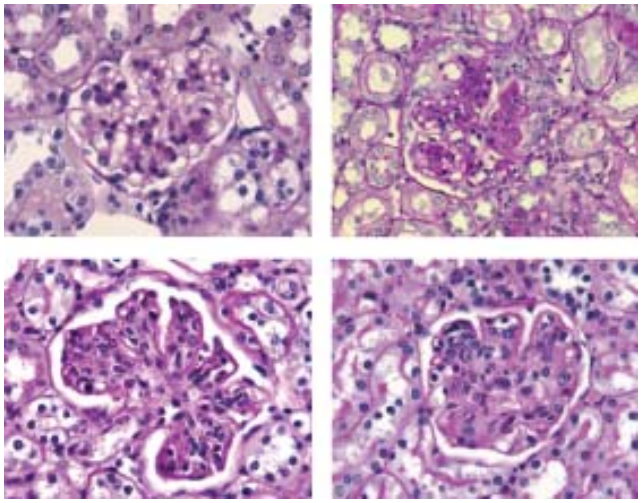

A mouse kidney glomerulus (upper left panel, center) becomes scarred and/or physically deformed in mice deficient in an important glomerular protein, CD2AP (other three panels). These findings suggest that deficiency in the protein may contribute to glomerular kidney disease. Photo: Dr. Jeong M. Kim and Dr. Andrey S. Shaw, Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO. Reprinted with permission from Kim JM *et al, Science* 300:1298-300, 2003. © 2003 AAAS.

REGRESSION TO NORMAL KIDNEY FUNCTION IS COMMON IN TYPE 1 DIABETES PATIENTS

Type 1 diabetes patients are at increased risk for developing complications, such as kidney disease. Previous research had suggested that patients who secreted very slightly elevated levels of the protein albumin in their urine (microalbuminuria) had a very high risk of developing kidney damage. In a recent advance, researchers conducted a six-year study of nearly 400 type 1 diabetes patients, all of whom had microalbuminuria. Strikingly, they found that only 19 percent of these patients developed kidney disease, while approximately 60 percent underwent a regression to normal levels of urinary albumin. They found the regression to be dependent on factors such as age, cholesterol or triglyceride levels, blood pressure, and hemoglobin-A1c levels (a measure of long-term blood glucose control). Therefore, microalbuminuria in patients with type 1 diabetes does not always lead to diabetic kidney disease. The study also emphasizes that good control of blood pressure, lipids, and HbA1c levels may promote this beneficial regression.

The NIDDK is supporting many efforts aimed at reducing the onset or burden of kidney disease as a complication of diabetes. For example, the Institute is supporting the Mouse Models of Diabetes Complications Consortium. The Consortium is generating genetic mouse models to analyze the initiation and progression of diabetic complications, including kidney disease. Such accurate models of human diabetic kidney disease, once developed, will be especially valuable in uncovering the genes and cellular processes that confer disease susceptibility or resistance. Candidate methods for the prevention, detection, and treatment of diabetic kidney disease may also be effectively tested in these mouse models.

The Institute is also supporting studies of genetic influences on the development of kidney complications in diabetes. Families of patients with diabetic nephropathy have an increased prevalence of renal disease and certain populations appear to be more susceptible. Delineating the genetic loci associated with the development and progression of diabetic nephropathy could lead to improved outcomes; therefore, the NIDDK and the NIH National Center for Minority Health and Health Disparities have established the Family Investigation of Nephropathy of Diabetes (FIND) Consortium. FIND began in September 1999 and will conclude in September 2004. The overall goal of FIND is to identify genetic pathways that may be critical for the development of nephropathy, and that may lead to candidate genes or genetic pathways amenable to therapeutic strategies to prevent disease onset or progression.

To foster promising research more effectively on diabetes complications, including kidney complications, the NIDDK recently established an Institute Working Group for Diabetes Complications. The goals of this group are to provide seamless integration of NIDDK activities related to complications, including workshops, initiative planning and oversight of existing projects and trials; to establish liaison with other Institutes and to develop activities that will increase interest in diabetes complications in other scientific communities; and to lead future strategic planning activities on diabetes complications. Through these and other efforts, the NIDDK seeks to ensure continued progress in research leading toward improved clinical management of the kidney complications of diabetes.

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ELIMINATING HEALTH DISPARITIES IN KIDNEY DISEASE

Chronic kidney disease and kidney failure disproportionately affect ethnic and racial minority populations in the U.S. The NIDDK is striving to reduce the burden of kidney disease in these populations through its support of focused clinical research efforts and initiatives. Steady progress is being made, as illustrated by the following recent advances.

Testing the Effects of Lowered Blood Pressure on Kidney Disease in African Americans: Within the general U.S. population, high blood pressure (hypertension) is a leading cause of end-stage renal disease (ESRD). However, African Americans have a particularly high risk for developing ESRD as a result of hypertension. The African American Study of Kidney Disease and Hypertension (AASK) was a clinical trial of over 1,000 African Americans with signs of hypertensive kidney disease. Participants received one of three medications–a beta-blocker, a calcium channel blocker, or an ACE inhibitor–and were treated with the goal of lowering blood pressure to either normal levels or lower-than-normal levels. During the trial, treatment with the calcium channel blocker was discontinued because it was less effective than either of the other two drugs at slowing the progression of kidney disease. Recent analysis of the data now reveals that there was no difference in rates of kidney disease progression between the groups that maintained either “normal” or “low” blood pressure.

However, kidney function in patients taking the ACE inhibitor was better than in those taking the other drugs. This study has important implications for the medical management of hypertensive kidney disease.

Nurse-Directed Diabetes Care Is Beneficial to Minorities with Diabetes: Most diabetes patients do not achieve the recommended strict control of their disease that decreases their risk for developing disease complications. This is a serious problem in minority populations, who are already at disproportionately increased risk for developing complications. A recent study determined that type 2 diabetes care directed by specially-trained nurses, who are under the direction of a physician, improved disease management in minority patients, compared to standard physician-only directed care. Nurse-directed care was already known to improve diabetes management in middle-class populations, and this study confirms the same benefits in a minority population of Hispanic- and African-American patients. Researchers studied several parameters of diabetes management, such as the number of times patients visited the clinic for routine diabetes monitoring. In nearly every parameter, patients under the care of a nurse had better management than patients under standard physician-directed care. Thus, nurse-directed care can improve disease management, which may have a dramatic effect in reducing morbidity and mortality in this high-risk population.

Encouraging Kidney Donation: Members of racial and ethnic minority groups, particularly African Americans, American Indians, Alaska Natives, and Hispanic Americans, are disproportionately afflicted with end-stage renal disease (ESRD). The most effective therapy for ESRD is kidney transplantation because it most improves patients' quality-of-life and survival rates. However, the number of organs and tissues donated by members of minority groups and other underserved populations is low; therefore, the likelihood is reduced for a good match between donor and recipient and, ultimately, survival of the transplanted organ. To address the present health disparities, the NIDDK, in collaboration with the NIH National Center on Minority Health and Health Disparities (NCMHD), established the Minority Organ and Tissue Donation Program. The program is expected to create an environment supportive of organ donation in racial and ethnic minority communities by increasing their exposure to organ donation messages and their opportunities to express donation commitments; evaluating the impact of increased support for living organ donation; increasing minority cadaveric and living organ donations; and increasing donation from non-traditional donors (for example, older donors and living donors). With more organs and tissues from minority groups in the donor pool, the survival rates and quality-of-life are expected to improve for ESRD patients from racial and ethnic minority groups.

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EFFORTS TO HALT PEDIATRIC RENAL DISEASE

Kidney disease in children has numerous causes and can have long-lasting effects on health and development. Acute renal (kidney) failure, though often transient, can be devastating in pediatric patients. Diarrhea-associated hemolytic uremic syndrome (HUS), although rare, is the most common cause of acute renal failure in previously healthy children in the U.S. The trigger in most cases is intestinal infection with certain strains of the bacteria, *Escherichia coli*. While *E. coli* is a normal component of the human gut flora, some strains, called STEC strains, produce "Shiga toxins." These toxins

are absorbed from the gastrointestinal tract and bind to the surface of cells lining the blood vessels, leading to diffuse vascular injury and organ failure. One example of a Shiga toxin *E. coli* strain is *E. coli* O157. STEC infection is commonly acquired through undercooked, contaminated meat, particularly beef. Because recent reports estimate that nearly 40 percent of pediatric cases of diarrhea-associated HUS require temporary dialysis and the mortality rate is 3 to 5 percent despite intensive supportive care, researchers are trying to identify effective interventions to prevent absorption and of the Shiga toxins.

