Each kidney contains about 1 million nephrons, which are the working units of the kidneys. Nephrons remove wastes and excess fluids from the blood. Illustration: Maryetta Lancaster, for NIH Medical Arts and Photography Branch.

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.

Chronic kidney disease is a growing epidemic in the U.S. It often progresses to irreversible kidney failure, which requires treatment with dialysis or kidney transplantation for patient survival. Presently, it is estimated that from 10 to 20 million Americans have substantially impaired kidney function. Diabetes and, to a lesser extent, high blood pressure are the main causes of kidney disease, accounting for up to 70 percent of all new cases of chronic kidney disease. The epidemic is due in large part to the increase of type 2 diabetes in the U.S.

The U.S. has seen an enormous increase in people with end-stage renal disease (ESRD). In the year 2000, almost 100,000 people had progressed to ESRD, with the result that a total population of about 300,000 patients with ESRD was sustained on dialysis, while an additional 80,000 people had functioning transplanted kidneys. These numbers have doubled since 1990 and are expected to nearly double again by 2010. The cost of ESRD is high—almost $18 billion for healthcare alone in 1999, as well as $2 billion to $4 billion of lost income for patients.

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 whites. Hispanics have a significantly increased risk for kidney failure, as well.

The NIDDK devotes considerable resources to understanding the basic mechanisms underlying the causes and progression of kidney disease to ESRD. The Institute's efforts to combat ESRD include research to reduce morbidity and mortality from bone, blood, nervous system, metabolic, gastrointestinal, cardiovascular, and endocrine abnormalities in ESRD, and to improve the effectiveness of dialysis and transplantation. Major areas of research focus include identification and testing of possible therapeutic interventions to prevent development or halt progression of kidney disease, and identification of the risk factors for ESRD and cardiovascular disease. A major new outreach initiative is the National Kidney Disease Education Program.

Urologic diseases affect persons of all ages, result in significant health care expenditures, and, if improperly diagnosed or improperly treated, may lead to irreversible kidney and/or bladder damage and possibly death. 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 affects one half of men age 51 to 60, and 90 percent of men past age 80. 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.

In 1997, urinary tract infections accounted for well over 8 million physician visits at a cost of $1 billion. Urinary tract stone disease, commonly referred to as kidney stones, accounted for over 1.3 million physician visits in 1997. Interstitial cystitis (IC) is a debilitating, chronic bladder disorder, which has been estimated to affect as many as 1 million Americans, 90 percent of whom are women. In 1998, IC was estimated to cost about $1.7 billion in medical expenses and lost wages. About 13 million Americans, most of them women, suffer from urinary incontinence. In 1995, the "societal" cost of urinary incontinence was estimated to be $26.3 billion for individuals 65 and older. Genitourinary tract abnormalities are the most common birth defect. One such abnormality, vesicoureteral reflux, is one of the most common causes of kidney failure in children, occurring in an estimated 1-to-2 percent of newborns.

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 priority of the urology program is the study of chronic inflammatory disorders of the lower urinary tract.

The Institute's hematology research program emphasizes a broad approach to understanding the normal and pathologic function of blood cells and the blood forming system. Major areas of interest include diseases such as sickle cell anemia, thalassemias, aplastic anemia, iron deficiency anemia, hemolytic anemias, and thrombocytopenia. The Institute has issued several research solicitations recently to emphasize research on the biology and genetic regulation of stem cells. Stem cells are crucial to the eventual broad application of gene therapy and for improved transplantation of bone marrow cells. An additional area of long-term priority has been the development of improved iron chelating drugs to reduce the toxic iron burden in people who receive multiple blood transfusions for diseases such as Cooley's anemia (thalassemia major).

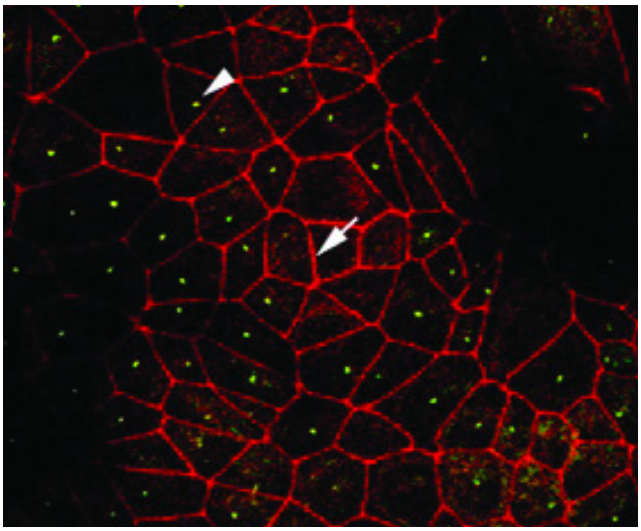
CILIA AND POLYCYSTIC KIDNEY DISEASE

Polycystic kidney disease (PKD) has been estimated to affect as many as 500,000 to 600,000 children and adults in the U.S. PKD is characterized by massive enlargement of the kidneys due to the presence of fluid-filled cysts and is the fourth leading cause of kidney failure. Most patients with the most common form of PKD, ADPKD, have a mutation in either one of two genes, *PKD1* or *PKD2*. Recently, the gene causing ARPKD, a less common but more lethal form of PKD, was identified.

The proteins encoded by *PKD1* and *PKD2*, polycystin-1 and 2, respectively, can form a functional complex that may be involved in cell signaling in kidney epithelial cells. Versions of genes very similar to human *PKD1* and *PKD2*, gene "homologs," have been found in the genomes of a number of model organisms, from worms to mice. In mice, researchers have also found defects in a number of other genes that can cause PKD. All of these discoveries have propelled research to figure out how disruptions in PKD-related genes derail normal kidney tissue development or maintenance to cause cyst formation and progressive renal (kidney) disease.

Fascinating new studies in model organisms suggest that mutations in PKD-related genes cause structural or functional defects in cilia, which in turn contribute to the development of PKD. Cilia are hair-like projections found on the surface of cells in certain tissues. They are composed of cell membrane stretched over a protein "scaffold," and serve many different functions. Cilia are used by some cells to sweep particles in a polarized direction, as in the cilia on cells lining the trachea (windpipe). Other cells use cilia as "antennae" to sense and respond to changes in the extracellular environment.