In a recent randomized, controlled, double-blind clinical trial in nearly 150 children, researchers tested whether oral administration of a Shiga-toxin-binding agent diminishes the severity and improves the clinical course of diarrhea-associated HUS. The main outcome measures were the frequency of death or other serious extra-renal events and need for dialysis in the treated group as compared to the placebo group. Unfortunately, the researchers found that similar numbers of serious events occurred in the groups (18 and 20 percent, respectively) and there was a similar need for dialysis (42 and 39 percent, respectively). However, these results, although negative, are important, because they will help point researchers in other directions and reinforce the current efforts to prevent diarrhea-associated HUS through safer food handling and preparation.

Chronic kidney disease is another serious burden in children, with consequences for growth and development lying beyond the immediate reduction in kidney function. To stimulate research in understanding pediatric kidney disease and its complications, the NIDDK–in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Child Health and Human Development (NICHD)–has funded the Prospective Study of Chronic Kidney Disease in Children. The primary goals are to determine the risk factors for the decline in kidney function in these patients; the incidence of, and risk factors for, impaired neurocognitive development and function; and the prevalence of risk factors for cardiovascular disease; and long-term effects of growth failure and its treatment. The information obtained from this study will establish natural history and outcome measures for future intervention or prevention trials. In addition, the NIDDK is funding a study of focal segmental glomerulosclerosis (FSGS) in children and young adults that may yield further insights into the problem of kidney disease in young people. Finally, in 2004, the NIDDK is planning an initiative on vesicoureteral reflux (VUR), a urologic disease primarily affecting children that can lead to serious infection and kidney failure. These efforts are intended to lead to greater progress in reducing the serious effects of kidney disease in children.

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IMPROVING OUTCOMES ON DIALYSIS

Kidney failure is a growing problem that can be prevented or slowed, but only a fraction of people who are at high risk are screened or managed appropriately. People with irreversible kidney failure, also known as end-stage renal disease (ESRD), require dialysis or a kidney transplant to survive. Patients, insurers, and the U.S. Government's Medicare program paid nearly $23 billion to treat nearly 400,000 people for kidney failure in 2001. Most are on dialysis, and most dialysis patients are on hemodialysis. Diabetes and hypertension are leading causes of kidney failure.

Although current standards for hemodialysis treatment are effective, some physicians believed that an increased dialysis dose or the removal of larger waste particles, using a high-flux dialysis filter, would improve survival. The NIDDK's Hemodialysis (HEMO) Study Group directly tested this hypothesis in a large-scale, randomized clinical trial. Over 1,800 patients received either standard or high-dose hemodialysis, through either a low- or high-flux

dialyzer, three times weekly. Patients were followed for an average of over three years. Researchers found that, overall, patients on the high-dose therapy, or using a high-flux dialyzer, did not experience any additional benefit over patients treated with standard therapy or a low-flux filter. These results suggest that physicians should continue to administer hemodialysis to their patients using current clinical practice guidelines.

The NIDDK continues to support studies to improve the dialysis process and the lives of patients on dialysis. The Institute is planning large clinical trials to examine whether there are health benefits to be gained from more frequent dialysis. It is expected that two trials will be initiated, one comparing short daily hemodialysis with conventional dialysis, and one comparing long nocturnal dialysis with conventional dialysis. Previous studies of increased dialysis frequency have reported good results, including reductions in blood pressure, serum phosphate levels, and requirements for erythropoietin (a factor critical for red blood cell formation). Improved patient well-being has also been reported. These observations, however, derive from small groups of selected patients in a few centers.

One of the major challenges in caring for the hemodialysis patient is maintenance of vascular access for hemodialysis. Access-related problems are among the most frequent reasons for hospitalization in the ESRD population, and the cost of vascular access placement and repair in the U.S. exceeds $700 million annually. In FY 2000, the NIDDK established the Dialysis Access Consortium to undertake interventional clinical trials to improve outcomes in patients with fistulas* and kidney transplants. Two clinical trials have now been designed and are recruiting patients. The first trial will evaluate the effects of the anti-platelet agent, clopidogrel, on prevention of early fistula failure. The second trial will study a drug combination (dipyridamole and aspirin), with the goal of preventing access stenosis (blood vessel narrowing) in hemodialysis patients who have received a kidney transplant.

Another clinical trial the Institute is supporting is entitled "Hypertension in Hemodialysis." This trial is determining how to diagnose high blood pressure in hemodialysis patients, and to treat it using angiotensin converting enzyme inhibitors or beta blockers.

The NIDDK also has implemented a new research initiative to study aspects of chronic kidney disease, including kidney dialysis. This initiative is soliciting exploratory and developmental grants that aim to assess dialysis therapy, dialysis access, anemia of kidney disease, and nutritional or cardiovascular aspects of ESRD.

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PROGRESS ON TREATING PROSTATE DISEASE

Benign prostatic hyperplasia (BPH) and prostatitis are the two leading benign prostate conditions affecting men across the lifespan. BPH affects an estimated 9 percent of men 30 years of age and older, but most cases occur in men 55 and older, with prevalence increasing with age. Prostatitis is inflammation of the prostate gland that accounts for a significant percentage of all office visits by young and middle-aged men for complaints involving the genital and urinary systems. Although termed "benign" because they are not cancerous or life-threatening, these prostate problems can have significant impact on men's quality of life. Prostate diseases can cause symptoms ranging from sensations of irritation and burning during urination to increased frequency or urgency of urination, weak streams of urine, urine leakage, and pain. Prostate diseases can also interfere with normal sexual function. While progress is being made in the under-

* Fistula: A surgically created communication between an artery and vein, usually performed in the forearm or leg of patients undergoing kidney dialysis.

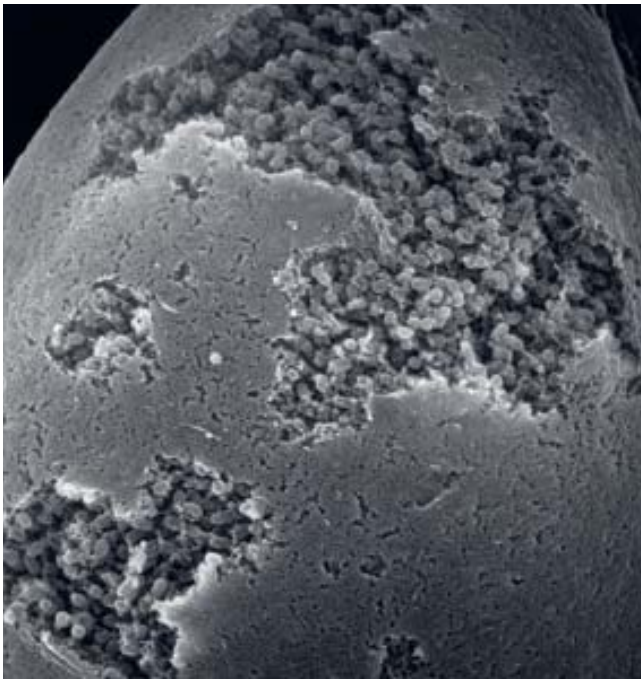
standing and treatment of prostate diseases, much work remains to be done to improve diagnosis and treatment, and possibly, to enable prevention.