NIDDK-supported researchers studying gene homologs of human *PKD1* and *PKD2* in the nematode worm *C. elegans*—*lov-1* and *pkd-2*, respectively—recently found evidence that the two genes function in the same cellular pathway, similarly to human *PKD1* and *2*. *C. elegans* doesn't have kidneys,



In polarized kidney epithelial cells grown in culture (outlined in red), proteins involved in polycystic kidney disease (PKD), such as polycystin-1, can be found in the cell cilia (yellow). Photo: Dr. Bradley Yoder and Dr. Lisa Guay-Woodford. From The Journal of the American Society of Nephrology, Vol 13, 2002, 2508-16. Reprinted with permission from Lippincott Williams & Wilkins.

however. Instead, both *lov-1* and *pkd-2* are necessary for proper male worm mating behavior—which requires sensing environmental cues. The researchers found that the *C. elegans* PKD-2 protein, like the LOV-1 protein, appears to be exclusively expressed in male-specific sensory neurons used in mating—which are also ciliated. Furthermore, both LOV-1 and PKD-2 proteins are enriched in the cilia.

As it turns out, polarized kidney epithelial cells, specialized cells that line both normal kidney tubules and PKD cysts, are also ciliated, possessing a single cilium per cell. The function of this cilium is unknown, but there is evidence that it may fulfill a sensory function, possibly detecting changes in fluid flow in the kidney. Previously, researchers had observed that mutations in the gene coding for "polaris," a PKD-related protein in mice, disrupt cilia formation in polarized kidney epithelial cells. In a recent study, NIDDK-supported researchers identified and characterized the *cpk* gene, which is linked to PKD in one mouse model of the disease. The *cpk* gene is expressed primarily in mouse kidney and liver and encodes cystin, a novel small protein. When the researchers engineered an easily detectable version of cystin and expressed it in polarized kidney epithelial cells grown in a culture dish, they observed it in the cilium—similarly to polaris.

But are polycystin-1 and polycystin-2, the proteins directly implicated in human PKD, also localized to kidney cell cilia? The two proteins had already been detected in other parts of these cells, including specialized patches of cell membrane and in cellular organelles. NIDDK-supported researchers re-examined these cells and found that, indeed, mouse polycystins-1 and -2, like cystin and polaris, can be found in the cilium of polarized kidney epithelial cells grown *in vitro*. Furthermore, another NIDDK-supported research team recently examined what the PKD proteins may be doing in the cilium. They found that when they first blocked the activation of polycystin-1 or polycystin-2 on cultured kidney epithelium cells and then used fluid flow to bend the cells' cilia, the cells no longer engaged in normal signaling pathways in response to this mechanical stress. These results suggest that the presence of polycystin-1 and polycystin-2 in the cilium is necessary for fluid-flow sensation, which may in turn help regulate tissue growth and change in the kidney.

The roles of the kidney epithelial cell cilium in normal development or maintenance of polarized kidney epithelium—and hence, its possible role in cyst formation—are still under investigation. The results of these studies now suggest, however, that proper function of the cilia and at least some of its associated proteins may be necessary to prevent PKD—a significant new twist in our understanding of PKD. 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.

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UNDERSTANDING AND PREVENTING KIDNEY DISEASE PROGRESSION

Chronic kidney disease affects an estimated 10 to 20 million Americans. It can result from a number of kidney diseases, including polycystic kidney disease (see preceding section) and focal segmental glomerulosclerosis, or as a secondary complication of other diseases or conditions, such as diabetes and hypertension (high blood pressure; see also "Vision Statement—Robert Schrier, M.D."). Exposure to toxins or high-protein diets in some cases can also contribute to kidney problems and the development of chronic kidney disease.

Chronic kidney disease can progress slowly over many years, and patients are often unaware of the condition until they have advanced loss of kidney function. In its most severe stage, chronic kidney disease develops into end-stage renal disease (ESRD)—irreversible kidney failure. The factors underlying kidney disease progression are not well understood. Genetics, environment, and nutrition are all thought to contribute to a greater or lesser degree. Because chronic kidney disease is linked to higher risk for cardiovascular disease (see "Story of Discovery—Chronic Kidney Disease and Cardiovascular Disease") and can ultimately progress to kidney failure, it is imperative to more fully understand the factors driving progression of disease.

Identifying Novel Genes Involved in Kidney Disease Progression: A better understanding of the large number of genes expressed in normal and diseased kidneys and how they interact should help clarify how kidney disease begins and how it progresses. Serial analysis of gene expression (SAGE) is a technique that allows researchers to generate a relatively comprehensive profile of the large number of genes expressed in a particular cell type or tissue. These "snapshots" of global patterns of gene expression may allow scientists to better define cell biology at the molecular level without making assumptions *a priori* about which genes might be important. This approach can be valuable in identifying novel targets for therapy that might otherwise not be considered.

One recent application of SAGE has been the comparison of gene expression profiles in the kidneys of two different strains of mice, ROP and C57Bl/6, that exhibit divergent physical manifestations of the same genetic defect. When present in the ROP strain of mice, this defect, known as Os/+, causes skeletal abnormalities; a 50 percent reduction in the number of nephrons, the tiny filtration units in the kidney; and progressive kidney damage that resembles the human disease focal segmental glomerulosclerosis. However, in the C57Bl/6 strain of mice, Os/+ produces the same skeletal defects and similar kidney defects, but not progressive kidney disease.

Using SAGE, NIDDK-supported researchers recently identified 63 genes whose expression was significantly different between the two mouse strains. Thirty-eight of these gene products were more abundant in the sclerosis-prone ROP-Os/+ mouse kidney, including antioxidant genes involved in stress response. Gene products relatively under-represented in the ROP-Os/+ kidney included ones important in the maintenance of normal cell structure and function. By using this approach, researchers now have clues about genes and pathways that may play a role in the progression of kidney disease that might not have been expected or anticipated using approaches focusing narrowly on the Os/+ defect.

Finding Factors That Contribute to Kidney Disease Progression—Clinical Efforts: It is imperative to discover the factors that contribute to the decline in kidney function and the development of cardiovascular disease in people with chronic renal insufficiency. Further research is needed before interventions can be evaluated and implemented. To date, few studies have focused on people with chronic kidney disease before they reach ESRD.

One type of study that has played an important role in defining risk factors for a wide-range of diseases is the prospective cohort study. To determine the risk factors for rapid decline in kidney function and development of cardiovascular disease, the NIDDK recently established the Chronic Renal Insufficiency Cohort (CRIC) Study. This is a seven-year prospective, multi-ethnic, multi-racial study of approximately 3,000 patients with chronic kidney disease. Participants will reflect the racial, ethnic, and gender composition of the U.S. ESRD patient population. The data and samples obtained from people in this study will serve as a national resource for investigating chronic kidney disease and cardiovascular disease. Establishing this cohort of patients and following them prospectively will also provide researchers with an opportunity to examine genetic, environmental, behavioral, nutritional, quality-of-life, and health resource utilization factors in this population. Five geographically diverse centers are participating in the study. The CRIC study began protocol development in September 2001, and enrollment for the study is expected to begin in Spring 2003.

Another clinical study supported by the NIDDK, the Continuation of AASK Cohort Study, focuses specifically on defining factors contributing to kidney disease progression in African Americans. African Americans are disproportionately afflicted with ESRD: although they constitute approximately 12 percent of the U.S. population, African Americans comprise 32 percent of the prevalent ESRD population. The Continuation of AASK Cohort Study commenced at the conclusion of the African American Study of Kidney (AASK) Disease and Hypertension. A landmark clinical trial, the AASK study demonstrated that persons with kidney disease caused by hypertension (high blood pressure) have a better chance of reducing the risk of kidney failure if they take an angiotensin converting enzyme inhibitor medication. The primary goal of the continuation study is to investigate environmental, socio-economic, genetic, physiologic, and other factors that influence progression of kidney disease in a well-characterized cohort of African Americans with hypertensive kidney disease.

Preventing Progression of Kidney Disease: The NIDDK is supporting a number of studies and clinical trials that are evaluating therapeutic interventions to prevent kidney disease progression. One new study, the Focal Segmental Glomerulosclerosis (FSGS) clinical trial, will examine interventions to prevent progression of this disease. FSGS causes scarring in the kidney and is a major cause of renal disease in children and young adults. It can also recur post-kidney-transplant leading to kidney transplant injury or loss. The NIDDK has also established a Polycystic Kidney Disease (PKD) Clinical Trials Network to design and implement clinical trials of agents that might slow progressive loss of kidney function in PKD, the fourth leading cause of ESRD.

Another extremely important aspect of intervention in chronic kidney disease is increasing public awareness. The NIDDK recently launched the National Kidney Disease Education Program (NKDEP) to educate and inform the public about the risks for and complications of chronic kidney disease, and ways that disease can be slowed or even prevented (see sidebar, "The National Kidney Disease Education Program"). The NKDEP has begun a pilot campaign in four U.S. cities, targeting health care providers, patients, and insurers with a message focused on identifying risks, patient screening, and appropriate treatment. The initial campaign is especially focused on African Americans, a patient group at particularly high risk for kidney disease. In later phases, the campaign will extend to other minority groups at high risk.

Ultimately, the goal of this educational campaign is to reduce complications and death due to kidney disease and kidney failure among all Americans.

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NEW KNOWLEDGE IN DIALYSIS

The introduction of hemodialysis in the early 1960s has saved the lives of countless persons suffering from kidney failure, also called end-stage renal disease (ESRD) (see sidebar, "Lasker Awardees—Dr. Willem Kolff and Dr. Belding Scribner"). Normally, the kidneys remove toxic by-products of metabolism, such as urea and creatinine, for excretion in urine, and maintain salt balance in the blood. These functions are lost in ESRD. In hemodialysis, these functions are approximated by circulating a patient's blood through a specialized external filter to remove toxins and then returning it to the body. ESRD patients typically undergo this procedure at least three times a week, for 2-to-4 hours at each session. This enables patients to survive as they await the only cure for ESRD—a kidney transplant.

Unfortunately, despite the success of hemodialysis, it is far from perfect. Mortality on hemodialysis is still high—current projections are 70 percent mortality within 5 years of starting dialysis. Moreover, quality of life is poor. The dramatic rise in diabetes, the leading cause of ESRD, has fueled the increasing number of persons on dialysis. In turn, the average time a person remains on dialysis has increased, because the number of kidneys available for transplant has become further outstripped by the need. Also noteworthy is that the population receiving maintenance hemodialysis now, as compared to three decades ago, is older and has more co-morbid conditions to contend with, which may be adversely affected by the current limitations of dialysis.

To address these issues, the NIDDK sponsored a major clinical trial, the HEMO study, to carefully evaluate whether patient survival on dialysis could be improved either by making dialysis doses more intense, or by using a different type of dialysis filter—a "high-flux" filter that can remove larger waste particles from the blood. This study enrolled more than 1,800 patients, who were randomly assigned to standard or high dialysis doses with low- or high-flux filters. The HEMO study investigators found that, on average, treatment under the dialysis guidelines currently in use provides essentially the same benefits as more intensive regimens.

The HEMO study is the most comprehensive, randomized clinical trial to date to evaluate the efficacy of hemodialysis protocols. However, researchers are still investigating whether specific patient subgroups within the ESRD population on maintenance hemodialysis, such as women and ethnic minorities, may benefit from revised hemodialysis regimens.

Another consideration for improving hemodialysis outcomes is the health status of persons as they enter dialysis. Although the population on hemodialysis is predominantly older and suffering from type 2 diabetes, children can develop serious kidney disease that leads to ESRD. Because their bodies are still developing, children are especially vulnerable to the complications imposed by ESRD and dialysis. In a recent study, researchers found that children requiring dialysis have a poor clinical outcome if they also have experienced poor growth. NIDDK-supported researchers prospectively monitored a national cohort of over 2,300 children initiating dialysis in terms of school attendance, hospitalization rate, and survival. The results showed that poor growth preceding the initiation of dialysis was associated with poor school attendance (an important marker of functional status for children), increased frequency of hospitalization, and a two-fold greater risk of death as compared with more normal growth. The researchers emphasized in their report that aggressive nutritional measures should be taken to maximize growth in children as soon as chronically deficient kidney function is documented.