Until the past 10 or 15 years, one type of surgical therapy, transurethral resection of the prostate (TURP), was the "gold standard" for treatment of symptomatic BPH. However, this is an invasive procedure that carries the inherent risks of surgery. New, less invasive approaches are rapidly being developed. Recently, investigators in the clinical trial, Medical Therapy of Prostate Symptoms (MTOPS), published results demonstrating that two drugs commonly used to treat BPH, finasteride and doxasozin, are significantly more effective at preventing symptomatic BPH incidence and progression when given in combination. Together, the drugs reduced overall risk of progression of BPH by 66 percent, versus 39 percent with doxasozin alone and 34 percent with finasteride alone. Importantly, the combination therapy and finasteride alone reduced the risk for invasive therapy by 67 percent and 64 percent, respectively. (Please see the "Story of Discovery," "Evolving Therapies for Benign Prostatic Hyperplasia.") Currently, the NIDDK is supporting two major clinical trials of alternative approaches to TURP for treating BPH. The Minimally Invasive Surgical Therapies (MIST) Treatment Consortium for BPH is designing trials to assess the safety and efficacy of new, less-invasive surgical treatments for BPH. The first trial to be conducted by this consortium is evaluating two surgical procedures, transurethral needle ablation (TUNA) and transurethral microwave therapy (TUMT), as well as a medical therapy similar to that used in the MTOPS study. Patient enrollment for this study began in 2003. A second trial, Complementary and Alternative Therapy for Benign Prostatic Hyperplasia (CAMUS), is a large clinical trial to examine the effects and efficacy of two commonly used, orally administered alternative therapies for BPH–so-called "phytotherapies"–saw palmetto and *Pygeum africanum*. CAMUS will use the same definition of clinical progression of BPH as used in the MTOPS trial.

Chronic prostatitis/chronic pelvic pain syndrome is a disabling condition of unknown origin which affects men of all ages and ethnic groups. Unlike prostatitis caused by a bacterial infection, chronic prostatitis cannot be cured with antibiotic treatment. Like interstitial cystitis (IC), another urologic disorder of unknown origin, one of the major symptoms associated with chronic prostatitis is pelvic pain. The NIDDK-supported Chronic Prostatitis Clinical Research Network (CPCRN) was established to perform a longitudinal study of a well-characterized group of patients with this disease, and to conduct trials of treatments for disease symptoms. The NIDDK has recently expanded the CPCRN to continue trials of therapies to alleviate symptoms of this disease, and to conduct ancillary research studies using data and samples collected from the cohort. Importantly, because of similar needs and approaches for the urologic conditions under study, investigators in the CPCRN will collaborate with researchers in the Interstitial Cystitis Clinical Research Network (ICCRN) in a "Urological Pelvic Pain Collaborative Research Network." This collaboration will improve the efficiency of protocol development, develop common definitions and criteria, and facilitate common data collection to permit comparisons between the clinical trials. Through support of these new and continued research efforts, the NIDDK is seeking to improve men's urologic health.

INVASION OF THE BLADDER SNATCHERS–BACTERIAL PODS IN ACUTE URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are extremely common in women, and many women suffer repeated infections. Most infections are caused by the common *Escherichia coli (E. coli)* bacteria. A UTI begins when bacteria attach to the cells lining the inside of the bladder. This adhesion provokes a defense response in the host, including activation of the immune system and sloughing off of bladder cells into the urine in the body's attempt to rid itself of offending bacteria. However, some strains of



A dense population of bacteria (grape-like objects) living in a "pod" at the surface of a mouse bladder cell is made visible through sophisticated imaging techniques. Photo: Dr. Joseph Palermo and Dr. Scott Hultgren, Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO. Reprinted with permission from Anderson GG *et al, Science* 301: 105-7, 2003. © 2003 AAAS.

bacteria are able to persist in the bladder despite a vigorous host response and antibiotic treatment. One way bacteria avoid destruction is by invading the bladder cells, effectively "hiding out." This can give rise to a chronic, undetectable infection that can return at any time as a full-blown UTI.

To find out how bacteria can survive the onslaught of immune cells and other physiologic responses that follow infection–not to mention antibiotic therapy–researchers examined the bladders of immune-compromised mice inoculated with *E. coli*. Using scanning electron microscopy, they found that, while the inner surface of uninfected bladders was smooth, the surface of infected bladders was covered with pod-like protrusions. Closer examination revealed that the pods were filled with bacteria. The pods' contents resembled a "biofilm," a complex microbial community consisting of bacterial cells suspended in a matrix. Examples of biofilm in nature include dental plaque and the slimy coating on rocks in a stream. However, this biofilm-like structure was growing inside a living cell! Within a biofilm, bacteria located in different regions express different genes, which leads to distinct bacterial subpopulations within the larger community. Biofilms have previously been shown to protect bacteria from immune defenses and antibiotics. The growth of UTI-causing *E. coli* within a biofilm-like matrix in the bladder may make these bacteria more difficult to eliminate and infection more likely to recur.

These bacterial pods associated with an acute UTI represent a previously undescribed bacterial community. The protection presumably conferred on the bacteria by the biofilm-like structure, and the emergence of different subpopulations within the larger group, may afford a survival advantage. These structures may represent a mechanism through which the bacteria avoid being eliminated by host responses and survive to reinfect bladder cells over and over again. Finally, although these studies examined UTIs in mice, biofilm-like structures might prove to be important in many human conditions, such as pneumonia, tuberculosis, and cystic fibrosis, which involve bacterial infections as causes or complications.

The discovery of biofilms that house bacteria in the bladders of mice is just one example of basic research studies that are both fascinating and important for better understanding infectious and noninfectious diseases. The NIDDK is supporting both basic and clinical research efforts in bladder and other urologic diseases and disorders. The Institute recently launched an initiative to support studies of the basic biology of interstitial cystitis (IC), a debilitating bladder disease of unknown cause (please see sidebar, "Basic Research on Interstitial Cystitis–Advancing Toward Clinical Tools"). Support will also continue for the development of new research tools and innovative methods to study the cells of the bladder, prostate, and other organs of the genitourinary tract. The Institute is also co-supporting, with the NIH Office of Research on Women's Health, Specialized Centers of Research that have as their focus basic and clinical studies of UTIs, urinary

incontinence, and IC. Additionally, to ensure that advances in science are translated effectively to the public and to health care providers, the NIDDK plans to undertake a Women's Urologic Health Outreach Initiative in partnership with the American Urological Association and the Interstitial Cystitis Association. The program will be a campaign to increase awareness and knowledge among primary care physicians about current health care recommendations for women's urological problems, including interstitial cystitis, urinary incontinence, and UTIs.

Anderson GG, Palermo JJ, Schilling JD, Roth R, Heuser J and Hultgren SJ: Intracellular bacterial biofilm-like pods in urinary tract infections. *Science* 301: 105-7, 2003.

NITRITE IMPROVES BLOOD FLOW

A century ago, Alfred Nobel invented dynamite, with nitroglycerine as the active component. Nitroglycerine has an equally important and less-destructive aspect, however. During Nobel's lifetime, it was recognized that nitroglycerine could relieve chest pains caused by heart disease, and physicians began prescribing it for this purpose. Recently, scientists have uncovered the mechanisms behind nitroglycerine's ability to relieve cardiac pain: it generates nitric oxide (NO), a gaseous mediator of cell-to-cell communication and a potent dilator of blood vessels (vasodilator). In 1998, the Nobel Prize in Physiology or Medicine was given to Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system.

Research scientists continue to investigate the molecular characteristics of the NO molecule and the mechanisms involved in its biological activities. One goal researchers have been pursuing is to identify molecules in the body's network of blood vessels (vasculature) that can be rapidly converted to NO to cause vasodilation. Identifying such molecules could have important therapeutic implications for diseases and conditions involving vascular blockage or constriction. In a recent advance, researchers have found that nitrite–a molecule present in high concentrations in the plasma and vasculature–is converted to NO by hemoglobin and causes vasodilation. The researchers found that when they injected sodium nitrite into arteries in the forearms of 18 human study participants, the participants' blood flow increased by an average of 175 percent over resting levels and their systemic blood pressure was reduced. When they investigated the underlying mechanism of the nitrite-induced vasodilation in experiments *in vivo* and *in vitro*, the researchers found that hemoglobin–the molecule in red blood cells that transports oxygen–was facilitating the conversion of sodium nitrite into NO. Specifically, it was the deoxygenated form of hemoglobin that was interacting with nitrite to produce NO-modified hemoglobin molecules. Based upon their data, the researchers propose that, as hemoglobin releases oxygen in body tissues with low oxygen, the resulting deoxygenated hemoglobin can then convert nitrite to NO, causing vasodilation and enhancing blood flow to–and, hence, oxygenation of–the surrounding tissue.