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GROWING PROSTATE-GLAND-LIKE STRUCTURES FROM STEM CELLS

One hope held by researchers working with stem cells is to one day be able to use them in treating injury and disease. Thus, scientists are working to isolate and characterize adult stem cells from all major organs and tissues, including those of the genitourinary tract, such as the prostate. NIDDK-supported investigators recently defined a small region of the mouse prostatic duct, called the "proximal region," that contains cells having stem cell properties. The cells divide slowly (slow cycling), have high proliferative potential, and have the ability to give rise to complex glandular structures *in vitro*.

Using established cell-labeling analytic techniques, the researchers initially localized slow cycling cells to the proximal prostatic duct. They then dissected proximal and distal duct cells from animals, grew them *in vitro*, and examined their proliferative capacity. Proximal prostatic duct cells were shown to generate over 200 times as many progeny as those originating from the distal prostatic duct, indicating that the proximal cells have high proliferative potential.

To examine whether the cells were capable of forming glands, the researchers grew the proximal and distal prostatic duct cells in a special collagen gel matrix. Cells from the proximal region gave rise to numerous, large-branched ducts that contained typical prostate cells that produced prostatic secretory substances. By contrast, cells from the distal duct region produced far smaller and simpler gland-like structures.

These results strongly suggest that the proximal region of the prostatic duct contains a concentration of stem cells that are capable of reconstituting large, branched glandular structures that produce prostatic secretory substances. Future characterization of these cells—particularly their developmental pathways, cell surface markers, and the signals involved—should help in understanding the processes involved in prostatic homeostasis and the causes(s) of prostate diseases, including benign prostatic hyperplasia (see "Vision Statement—John McConnell, M.D.") and prostate cancer. To help accelerate such studies, the NIDDK recently launched an initiative to encourage researchers to develop new, cell-selective tools and methods applicable to studies of the prostate, bladder, and other organs of the genitourinary tract.

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EXPANDING BASIC RESEARCH STUDIES OF THE URINARY BLADDER

Through research, scientists are discovering that the urinary bladder is much more than a reservoir for liquid waste. Rather, it is a dynamic organ with many important structural and physiological properties. It is made of smooth muscle connected to nerves and lined with a unique "transitional epithelium" that makes specialized proteins to protect the bladder cells from the urine. It is also the only organ in the body able to fill and then empty on command. Proper function of the bladder is vital to rid the body of wastes and prevent infections. Unfortunately, millions of Americans suffer from both acute and chronic bladder disorders that interfere with proper bladder function. Urinary

tract infections, congenital obstructions, and urinary incontinence are just a few of the common clinical conditions affecting the bladder and lower genitourinary tract. Researchers have turned their attention to understanding the normal biology of the bladder and its component tissues, in order to gain insights that may lead to better tests, treatments, and prevention strategies for bladder disease.

Unfolding Umbrella Cells Requires New Membrane: In a recent study, NIDDK-supported researchers found that, as the urinary bladder increases in volume with filling, changes are elicited in the cells that line the bladder to ensure that the permeability barrier of this organ is maintained. To simulate bladder expansion, researchers stretched animal bladder tissue in an experimental chamber under normal physiological conditions, and performed a series of rigorous electrical, physical, microscopic, and biological analyses. Important new basic information about bladder structure was revealed. One major finding concerned the cells lining the inner surface of the bladder, called "umbrella" cells. Previously, it was hypothesized that increased cellular membrane surface area was achieved by simple unfolding of existing membrane structure, like the unfolding of an umbrella. Instead, the researchers found that the cells actually increase in size by synthesizing new membrane.

Upon stretching, the umbrella cells also underwent a dramatic change in shape, decreasing in depth and increasing in length. Vesicles—small "bubbles" of membrane components—also fused with the cell membrane, a process known as exocytosis. Stretching also prompted a rapid and continual secretion of protein from within the umbrella cells into the external environment. Surprisingly, stretching also induced involution of the umbrella cell membrane into vesicles by an energy-dependent process called endocytosis; the vesicles were subsequently degraded within the cell. While exocytosis and endocytosis are known to occur simultaneously in all cells, even under resting conditions, it previously was thought that endocytosis in umbrella cells took place only as bladder volume decreased. The specific functions and regulations associated with these newly discovered structural changes in umbrella cell membranes will be the subject of future investigations.

Uncovering fundamental knowledge on urinary bladder structure and function through basic research is expected to lead to more effective treatments for bladder diseases and disorders. Expanding basic research studies of the bladder and lower genitourinary tract is one of the strategic priorities put forward by the Bladder Research Progress Review Group (PRG). This task force was convened by the NIDDK two years ago to assess and make recommendations about needs and future directions in bladder research (see sidebar, "The Bladder Research Progress Review Group: Generating a Strategic Plan for Bladder Research"). The Bladder Research PRG released its report in August 2002. Already, guided by recommendations contained within the report, the NIDDK expects to launch two new initiatives later in 2003 that are intended to support bladder studies. One initiative will encourage basic research on the biology of the bladder. The other initiative, entitled "Basic Research Related to Interstitial Cystitis," will support research on the underlying causes of interstitial cystitis (IC), a painful and debilitating bladder disease (see "Patient Profile—Kara Fishbein Goldman"). It is anticipated that new knowledge gained from this research will feed into the development of new therapeutics for bladder diseases.

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HEREDITARY HEMOCHROMATOSIS: A COMMON MUTATION THAT MAY NOT COMMONLY LEAD TO DISEASE

Hereditary hemochromatosis is a genetic disease that causes overabsorption of dietary iron. Because the body cannot excrete excess iron, it accumulates to toxic levels in body tissues ("iron overload") and leads to a number of complications, including diabetes, heart arrhythmias, and cirrhosis of the liver. Hereditary hemochromatosis is linked to mutations in the *HFE* gene, which was identified in 1996. Over 80 percent of hereditary hemochromatosis patients have a specific mutation in both copies of the *HFE* gene, a mutation called C282Y, which alters the *HFE* protein.

However, there are conflicting data about the actual risk of developing clinical symptoms when a person has two copies of the C282Y mutation. It had been proposed that being a C282Y "homozygote" may be necessary but not sufficient to cause clinical hereditary hemochromatosis. The C282Y mutation is highly common—one in 200 to 500 Americans are C282Y homozygotes. Because hemochromatosis is treatable with phlebotomy (periodic bloodletting), but its associated complications are not easily reversed, it is important to ascertain whether population screening for *HFE* mutations will effectively prevent disease.

To determine how well the genotype *HFE* C282Y predicts clinical disease, NIDDK-supported investigators screened 41,038 individuals to find those with the C282Y mutation. They then assessed whether individuals with the C282Y mutation were more likely to have symptoms or diseases associated with hereditary hemochromatosis than the control group, which lacked the mutation. At the same time, the researchers measured body iron stores. Iron burden was determined by two measures: saturation of the iron transporting protein, transferrin, and concentration of serum ferritin, an iron storage protein. By these measures, at least 75 percent of male and 40 percent of female C282Y homozygotes had significant iron burdens.

However, the prevalence of most of the clinical conditions associated with hereditary hemochromatosis, including diabetes, arrhythmias, and impotence, was not statistically different between C282Y homozygotes and the control patients. The only clinical symptoms occurring more frequently in C282Y homozygotes than in the control group was a history of hepatitis or other liver disorder, about a two-fold increase. Only one individual homozygous for C282Y had the broad spectrum of clinical symptoms diagnostic of hereditary hemochromatosis. From these results, the investigators estimate that less than one percent of C282Y homozygotes proceed to clinical disease.

Prevalence, intervention, and penetrance are the three most important factors in determining whether to engage in population screening for a genetic disease. The C282Y mutation in *HFE* is quite prevalent, and hereditary hemochromatosis is easily treatable. However, the results of this study suggest that the presence of the C282Y mutation alone is not an effective predictor of clinical disease. These findings will encourage investigators to seek secondary mutations or environmental factors—which may vary between populations—that influence the course of disease.

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NEWLY DISCOVERED PROTEIN STABILIZES HEMOGLOBIN CHAIN

Hemoglobin in red blood cells carries oxygen throughout the body and is essential for life. Adult hemoglobin, or HbA, consists of two pairs of identical protein chains, two alpha-globin and two beta-globin chains. Red blood cells generally have balanced amounts of both chains that go into making the complete HbA molecules. However, if a red blood cell develops pools of excess "free" alpha- or beta-globin chains, these extra proteins can become unstable and clump

together, forming toxic precipitates that damage and ultimately kill the cell.

Beta thalassemia major, also known as Cooley's anemia, is a genetic disease caused by mutations affecting the beta-globin chain of HbA. These mutations reduce beta-globin production and create such an excess of alpha-globin that there is tremendous red blood cell death. This causes life-threatening anemia and other serious health problems. Cooley's anemia patients require lifelong blood transfusions to overcome the anemia and survive. Over time, these transfusions create health complications of their own, including transfusion-induced iron overload (see next section). For Cooley's anemia patients, iron overload and other complications require burdensome secondary therapies that can severely diminish quality of life. Scientists are therefore trying to develop molecular methods to control or compensate for the imbalances in hemoglobin production as an alternative therapeutic approach to Cooley's anemia and other forms of beta thalassemia.

In one recent study, an NIDDK-supported research team identified an abundant protein in red blood cells that interacts with and stabilizes free alpha-globin. Such stabilizing proteins are also called "chaperones." Studying both mouse and human red blood cells, the researchers found that Alpha Hemoglobin Stabilizing Protein, or AHSP, binds to alpha-globin, but not beta-globin or HbA. In biochemical assays and in live cells, recombinant AHSP prevented free alpha-globin from precipitating. Most significantly, when the team genetically-engineered mice to lack AHSP, the mice were viable, but their red blood cells showed evidence of globin precipitates, and red blood cell turnover was higher than normal—suggesting a physiologically important role for AHSP.

AHSP is the first red blood cell-specific molecular chaperone to be identified. These findings strongly suggest a role for AHSP in routine stabilization of free alpha-globin, and a possible role for AHSP in modifying disease severity in beta thalassemia. Future investigation of the AHSP protein may determine whether AHSP might be a possible therapeutic target for Cooley's anemia and other forms of beta thalassemia. Similar candidates may be identified through ongoing genomics studies that are using cutting-edge genetic and molecular techniques to identify human genes that modify disease severity in beta thalassemia, in hopes of finding possible therapeutic targets for this life-threatening illness.

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WORKING TO LIFT THE BURDEN OF IRON OVERLOAD

Hereditary hemochromatosis and Cooley's anemia are quite different diseases, but share a common complication—iron overload. While iron is an essential nutrient used by all body cells, in excess of body needs it can accumulate to toxic levels in body tissues and cause a number of serious health conditions. The development and severity of these conditions, including organ damage, are closely correlated with the magnitude of the body iron excess. Patients with iron overload may suffer from liver disease with the eventual development of cirrhosis and, often, hepatocellular carcinoma, diabetes mellitus, gonadal insufficiency and other endocrine disorders, increased skin pigmentation, and iron-induced cardiomyopathy, which may be lethal. To effectively combat iron overload, both accurate techniques for measuring body iron stores and minimally burdensome therapies to remove excess iron are necessary. The NIDDK is supporting research in both of these areas.

Iron Overload Technologies: Physicians need to be able to assess body iron stores in order to provide appropriate care and treatment for their patients—such as phlebotomy for hereditary hemochromatosis patients and management of iron-removing "chelation therapy" for Cooley's anemia patients. Unfortunately, blood tests that measure iron saturation in iron transport and storage proteins

provide only a limited picture of total body iron stores. Because the most excess iron is stored in the liver, the "gold standard" for assessing body iron stores is a liver biopsy—an invasive, painful procedure. In April 2001, the NIDDK led an international workshop on the non-invasive measurement of iron to assess the current state of the science and to identify areas needing further investigation. The workshop participants concluded that additional research was needed to develop better quantitative means of measuring body storage iron that would be non-invasive, safe, accurate and readily available to improve the diagnosis and management of patients with iron overload.