These research findings hold the potential for far-reaching therapeutic applications for acute and chronic conditions involving restricted blood flow. Nitrite could represent a potential new treatment for conditions such as high blood pressure, heart attacks, sickle cell disease, and leg vascular problems. Such promising applications await the clinical testing of the safety of nitrite when administered at the concentrations necessary to induce its positive effects on the vasculature of patients.

Cosby K, Partovi KS, Crawford JH, Patel RP, Reiter CD, Martyr S, Yang BK, Waclawiw MA, Zalos G, Xu X, Huang KT, Shields H, Kim-Shapiro DB, Schechter AN, Cannon RO, III, and Gladwin MT: Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. *Nat Med.* 9: 1498-505, 2003.

SEEKING NEW WAYS TO MEASURE BODILY IRON

Although many people suffer from a lack of iron in the diet, too much iron can be equally unhealthy. The body has no way to get rid of iron in excess of need. Over time, chronic excess can lead to a toxic buildup of iron in organs and tissues, especially the heart, liver, and brain. When a disease or disease therapy causes so-called "iron overload," patients may need to be monitored for iron accumulation and also take drugs, called chelators, to help get rid of excess iron. This is the case with Cooley's anemia, a blood disorder that requires lifelong blood transfusions that result in the accumulation of excess iron (see "Patient Profile," "Living with Cooley's Anemia"). The NIDDK supports research on both better tools to measure the body's iron stores and on improvements to current chelator therapy.

Currently, the only non-invasive means to measure body iron that has been calibrated and validated for clinical use is a device known as a Superconducting Quantum Interference Device (SQUID). However, this device is not widely available, and is very costly to run. The NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) have been collaborating to solicit new research grants for projects that may improve the utility of magnetic resonance imaging (MRI) as a method for quantitative determinations of body iron. MRI potentially provides a useful and widely available technique for monitoring excess iron in the body in conditions of iron overload, such as found in Cooley's anemia and sickle cell disease patients. The NIDDK and the NIBIB recently funded an initiative supporting projects that have the potential to improve the utility of MRI as a method for quantitative determinations of tissue iron, especially in the liver, heart, and brain.

The NIDDK also continues to support research to find effective and less burdensome alternatives to the injected iron chelating drug, desferrioxamine (Desferal® or DFO). One drug that is moving into clinical trials, HBED, appears to be a more effective chelator than DFO, indicating that it may need to be used less frequently and for shorter periods of time, which would be a great relief for patients. However, as with DFO, HBED still must be injected, so the NIDDK continues to search for better iron chelating drugs. Already, these studies have resulted in successful preclinical evaluation of a re-engineered version of the oral chelator desferrithiocin, and this new compound has recently been approved by the Food and Drug Administration for use in clinical studies. The NIDDK is planning additional studies on related chelators that may be even more effective.

STORY OF DISCOVERY

Evolving Therapies for Benign Prostatic Hyperplasia

If you are a man, chances are that someday you will have an enlarged prostate. Benign prostatic hyperplasia, or BPH, is a condition that affects an estimated 9 percent of men 30 years of age and older, even if they are unaware of it. Prevalence increases significantly in middle age, with the majority of cases reported in men age 55 and older. Not everyone with BPH will develop symptoms, but–for those who do–until recently, surgery provided the only relief. Now, new medical approaches to the treatment of BPH, built on basic research stretching back over 50 years, offer an effective, non-surgical option. For men who still require surgery, less invasive techniques may provide effective, less traumatic alternatives.

The walnut-sized prostate gland is located below the bladder and surrounds the urethra as it leaves the bladder. The urethra and the fluids it transports pass through the prostate. One important function of the prostate gland is to release seminal fluid into the urethra at sexual climax to provide a vehicle for sperm.

The prostate gland undergoes two phases of growth. The first, during puberty, results in a relatively rapid doubling in size of the gland. The second, slower phase begins at around age 25 and continues throughout a man's life. As the region of the prostate immediately surrounding the urethra grows, it can, in some men, compress the urethra and inhibit the flow of urine. As a result, the bladder does not empty completely during urination. The narrowing of the urethra and partial emptying of the bladder are the cause of the complaints most commonly associated with BPH, such as frequent urination, inability to urinate, and urinary tract infections. Thus, while prostatic hyperplasia is "benign" in the sense that it is not cancerous, it can nevertheless cause serious health problems.

The male sex hormone testosterone plays an important role in a wide range of biological and physiological processes, ranging from development of the male urogenital tract during embryogenesis to the emergence of secondary sexual characteristics, such as facial and body hair, in the post-pubescent adult. In the late 1950s, researchers working with rats knew that experimental administration of testosterone resulted in an accumulation of protein in the male urogenital tract. By the mid-1960s, scientists could purify the hormone from these cells, but found–to their great surprise–not testosterone, which had been given to the animals, but a closely-related derivative: dihydrotestosterone, also known as DHT. Previously, it had been widely thought that DHT was a relatively unimportant breakdown product of testosterone. However, the finding of DHT in testosterone's target cells caused researchers to take a second look at this molecule.

An important role for DHT in male urogenital development was postulated in the mid-1970s from studies of a rare inherited form of hermaphroditism. Individuals with this condition are genetically male but appear female at birth, insofar as they lack external male genitalia and a prostate gland. Oddly, blood tests of these individuals found normal circulating levels of testosterone. However, closer analysis revealed markedly reduced levels of DHT. This finding suggested that the genitalia and prostate require

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DHT to develop, because these features were absent in affected individuals, while other components of the male urogenital tract, which were present, do not. Years later, in the 1990s, sophisticated molecular analysis would reveal that the cause of this condition is a mutation in one of the proteins that converts testosterone to DHT, an enzyme known as 5-alpha reductase.

In the late 1970s, scientists had developed a model system in which they could induce prostatic hyperplasia in dogs by administering male sex hormones. Furthermore, they could block or reverse it by administering agents that inhibited 5-alpha reductase. This observation suggested that it was DHT that was responsible for the continued growth in the prostate in the adult, and stimulated pharmaceutical firms to pursue drugs that target the 5-alpha reductase enzyme as possible therapies for BPH. In 1992, the Food and Drug Administration approved for use in humans the drug finasteride–the first drug to block the conversion of testosterone to DHT by inhibiting 5-alpha reductase.

In the early 1990s, treatment of BPH generally involved a surgical procedure called Transurethral Resection of the Prostate, or TURP. As its name implies, TURP involves inserting a small scope up the urethra to the prostate and cutting away the obstructing tissue, thereby restoring normal urine flow. While TURP is an excellent treatment for BPH, it is expensive, requires several weeks of convalescence during recovery, and carries risks inherent in any surgical procedure. Because of these drawbacks, as an alternative to surgery some physicians began using finasteride to inhibit DHT production and thereby shrink the size of the prostate. Others used alpha blockers, a class of drugs that relax the smooth muscle in the prostate and bladder neck, and thus allow urine to flow more easily. However, urologists were not sure whether medical therapy was truly treating the BPH or was only relieving the symptoms while the underlying disease silently progressed.

To help answer this question, the NIH launched the Medical Therapy of Prostatic Symptoms (MTOPS) trial in 1994. A large, randomized clinical trial to assess the overall effectiveness of medical therapy on BPH symptoms and progression, the MTOPS trial would ultimately enroll over 3,000 men with BPH. Participants received one of four interventions: placebo (sugar pill), the 5-alpha reductase inhibitor finasteride, the alpha blocker doxazosin, or finasteride and doxazosin together. The study followed participants for an average of five years and monitored them for signs of BPH progression such as an inability to urinate, incontinence, or recurrent urinary tract infections. The results of the MTOPS trial were announced in 2002 and published in 2003, and were unequivocal: combination therapy, consisting of finasteride and doxazosin together, reduced the risk of BPH progression by 66 percent compared to placebo. Each drug was also effective when used alone: the risk of progression was reduced by 39 percent with doxazosin and by 34 percent with finasteride. However, the results with combination therapy surprised all involved and will likely lead to important changes in the way BPH is treated.

Even with improvements in drug therapy, a fraction of men will ultimately require a surgical procedure to alleviate symptoms of BPH. While TURP remains the “gold standard,” a number of new surgical treatments for BPH have been developed over the past decade. These procedures aim to achieve the same long-term outcomes of TURP, but to do so with lower costs, more rapid recovery, and less risk. However, the relative effectiveness and long-term safety of these new surgical approaches is unknown.