The NIDDK has been at the forefront of developing new technologies for the non-invasive measurement of body iron. Thirty years ago, the NIDDK supported research that 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. The method employs a device called "SQUID" (superconducting quantum interference device). However, the complexity, cost, and technical demands of the instruments used in this method have restricted its widespread clinical use. With support from both the NIDDK and the National Heart, Lung, and Blood Institute, the researchers involved in the original development of SQUID are now engaged in a large-scale NIH Bioengineering Research Partnership project to modify the SQUID technology in ways to make it more affordable and ready for more widespread clinical use.

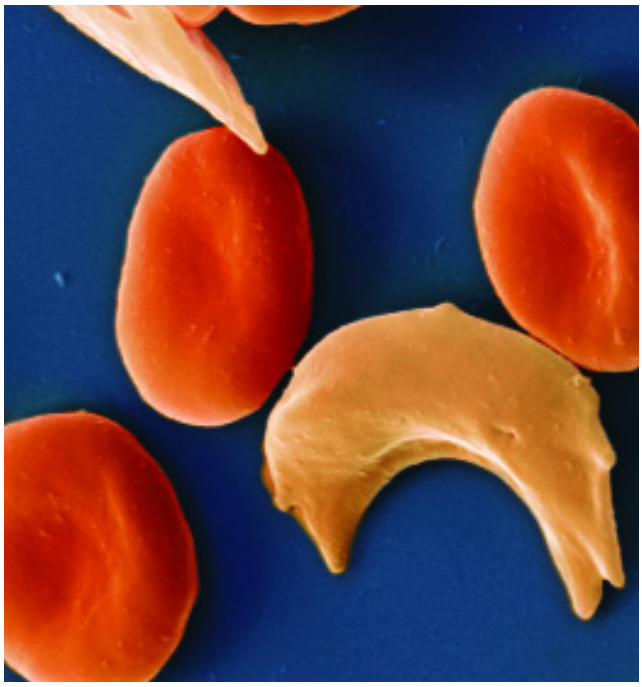
Magnetic resonance imaging (MRI) technology is already in widespread use for a number of clinical applications, from visualizing damaged tissues to monitoring chemical changes in the brain. At present, MRI also provides a means of probing the distribution of excess iron in the body, but further efforts are needed to make measurements quantitative. The NIDDK, in collaboration with the new National Institute of Biomedical Imaging and Bioengineering (NIBIB), has recently issued two new research solicitations to encourage both academic laboratories and small businesses to find ways to adapt MRI technology for application to the clinically useful measurement of body iron stores.

Alternatives to Current Chelation Therapy: Cooley's anemia patients with transfusion-induced iron overload must undergo "chelation therapy" to rid their bodies of excess iron. In chelation therapy, patients are infused by needle with a drug, deferoxamine, which will bind, or chelate, iron. The body can then eliminate these chelator-iron compounds. This treatment is the only therapy currently approved for use. However, the therapy is painful and takes up to 12 hours at a time, five to seven times a week. Since Cooley's anemia strikes in very early childhood, therapy can become an ordeal, and compliance can be a serious issue. Optimally, new chelator drugs would be less burdensome to use.

One drug that is progressing into clinical trials, HBED, appears to be more effective at chelation than deferoxamine, indicating that it may need to be used less frequently and for shorter periods of time. However, like deferoxamine, HBED still needs to be injected. The NIDDK is currently supporting basic and pre-clinical research studies to identify and evaluate oral iron chelator drugs as an alternative to injected chelators. Recently, a re-engineered version of a compound, desferrithiocin, was approved by the FDA for clinical studies. The Institute is also seeking proposals to perform pre-clinical evaluations of other iron chelating compounds.

ADVANCING THERAPIES FOR SICKLE CELL DISEASE

Sickle cell disease (SCD) is a genetic disorder affecting the essential oxygen-carrying molecule in the blood, hemoglobin. Like Cooley's anemia, SCD is caused by a mutation affecting the beta-globin subunit of hemoglobin HbA (see "Newly Discovered Protein Stabilizes Hemoglobin Chain"). However, whereas beta thalassemia patients lose production of the beta-globin molecule, SCD patients have defective beta-globin molecules.



Sickle cell disease causes the normally doughnut-shaped red cells in the blood to assume a crescent, or "sickle," shape (yellow cell). When large numbers of these sickle cells are trapped in tiny blood vessels, blood flow is blocked, causing tissue and organ damage and excruciating pain.
Photo: Dr. Mark Gladwin, NIDDK. ©2002 Nature Publishing Group (http://www.nature.com/).

Sickle cell disease results when an individual inherits a specific mutation in each of two copies of the gene encoding beta-globin. The mutant beta-globin chains are then incorporated into the complete hemoglobin molecules. The resulting defective hemoglobin molecules often stick together in long rods ("polymers") that cause the red blood cells, which are typically "doughnut"-shaped, to take on a "sickle" form. Such misshapen red blood cells are much more fragile than normal. Up to 10 percent of these cells die every day and spill their contents, which include large quantities of hemoglobin, into the bloodstream. In addition, sickle cells have difficulty passing through narrow blood vessels, and can block blood flow to vital organs or joints. This process causes extremely painful episodes, called "crises," that can last from a few hours to several weeks and may ultimately result in severe tissue damage.

Sickle cell disease is especially prevalent in African Americans. Current therapies for SCD are limited to drugs to help manage pain, treatment of complications, and experimental therapies to induce red blood cells to use alternate forms of hemoglobin instead of HbA. The only cure for severe cases of SCD is a bone marrow transplant, a serious operation with a number of risks. Scientists have recently made significant advances in pre-clinical and clinical research that should improve current therapies for sickle cell disease.

Gene Therapy for Sickle Cell Disease: In a recent pre-clinical study, genetic manipulation of beta-globin corrected sickle cell disease in two mouse models of the disease. From earlier studies, researchers knew that substituting "anti-sickling globins" for some of the mutant beta-globin chains could prevent the formation of hemoglobin polymers. In applying this knowledge toward the treatment of SCD, a significant challenge has been to incorporate a minimum therapeutic amount of anti-sickling globin into the beta-globin pool of almost every red blood cell. NIDDK-supported researchers designed a viral vector optimized for the transfer of genes into hematopoietic stem cells (the cells that give rise to all blood cells, found primarily in the bone marrow) and subsequent expression in red blood cells. Using the vector, they transferred an anti-sickling version of human beta-globin into bone marrow extracted from mouse models of SCD. This marrow was used to reconstitute the blood cells of both normal and SCD adult mice. The red blood cells that developed in these mice achieved a sufficient level of the anti-sickling beta-globin–up to 52 percent of total beta-globin–to significantly reverse the sickling of cells, enlargement of spleen, and disruption of urine concentration typical of SCD over the several-month course of the study. This study provides important "proof-of-principle" that gene therapy for SCD may someday be applied in treating human disease.