To bridge this gap in knowledge, the newly-launched Minimally Invasive Surgical Therapies (MIST) clinical trial will compare two new, less invasive surgical approaches, Transurethral Needle Ablation (TUNA) and Transurethral Microwave Therapy (TUMT), with combination medical therapy in men with BPH. The results of this trial are expected to further expand treatment options for men with BPH, to provide both physicians and patients with valuable information, and to give all involved the knowledge needed to make the most appropriate choices for long-term management of BPH.

The National Kidney Disease Education Program

Early in 2002, the NIDDK launched the initial efforts of the National Kidney Disease Education Program (NKDEP). The mission of this pilot public education program is to raise awareness about the seriousness of kidney disease, the importance of testing, and the availability of treatment to slow or prevent kidney failure. An estimated 7.4 million Americans currently suffer from kidney damage, also called chronic kidney disease, and, each year, nearly 400,000 must have either dialysis or a kidney transplant to stay alive. The number of people developing irreversible kidney failure, also called end-stage renal disease (ESRD), has doubled each decade for the last two decades, and disease statistics indicate that this trend is likely to continue. The leading causes of kidney disease are diabetes and hypertension (high blood pressure). If current trends continue, the recent increases in obesity and type 2 diabetes in the U.S. will have grave implications, as more and more people develop kidney complications related to diabetes. For example, the current public and private costs of treating ESRD were estimated at $23 billion in 2001.

Fortunately, chronic kidney disease can be slowed, if not prevented, provided it is detected early enough. Good control of blood sugar and blood pressure can reduce the risk of developing kidney disease. Diets low in protein can also slow kidney disease progression. In spite of these advances in treatment and prevention, only a small number of those who most need proper screening or treatment receive it. The NKDEP will strive to disseminate information on prevention and treatment to physicians and patients who can most benefit from it.

Racial and ethnic minorities suffer a far higher incidence and prevalence of irreversible kidney failure than Caucasians. Rates of ESRD are disproportionately greater in African Americans, American Indian and Alaska Natives, Native Hawaiians and other Pacific Islanders, and Hispanic Americans. Diabetic kidney disease is the most common cause of ESRD in all of the aforementioned minority groups except for African-Americans, in whom high blood pressure-induced kidney damage is also a major cause.

The ultimate goal of the NKDEP is to reduce complications and death due to kidney disease and kidney failure among all Americans. Currently in its early, pilot phase, the NKDEP is targeting primary care providers and people at high risk for kidney disease–particularly African Americans with diabetes, hypertension, and/or a family history of kidney failure–in four pilot sites: Atlanta, GA; Baltimore, MD; Cleveland, OH; and Jackson, MS. In April 2003, the four pilot sites launched the campaign, “You Have the Power to Prevent Kidney Disease,” which emphasizes three key messages:

- Early detection is important. If you are at risk due to diabetes, hypertension or a family history of kidney failure, talk to your doctor about having your kidneys checked.
- Effective treatment can prevent or slow kidney damage.
- Left undiagnosed and untreated, kidney disease can lead to kidney failure.

Prior to launching the pilot site activities, the NKDEP conducted two baseline surveys. The first survey assessed African-American adults' knowledge, attitudes, and behaviors related to kidney disease. Ten-minute telephone interviews were conducted with 400 randomly sampled African-American adults over the age of 30 in each of the four pilot sites and in a composite control site, for a total of 2,000 respondents. The second survey was conducted with primary care physicians. Surveys were faxed to 100 primary care providers in each of the four pilot sites and 200 in a composite control site, for a total of 600 respondents.

After one year, follow-up surveys will be conducted to determine the extent to which the pilot interventions achieved their goals of increasing awareness about the seriousness of kidney disease and the availability of effective treatments to prevent or slow kidney failure. The follow-up survey also will evaluate which program activities were most related to changes in the awareness, attitudes, and behaviors of the target audiences. Successful strategies identified through the pilot sites will be used to develop a broader national campaign, which is planned to launch in June 2004.

In addition to public awareness activities, the NKDEP has several Work Groups that are working on removing specific barriers to better kidney disease awareness and care. The membership of these groups is drawn from the professional partnership network of the NKDEP, which includes non-profit groups, industry, and government. The NKDEP Laboratory Work Group has made efforts to encourage improvement and standardization of the serum creatinine assay–which is used to estimate how well the kidneys are functioning–in order to address issues of inter-laboratory variation in this assay. The Group has also begun efforts to encourage laboratories to report glomerular filtration rate (GFR) estimates as soon as possible in adults with low GFRs, to enable physicians to quickly identify individuals with impaired kidney function. The NKDEP Quality Indicators Working Group, in partnership with the Centers for Medicare and Medicaid Services (CMS), is undertaking a pilot project to spur the development of quality indicators of care for chronic kidney disease among Medicare beneficiaries hospitalized for cardiovascular disease.

Through all of its efforts, the NKDEP is striving to become a positive force in helping to reduce the burden of kidney disease in the U.S.

Basic Research on Interstitial Cystitis– Advancing Toward Clinical Tools

One of the most painful bladder experiences most people may ever have is waiting for the next rest stop on a crowded interstate. However, patients with interstitial cystitis (IC) live each day in constant awareness of their bladders. Interstitial cystitis is a chronic bladder disease characterized by pelvic pain (pain in the area below the navel) and increased frequency and urgency in urination. These symptoms can be quite debilitating, interfering with a patient's ability to work, go out, and enjoy family life. While the precise number of persons affected is unknown, as many as 870,000 American men, women, and children may suffer from IC; however, 90 percent of reported cases occur in women. The cause(s) of IC is as yet unknown. Current treatments for symptoms are not effective in all patients, and there is no cure. The NIDDK is supporting clinical and basic research investigations on several fronts to understand the cause(s) of IC, to develop and test more effective treatments, to develop better diagnostic tools, and, ultimately, to develop a cure for this disease.

Investigation of the fundamental mechanisms underlying the initiation and development of IC is critical to understanding the disease. When physicians examine the inside of the bladder of an IC patient using a cystoscope*, they often find that it is marked by glomerulations (hemorrhages) and/or deep ulcers. Most consistently, defects such as tears and thinning in the layer of epithelial cell tissue that lines the inside of the bladder are observed. This layer of cells normally expands as the bladder fills, and it protects the underlying nerves, blood vessels, and muscle of the bladder wall from toxic components of urine. Based upon investigations of the physical signs and symptoms associated with IC, there are several hypotheses regarding its cause(s) and development, including defects in nerve signals traveling to and from the bladder; autoimmune or other "immunogenic" disease; and intrinsic or induced defects in the protective lining of epithelial cells within the bladder.

While researchers are trying to investigate the cause(s) of IC, a major stumbling block is the lack of a specific biological marker (biomarker) for the disease. Biomarkers–which can be genes, proteins, or other molecules–help researchers distinguish one disease from another, ideally using minimally invasive or non-invasive techniques. Biomarkers may also provide clues to the stage of a disease, and, in some cases, can be used to assess whether or not a candidate disease therapy is working. Finally, in addition to their high value in diagnosing disease and gauging response to therapy, biomarkers may also simultaneously yield clues about a fundamental disease process. Because of their importance, research studies of biomarkers were solicited in a recent NIDDK-supported basic research initiative in IC, and emphasized at a recent scientific meeting on IC co-sponsored by the NIDDK and the Interstitial Cystitis Association.

Currently, an especially promising biomarker for IC is "anti-proliferative factor," or APF. One team of researchers has worked on the hypothesis that the damage to the bladder epithelium in IC is a distinguishing characteristic of the disease, and that it might be due to a toxic entity present in the urine of IC patients. Several years ago, Dr. Susan Keay and her colleagues at the University of Maryland first demonstrated that an anti-proliferative activity was present significantly

* A thin, lighted (usually fiber optic) instrument used to look inside the bladder and remove tissue samples (biopsy) or small tumors.

more often in the urine of IC patients than in control samples. This activity was measured by how much the growth of normal human bladder epithelial cells was inhibited when they were incubated in a solution containing urine from IC patients. This detection strategy for a biological activity is called a functional assay. The activity identified in the functional assay appeared to be linked to a small, heat-stable peptide (tiny protein) that was either "activated" in the urine or added to it when it reached the urinary bladder.

Although APF is not the only factor altered in the urine of IC patients, it is the one that, to date, appears to be most effective for distinguishing between IC patients and patients with different urogenital conditions or no disease at all. Researchers have reported that, in blinded studies, 86 to 94 percent of patients diagnosed with IC have significant APF activity in their urine, while only 9 percent of asymptomatic patients and 0 to 18 percent of patients with other urogenital disorders have significant APF activity. Based on the functional assay, the researchers reported that APF has a sensitivity of 94 percent, and a specificity of 95 percent, as a detection tool for IC. Furthermore, of 14 candidate factors for biomarkers detectable in the urine of IC patients, APF had the least overlap between IC patients and controls. Although these results need to be tested further in larger populations and in patients diagnosed with IC by using less restrictive criteria than those used for the initial clinical research studies, they offer a compelling rationale for possible clinical test development and validation of APF as a biomarker for IC.

Moreover, APF is not just a biomarker candidate, but may also be central to some or all of the pathology of IC. While working on validating APF as a biomarker, the research team led by Dr. Keay has continued to explore the hypothesis that bladder epithelial cell abnormalities lie at the root of the disease–and that APF might be directly involved in the disease by affecting the body's ability to regenerate damaged bladder epithelium. They first showed that the source of APF in the urine of IC patients is most likely the epithelial cells of the bladder. Using the APF functional assay, they detected the same APF activity in the growth medium from bladder epithelial cells biopsied and cultured from IC patients as they had found in patients' urine. Through biochemical purification steps, they obtained highly enriched APF from both sources, narrowing it to a small, heat-stable peptide. In contrast, identical purification steps performed with non-IC urine samples yielded no APF activity. These results indicate that the APF is produced by the affected epithelial cells themselves–which suggests that the pathology of IC may be due in part to an intrinsic abnormality in these cells.

The team has also observed that several molecules, called growth factors, are produced in different amounts in the urine of IC patients as compared to patients without IC. Growth factors can stimulate or inhibit the proliferation of target cells. Two of the molecules, epidermal growth factor (EGF) and heparin-binding epidermal growth-factor-like growth factor (HB-EGF), show significant changes in the urine of IC patients. EGF is significantly increased, and HB-EGF is significantly decreased. Notably, the growth of IC bladder epithelial cells is markedly slower than the growth of normalbladder epithelial cells when they are grown under identical conditions in the laboratory. Both the altered growth factor production and the growth defect in the IC bladder appear to be linked to APF activity. When APF enriched from IC bladder epithelial cells or from IC patient urine was applied to normal bladder epithelial cells, the cells released less HB-EGF and more EGF into their growth medium and ceased to proliferate. Furthermore, the results of other experiments *in vitro* suggest that bladder cells from IC patients can "recover" from the growth inhibition induced by exposure to APF by treating them with HB-EGF, further implicating HB-EGF as a primary target in APF-induced growth inhibition. Importantly, the cells' ability to recover from APF exposure in these experiments also firms up hope that the bladder epithelial cell damage observed in IC is reversible–which, in turn, may help reverse the course of the disease.

Most recently, Dr. Keay and her colleagues have delved even deeper into the biology of APF and examined its effect on bladder epithelial cell gene expression. In a study using DNA microarray technology, they looked for differences in gene expression between normal bladder epithelial cells and cells from IC patients, as well as between "mock-treated" normal bladder epithelial cells and cells treated with purified APF. They demonstrated for the first time that APF can alter expression of a number of genes in bladder epithelial cells. As might be expected, many of the genes that showed *decreased* expression in IC cells and APF-treated cells normally promote cell proliferation, and many of the genes that showed *increased* expression are associated with growth inhibition. Thus, the research team has hypothesized that not only might APF be interfering with the release of factors necessary for appropriate cellular growth, such as HB-EGF, but that it might also be "reprogramming" bladder cells to terminate their growth potential prematurely. These interesting results and their significance in the IC disease process await further confirmation in future studies.

The increasing wealth of data about APF is providing compelling support for one hypothesis regarding IC, which suggests that the disease may develop in susceptible individuals because of an inability to regenerate bladder epithelium after an assault that damages this tissue (for example, a bladder infection). This would leave the deeper layers of the bladder vulnerable to the toxic components of the urine, thus contributing to the observed hemorrhages, ulcerations, and inflammation. More knowledge of APF–such as the gene encoding it, APF's chemical sequence and structure, and the trigger(s) for its production–may explain both its role in IC and its presence in patients with other bladder diseases, and, if it turns out to be a risk factor for IC, why seemingly asymptomatic patients have shown APF activity.

At the same time as studies of APF are progressing, fundamental investigations of other hypotheses about the pathology of IC are ongoing. For example, there is evidence suggesting that sensory nerve cells in the bladders of IC patients may be hypersensitive to normal stimuli, which, in turn, may play a role in the initiation and/or progression of IC. Researchers are continuing to study bladder innervation and alterations in nerve function, especially in order to better understand the pain-receptor-pathways in the bladder that likely contribute to the pain experienced by IC patients. Another hypothesis is that neurogenic inflammation and mast cell activation are responsible for IC symptoms. Mast cells normally function in allergic and inflammatory reactions, and have been observed in bladder tissue of IC patients, where they may be activated by nearby nerves to induce bladder inflammation. Along those lines, investigators are also learning more about how the epithelial cells of the bladder produce signaling molecules, called chemokines and cytokines, that may participate in the initiation or progression of inappropriate signals that result in pain and/or inflammation. These and other promising investigative routes are, like studies of APF, important to elucidating the mechanisms underlying IC and its symptoms.

The study of APF illustrates that the feedback loop between basic and clinical research is bidirectional and dynamic. While basic research often paves the way to clinical progress, in this case, translating clinical research observations into fundamental investigations shed further light on a disease process. The importance of complementary fundamental research in IC has been further highlighted in a basic research initiative recently launched by the NIDDK. Through this initiative, the Institute is supporting over twenty large-scale research projects and smaller, exploratory projects that will test the viability of specific new research directions in IC. Research studies ranging from harnessing cutting-edge proteomics technology for IC research, to studying the role of immune system cells in the disease, to studying the genetics of IC–as well as studies of other candidate biomarkers for IC–are being supported through this initiative. Importantly, the IC investigators leading these studies will meet regularly to discuss their findings, thereby pooling resources and strengthening efforts to uncover the cause(s) and develop better treatments, preventive therapies, and strategies to cure this disease.

Recent Advances

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PATIENT PROFILE

Alicia Somma

Living with Cooley's Anemia

For most people, having to undergo a blood transfusion every two weeks would be difficult enough. But for 18-year-old Alicia Somma, who was diagnosed in infancy with Cooley's anemia, that's the relatively easy part of living with this life-threatening disease.

Cooley's anemia is an inherited blood disorder that results in failure to produce sufficient hemoglobin, the blood's oxygen-carrying component. This necessitates the "somewhat painful and unpleasant" blood transfusions, to treat the severe anemia. But, although these transfusions are life-saving today, they lead to an insidious buildup of excess iron, particularly in her heart and liver. Unfortunately, the body has no natural way of removing excess iron. So, in addition to bi-weekly blood transfusions, Alicia must painstakingly inject herself most evenings with a drug called a "chelator" that binds excess iron to itself and removes it from her body via her urine–a procedure that sounds a lot easier than it is.

Removing, or chelating, the excess iron requires several steps. First, Alicia must mix two parts of a powdery drug, called deferoxamine, with eight parts water. Next, she draws the dissolved drug into a syringe, places the syringe into an infusion pump, swabs with alcohol a place on her stomach or leg that is not already swollen or inflamed from countless other injections, and creates a fold in her skin into which she can insert the needle. She then adjusts the needle just beneath the surface of her skin and secures it by taping it down. Finally, she goes to bed, while the pump continually injects the life-prolonging chelating drug into her body for 10 to 12 hours.