Stem Cells from Blood—A Possible New Approach to Therapy: Currently, the only successful treatment for severe SCD is a bone marrow transplant. As noted previously, bone marrow contains the undifferentiated stem cells that can develop into red blood cells that can replenish the patient's blood with healthy cells. Siblings are most likely to be eligible bone marrow donors. Siblings of sickle cell disease patients, however, have at least a 50 percent chance of having sickle cell trait—the inheritance of one copy of the sickle cell mutant gene. Sickle cell trait usually does not cause symptoms, but can increase a person's chances for infection or other complications arising from the bone marrow transplant procedure.

NIDDK researchers recently tested the safety and feasibility of isolating stem cells from the blood of individuals with sickle cell trait for transplanting into siblings with sickle cell disease. If successful, this would be an easier technique for collecting cells and could present less risk to the donors. Participants in the study were given a "mobilizing" agent to increase the number of their circulating stem cells before blood was collected. Researchers obtained sufficient numbers of stem cells from these individuals to predict that transplantation of mobilized stem cells into sickle cell disease patients could become a successful alternative to a bone marrow transplant from a sibling. Moreover, no serious adverse side effects were observed in the sickle cell trait participants. This research opens up an important new avenue of potential treatment for sickle cell disease.

Uncovering a Role for Nitric Oxide in Sickle Cell Disease Pain: The molecular mechanisms underlying sickle cell pain, and methods to reverse these episodes, have not been well understood. In a recent study, NIDDK researchers uncovered a significant clue about sickle cell pain. Nitric oxide (NO), a gas produced by endothelial cells lining the inside of blood vessels, has many functions throughout the body. For example, NO contributes to the regulation of blood pressure by promoting blood vessel dilation—an increase in vessel diameter. NO levels are closely balanced between production by endothelial cells and destruction by a hemoglobin "scavenging" system that converts NO into a biologically inactive form. The researchers hypothesized that abnormally high levels of free hemoglobin in the blood of sickle cell disease patients might cause too much NO to be inactivated by the scavenging system. The resulting loss of NO activity could lead to narrowing of blood vessels, which in turn could trap sickled cells and unleash a pain crisis.

The researchers found that, indeed, plasma from sickle cell disease patients had higher levels of hemoglobin and scavenged three times as much NO as plasma from normal volunteers. Removal of hemoglobin from sickle cell plasma reduced the NO scavenging to a level close to that of normal plasma. Furthermore, when sickle cell disease patients who were not undergoing a pain crisis during the study inhaled NO gas, it caused the rapid conversion of circulating hemoglobin to a form that interacts with NO only weakly. Thus, this study supports a role for hemoglobin scavenging of NO in sickle cell pain through the constriction of blood vessels. Importantly, the results suggest a potential therapy for alleviating the pain by inhalation of NO gas to reduce plasma hemoglobin and restore the ability of NO to properly regulate blood vessel size. Uncovering the role of NO in sickle cell disease will help scientists to develop new and more effective therapies for this painful and debilitating disease.

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ONGOING AND NEWLY LAUNCHED NIDDK EFFORTS IN KIDNEY, UROLOGIC, AND HEMATOLOGIC DISEASES

The NIDDK continues to advance basic and clinical research in kidney, urologic, and hematologic diseases through numerous initiatives, clinical trials, and support for investigator-initiated research. In addition to the previously described efforts in understanding and preventing kidney disease progression, the NIDDK, in collaboration with the National Institute of Neurological Disorders and Stroke and the National Institute of Child Health and Human Development, is planning to initiate a new study of chronic kidney disease in pediatric patients. This study will evaluate outcomes similarly to the CRIC study, but with a special focus on neurological function and other aspects of development that appear to be adversely affected in children with chronic kidney disease, but which have not been comprehensively studied as of yet. The NIDDK is also conducting the Family Investigation of Nephropathy and Diabetes study, a multi-center consortium to investigate genetic susceptibility in diabetic kidney disease, the leading cause of irreversible kidney failure.

The strategic plan from the Bladder Research Progress Review Group will be an invaluable tool for developing and guiding future research in the bladder and lower genitourinary tract. A number of its recommendations are already being implemented. In addition to strengthening basic research on the bladder in general and on interstitial cystitis in particular, the Institute is planning to establish a second cycle of the Interstitial Cystitis Clinical Trials Group, which has been testing and evaluating a number of therapeutic interventions for the painful symptoms of interstitial cystitis.

The NIDDK is also capitalizing on and extending the clinical value of the Medical Therapy of Prostate Symptoms (MTOPS) trial. This major clinical trial recently demonstrated that two drugs commonly used to treat benign prostatic hyperplasia (BPH), finasteride and doxasozin, are significantly more effective at preventing symptomatic BPH incidence and progression when given in combination. Together, they reduced risk of progression of BPH by 67 percent, versus 39 percent with doxasozin alone and 34 percent with finasteride alone (see also "Vision Statement—John McConnell, M.D."). The Minimally Invasive Surgical Therapies (MIST) Treatment Consortium for BPH is designing trials to assess the safety and efficacy of new surgical treatments for BPH; the first trial will include evaluation of the combination of surgery with a drug regimen similar to that used in MTOPS. Furthermore, biological samples collected during the MTOPS trial will be used by the MTOPS Prostate Samples Analysis Consortium to discover and validate biologic markers or genetic susceptibility tests for detection, risk assessment, and disease assessment of BPH—which could generate important new clinical tools for treating or managing the disease. The NIDDK is also initiating the Complementary and Alternative Therapy for Benign Prostatic Hyperplasia study, a large clinical trial to examine the effects and efficacy of two commonly used alternate therapies for BPH (also called "phytotherapies"), saw palmetto and *Pygeum africanum*.