Alicia Somma

Aside from being enormously time consuming and terribly inconvenient, "It's really painful when you hit a sore spot with the needle," says Alicia. Extremely mature and articulate, Alicia is an ardent spokesperson on behalf of those with Cooley's anemia. "But it's something I've been doing about five times a week for the last 16 years." Without this chelating treatment, Alicia's heart and liver would rapidly fail. Even under the best of circumstances, these organs become damaged by excess iron in Cooley's anemia patients. In many cases, heart failure often occurs between the ages of 20 and 30. But close adherence to the chelating treatment could extend Alicia's life well into her 40s. Although researchers have discovered the genes that cause Cooley's anemia and other forms of thalassemia, to date there is no cure for this debilitating and deadly disease.

About Cooley's Anemia

Once believed to be common only to people of the Mediterranean region, Cooley's anemia is a one of a group of genetic blood disorders, called thalassemia, found also in many Asian and African populations. The most common disorder is "beta thalassemia trait" (also called beta thalassemia minor), which means that an individual carries the genetic trait for beta thalassemia. Today, because of the migration and intermarriage of different ethnic populations, the trait for beta thalassemia can be found in people with no obvious ethnic connection to the disorder. Except in extremely rare cases, this genetic trait causes no symptoms and requires no treatment. However, parents who both carry the same kind of genetic trait, as do Alicia's, have a one-in-four chance with each pregnancy of having a child with a serious form of beta thalassemia–the most serious being Cooley's anemia. Alicia's 20-year old sister, Christine, is thalassemia-free.

An estimated 2 million Americans carry the genetic trait for thalassemia.

Bone marrow transplantation from a perfectly matched donor is the only available cure for thalassemia at this time. However, of patients who have a matched donor and low risk factors, only a small percentage (estimated at 30 percent) can undergo the procedure. Bone marrow transplantation for thalassemia also has to be considered carefully because of the procedure's inherent risks. Overall, younger patients and those lacking the complications of the disease or its treatment have the best outcomes.

Living with Cooley's Anemia

It's been said that life isn't a matter of holding good cards, but rather playing well the cards you hold. Alicia is playing her cards as well as she can. "Shortly after I was diagnosed with Cooley's anemia at eight-months-old, a doctor told my parents that I wouldn't be able to participate in sports or do anything too strenuous, and that I wouldn't be smart," says Alicia. "But I've been taking dance lessons ever since I was three, and I was in gifted and talented classes from 1st to 6th grade," she adds with a hint of an adolescent "I-gotcha" giggle. While in high school, Alicia was extremely active in theater and, as a senior, played the leading role in her high school's production of a Broadway musical. Now, she's attending a community college. "I love to be on stage, to act and to sing," she says in a voice full of *joie de vivre*, but adds that she's not sure she's ready for the auditions and everything else that goes along with making acting a career.

Cooley's anemia is usually diagnosed within the first year of life. Most children with Cooley's anemia are relatively inactive and are unable to keep up with their playmates. In fact, listlessness, fatigue, shortness of breath and jaundice are symptoms of the disease.

But all this belies how difficult it's been for Alicia–and her family–to live with Cooley's anemia. Reflecting back nearly 18 years, Alicia's father, Frank Somma, who is president of the Cooley's Anemia Foundation (CAF), says with traces of pain in his voice, "To try to find a vein on an eight-month-old baby is difficult. But then to have to hold Alicia down while she stared back at us with this look of, 'how can you forsake me like this?,' is a lot for loving parents to bear."

Alicia can't remember as far back as being eight months old, but she does remember her parents sticking her with a syringe to inject her with deferoxamine. "I have a scar on my lower lip because at the age of two I tried to run from them (her parents) and hit my face on the side of the fireplace," says Alicia. But soon the situation changed. By age eight, she was mixing her chelating medicine and injecting

the needle into herself. Even when it came to blood transfusions, "I remember when I was five years old telling my nurse, who did my IV, where the best place was to put the needle….I was a very mellow kid," she adds. Mellow–and very honest with herself and others about the disease her body harbors. "I'm aware of what it means to have Cooley's anemia. Some days I have to wear the [deferoxamine] pump to school because the night before I forgot to push the start button or the needle fell out. I'm not embarrassed to be wearing this box on the side of my hip.I sometimes even carry it in my hand. Telling other people makes life so much easier. All my friends know I have Cooley's anemia."

As a result of the disease, Alicia is also experiencing early onset of osteoporosis–a condition which predominantly affects post-menopausal women. Says Mr. Somma, "Osteoporosis isn't a disease 18 year-old girls should be concerned about."

Both Alicia and her father have testified before Members of the U.S. Congress to advocate for intensified research programs benefiting thal assemia patients, as well as for increased blood safety monitoring. Because of their continual need for transfusions, patients with Cooley's anemia are highly vulnerable to blood-borne diseases. For example, before the availability of specific blood screening tests, the viruses causing HIV/AIDS and hepatitis C posed serious threats to people with Cooley's anemia.

Alicia also has appeared on national TV and radio to talk about Cooley's anemia and thalassemia. Her main message to others with Cooley's anemia is: Do the pump! In other words, comply with the chelating treatment. "Except for the transfusions and chelating treatments, people with Cooley's anemia are in no pain," says Mr. Somma, who, in Alicia's words, is a "real stickler" about her taking her injections as often as possible. He likens this insidious disease to smoking. "People who smoke don't realize the negative impact it's having on them until they're diagnosed later in life with a serious illness related to their habit," he says. "Well, the same holds true for people with Cooley's anemia. As unpleasant as it is to inject the chelating drug five to six nights a week, not taking the drug doesn't make them feel bad, but eventually the noncompliance will result in a much earlier onset of heart and liver disease."

Research Efforts in Cooley's Anemia

The NIDDK, along with the National Heart, Lung, and Blood Institute (NHLBI), is committed to fostering basic and clinical research that will lead to more effective treatments, and ultimately a cure, for Cooley's anemia.

NIDDK ongoing research is devoted to studying both the causative gene and genes that influence disease severity of Cooley's anemia through studies undertaken by NIDDK intramural researchers and through funding of projects at academic and other research institutions. For example, one research group recently discovered a protein in red blood cells that interacts with a subunit of hemoglobin to stabilize its structure. Researchers may now study the human gene encoding this protein for variations that could modify disease severity when present in Cooley's anemia patients. The hope is that greater knowledge of natural genetic modifiers of Cooley's anemia and other forms of thalassemia will help researchers devise new therapies to reduce disease burden.

The NIDDK also supports research related to more efficient and less painful ways of measuring iron in the body, less burdensome iron removal regimens, as well as to the development of safer and more cost-effective transfusion therapies.

In fact, NIDDK-supported research led to the development of the only non-invasive method for measurement of tissue iron stores that has been calibrated, validated, and used in clinical studies. Ongoing and newly launched efforts supported by the NIDDK include:

- A large-scale NIH Bioengineering Research Partnership that is supporting efforts to advance the "SQUID" (superconducting quantum interference device) technology that is at the core of the currentmethod of non-invasive iron measurement. The goal of this project, which is also supported by the NHLBI, is to modify the SQUID technology to make it more accessible and ready for more widespread clinical use, thus providing a viable alternative to liver biopsy.

- A Magnetic Resonance Imaging Technology (MRI) initiative. In response to a solicitation designed to encourage research in this area, the NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) are funding several studies exploring ways to adapt the relatively inexpensive MRI technology already in widespread clinical use for application to the clinically useful measurement of iron stores.

- Basic and preclinical research studies to identify and evaluate oral drugs for removing toxic iron from the body as an alternative to injected drugs.

Although researchers are making progress, to date there remains no cure for Cooley's anemia. Alicia's ace in the hole, however, is her courage and determination. She says she will continue to be vigilant with her iron removal treatment and live the best life that she can. "I understand it could be fatal if you don't take care of yourself," she says, "but as far back as I can remember my parents have told me 'this is what you have and this is what you've got to do to get through it.' When I get married, I hope I raise my children with the same strength my parents raised me."

PATIENT PROFILE

Jennifer Klann

Life With Polycystic Kidney Disease: Experiencing Hope Through Research

Jennifer Klann was 18 years old and a college student when she began experiencing severe pelvic pain. Her physician thought it might be from cysts on her ovaries. To confirm the diagnosis, he recommended that Jennifer undergo an ultrasound exam. During the exam, Jennifer–who is now 32, married, and the mother of a 3-year-old son–vividly recalls hearing the attending nurse say, "Oh my, I've got to get the doctor." It turns out that Jennifer does indeed have cysts, but not on her ovaries–on her kidneys.

Jennifer Klann and son, Dylan

Jennifer was diagnosed with polycystic kidney disease, or PKD, an inherited disorder that could result in chronic renal (kidney) disease and, ultimately, end-stage renal disease, or kidney failure. "I was in tears when I called my dad to tell him my results," says Jennifer, whose father had PKD, and whom Jennifer believes later died prematurely as a result. "He consoled me and said I was going to be just fine," says Jennifer, "but I'd seen him suffer so much from PKD that I knew the potentially life-threatening impact this disease could have on me." Although there are things Jennifer can do to keep herself as healthy as possible–and research on potential therapeutic strategies is progressing rapidly–to date, there is no treatment or cure for PKD directed at the basic mechanism of the disease.

PKD is the fourth leading cause of kidney failure in the United States.

Jennifer is currently taking part in an NIDDK-supported study, called the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease, or CRISP. The consortium consists of four participating clinical centers and a data-coordinating and imaging-analysis center located in various parts of the country. It is testing whether imaging techniques can help determine the progression of renal disease in patients with PKD.

Meanwhile, cysts continue to grow on Jennifer's kidneys, which she says scares her. But, she is grateful to be part of the CRISP study and is hopeful that her son, Dylan, is not genetically predisposed to develop the disease. PKD symptoms are usually manifested in mid-life. If Dylan eventually is diagnosed with PKD, Jennifer is counting on researchers by then to have discovered an effective treatment for the disease, or perhaps even a cure.

About Polycystic Kidney Disease

Jennifer is one of many people in the U.S. and worldwide who suffer from PKD. PKD is a genetic disease characterized by fluid-filled cysts that, over time, multiply and enlarge both kidneys. These cysts, which range in size from a pinhead to a grapefruit, eventually can take over and destroy functioning kidney tissue, which may result in chronic renal failure and end-stage renal disease. A normal kidney weighs approximately 8 ounces and is the size of a human fist. Jennifer's kidneys are already twice as large. Depending upon the severity of the disease, these growing cysts can result in kidneys that are the size of a football or larger and can weigh as much as 22 pounds each. Currently, Jennifer says her kidneys are functioning normally, "but I worry about my enlarged kidneys pushing on other organs," she says, "and the older I get the more concerned I become. My kidneys aren't getting any smaller."

There are two forms of inherited PKD. Autosomal dominant PKD (ADPKD) is the most common of all life-threatening genetic diseases and is indiscriminate, meaning it equally affects people regardless of sex, race, age or ethnic origin. Autosomal recessive PKD (ARPKD) is relatively rare and often causes significant mortality in the first month of life. PKD can be passed on from one generation to the next by an affected parent, and does not "skip" a generation as do some genetic diseases. Jennifer's father and grandfather both had ADPKD, as did a number of her father's cousins. Jennifer's son has a 50 percent chance of having the ADPKD gene.

Even if someone carries the gene, there is no way of knowing how adversely he or she will be affected by the disease. PKD can progress silently, for many years, without detectable cysts or symptoms. Although individuals with the ADPKD gene eventually develop cysts on their kidneys, not all will experience kidney failure, and if they do, it is rarely before the age of 40.

Currently there is no known treatment or cure for PKD. However, some people whose kidneys begin to fail may be fortunate enough to receive a kidney transplant. Jennifer's father received a transplant at age 55, after being on dialysis for only two weeks. "He went through a couple of bouts of organ rejection before he stabilized and started to regain his energy," says Jennifer. He died at age 66 from cancer. But Jennifer contends that the life-saving immunosuppressant drugs he was taking to ward off rejection of his kidney transplant simultaneously made it hard for him to fight other illnesses and diseases. "I often wonder if my father died prematurely due to his PKD," says Jennifer.

Living with PKD

Because the disease results in abnormally large kidneys, living with PKD can be quite painful. People with PKD commonly suffer from chronic pain in the flanks (the area between the ribs and hips) and back, and may also experience more infections and have high blood pressure. Of even greater concern are complications from the disease, which can include lethal brain aneurysms, cardiac abnormalities, and polycystic ovaries or testes.

Fortunately for Jennifer, she does not currently suffer from any chronic pain, nor does she normally need to take time off from her job selling real estate. But in 1998, Jennifer was admitted into the hospital with a 104 degree fever, flank pain and blood in her urine. One of the cysts on her kidneys had suddenly burst, which caused a serious infection. As a result, she was hospitalized for three days. Last year, although she doesn't know whether they were directly related to her having PKD, she passed 10 uric acid kidney stones and was hospitalized for two weeks.

Jennifer is keenly aware that her PKD may never result in complete kidney failure. "Just because my dad's disease progressed to the point where he needed a kidney transplant doesn't mean that mine will do the same." With that hope in mind, she does

all she can to take care of herself. She takes medication to control her high blood pressure; maintains a balanced, low-protein, low-salt diet; doesn't drink soda or coffee; and is actively involved with the PKD Foundation, where her husband, Scott, is the Development Director.

CRISP Study

Ultrasound is an imaging technique that clinicians currently use to diagnose PKD. Ideally, clinicians would like to expand the use of ultrasound and other non-invasive or minimally invasive imaging techniques to enable them to mark the progression of PKD, predict the course of the disease in individual patients, and detect positive responses of patients to new treatments. The CRISP study, in which Jennifer is participating, is an NIDDK-sponsored initiative designed to find ways, through imaging techniques, to monitor changes in the kidneys and in kidney cyst size in patients with PKD. The goal is to improve clinicians' ability to monitor the progression of kidney disease in these patients, in order to assess possible strategies for clinical intervention.

Overseen by NIDDK's Division of Kidney, Urologic and Hematologic Diseases, CRISP has been following more than 200 participants since March of 1999. All those enrolled in the study were very early in the course of the disease so that structural changes in their kidneys and cysts could be tracked through two widely used imaging techniques magnetic resonance imaging (MRI) and ultrasound.

For the study, Jennifer keeps a log of any illnesses and hospitalizations she may experience, as well as a record of her medications. A nurse periodically reviews her log with her by phone. Once a year, she receives a glomerular filtration rate (GFR) test to help establish the rate of progressive loss of her renal function, undergoes an MRI and/or ultrasound, and has a blood workup that includes a measurement of her creatinine levels. Creatinine is a waste product of muscle metabolism that is removed from the blood by the kidneys. As kidney disease progresses, the level of creatinine in the blood increases.

Researchers are gathering an incredible amount of information about PKD from CRISP and similar studies and are hopeful that, within five or ten years, they will achieve major strides in combating the disease.

In the meantime, Jennifer remains concerned that her cysts are gradually increasing in size. "It's hard for me to believe something like that is growing inside my body," she says. But she's forever hopeful. "With all the research they're doing, and how much they're discovering, I truly believe there will be some kind of treatment for PKD in the near future. It is fear, denial and ignorance of the disease that have become our greatest obstacles, so it is important we play an active role in managing our own healthcare. It is my vision and hope that one day no one will suffer the full effects of PKD." The many other people with PKD echo that same hope.

The CRISP study is a powerful effort to harness technology to enhance monitoring, treatment, and intervention in PKD. As CRISP moves forward, the NIDDK has also recently launched an interventional clinical initiative to study protective therapies for patients with PKD. The Polycystic Kidney Disease Clinical Trials Network was established in 2001 to design and implement clinical trials of treatments that will slow the progressive loss of renal function in PKD. It will also conduct one or more pilot and feasibility studies examining innovative strategies for slowing progression of PKD, and collect and store patient specimen samples and data for future research by PKD investigators. Four clinical centers from across the country, as well as a data-coordinating center, are currently collaborating on the first large interventional clinical trial conducted by this network. The HALT-PKD trial will be a randomized, controlled trial of the efficacy of anti-hypertensive agents that block the renin-angiotensin system on slowing the rate of decline of kidney function in patients with high blood pressure and PKD. Agents that block this system have demonstrated an advantage over other blood-pressure-lowering medications in reducing the loss of kidney function in patients with other types of kidney disease. The commonly used "ACE inhibitors" target the renin-angiotensin system, and an ACE inhibitor will be one of the drugs tested in this trial. It is expected that patient recruitment will be initiated in 2004.