Finally, facilitating future research on blood cell development and blood disorders, the NIDDK has initiated a Consortium of Genome Anatomy Projects (GAPs), involving eminent groups of hematopoietic stem cell investigators. These stem cell GAPs are aimed at developing the necessary biological procedures and reagents for characterization of cells of the hematopoietic lineage and characterizing gene expression patterns in these cells using advanced technologies and bioinformatics techniques. These projects will interact closely with similar projects related to bone, liver, intestine, kidney, and pancreatic cell development, with the promise for novel approaches to the study of pathogenesis and treatment of human diseases.

VISION STATEMENT

John McConnell, M.D.

The Future of Urology: Translational Research Opportunities and Challenges

As a leading medical researcher specializing in prostate biology and medical therapy for prostate disease, Dr. John McConnell has had the opportunity to both steer and observe the transformation of the urology field over the past two decades. Currently Executive Vice President for Administration at the University of Texas Southwestern Medical Center, Dr. McConnell had been engaged in both basic and clinical research as a professor of urology and director of the Prostate Disease Center, also at the University of Texas Southwestern Medical Center. Most recently, Dr. McConnell served as the lead investigator for the Medical Therapy of Prostate Symptoms (MTOPS) clinical trial, which demonstrated the benefits and efficacy of a combination drug therapy approach for benign prostatic hyperplasia (BPH). He also served on the Executive Committee of the Bladder Research Progress Review Group established by NIDDK (see sidebar, "The Bladder Research Progress Review Group: Generating a Strategic Plan for Bladder Research"). In his presentation to the NIDDK National Advisory Council in September 2002, Dr. McConnell offered a vision of the future for urology research that relies upon influencing the paths it will take, not just predicting them.

Major Challenges in Benign Urologic Diseases

Urologic diseases originate in several parts of the genitourinary tract—primarily the bladder, prostate, and urethra—and strike people across the age spectrum. The causes vary widely, from bacterial infections to anatomic abnormalities. Although the majority of these diseases are termed "benign" because they are non-cancerous, their symptoms can range from the irritation of the urinary tract to the inability to urinate normally, resulting in incontinence or urinary retention and creating the potential for toxicity and bladder or kidney infection. Benign urologic diseases can also interfere with normal sexual function. Many urologic diseases, such as congenital urinary obstruction and urinary incontinence, are somewhat age-dependent. Others, such as stone disease and interstitial cystitis, strike throughout life. All can severely decrease quality of life.

Dr. John McConnell

Dr. McConnell pointed out a number of clinical advances in urology from the past 20 years that have significantly transformed the field, improving patient care and disease outcomes. These include tests for levels of prostate-specific antigen (PSA), which can indicate abnormal prostate growth, and the development of laparoscopic surgery procedures for the kidney and prostate, which are less traumatic for the body than standard open surgery.

Yet, major challenges remain in several areas of benign urologic diseases research. As outlined in the accompanying figure, these challenges include identifying new therapeutic targets for benign

prostate and bladder disease, the assessment of a man's baseline risk for benign prostate disease, and developing more non-invasive techniques for diagnosis of urologic disorders. Organ replacement—namely, bladder replacement—is a particularly crucial challenge for combating pediatric urological disease.

In order for urologists to meet these challenges and continue the trend of successful clinical accomplishments, Dr. McConnell stressed the crucial need for improved progress in current basic urology research that will supply the next generation of therapies and surgical interventions for benign urologic diseases. "There have been a fairly large number of things that have really completely transformed the practice of urology in the 20 years that I've been engaged in urologic practice. I am somewhat pessimistic, though, unless there are further basic science breakthroughs in our understanding of basic prostatic growth and other aspects of urologic disease, that this list (of advances) may not change significantly in the coming decade."

Alternate Visions of the Future

Using the disease benign prostatic hyperplasia (BPH) as an example, Dr. McConnell presented a specific illustration of past accomplishments contrasted with future possibilities. BPH originates in the prostate, a walnut sized gland found wrapped around the urethra at the base of the bladder in men. This gland produces fluid that is a component of semen. Because of the prostate's location, however, prostate disorders can also lead to urologic problems. In men over fifty, the most common prostate disorder is BPH, a non-cancerous growth in prostate size that interferes with normal urination by squeezing the urethra. Symptoms and their severity vary from person to person, but include increased frequency or urgency of urination, weak streams of urine, and urine leakage.

Identifying major challenges in urology research is the first step toward making significant clinical advances in the future. In his Council presentation, Dr. McConnell listed some of the most pressing research needs for the "wide range of disease processes that impact the function of the genitourinary tract.

To illustrate past accomplishments, Dr. McConnell first noted the tremendous wave of new clinical findings and treatment options for BPH over the past decade. World-wide adoption of a standard for symptom evaluation, the AUA Symptom Score, has enabled standardization in the evaluation of treatment efficacy, while a less-invasive surgical procedure for BPH, transurethral resection of the prostate (TURP), has become the "platinum standard" for surgical treatment. Most significantly, there has been a radical change from exclusive treatment of BPH with surgery fifteen years ago to predominant use of drug therapy now, saving many men from the discomfort and complications of invasive treatment.

However, he also noted that these treatments and changes were fueled by scientific findings from 20 to 30 years ago, and expressed concern that the current state of prostate biology research is not keeping pace with the need for more clinical advances like these.

VISION STATEMENT

He then offered two alternate "visions of the future"—one in which basic research in prostate biology stagnates such that new therapeutic targets are not forthcoming and one in which basic research flourishes, leading to fundamental breakthroughs in understanding regulation of prostate growth. In the former, pessimistic vision, fourth generation drugs and non-validated phytotherapy regimens would provide the only "new" therapeutics for BPH. In the latter, optimistic vision, truly novel therapeutic targets would emerge, and there would be more and better diagnostic tools to use with BPH. The challenge is to ensure that the more optimistic vision prevails—not only for BPH, but for all benign urologic diseases.

Research Goals in BPH

To help address this challenge, Dr. McConnell identified a number of research needs and priorities for basic and clinical research on the prostate and on the bladder. For the prostate in general and BPH specifically, these include identifying and establishing genetics and biomarkers for disease susceptibility and predictors/assessors of response to therapy in BPH; the identification of new therapeutic targets; understanding the regulation of prostate growth (a "very urgent need"), understanding the bladder's response to obstruction in aging; and assessment of phytotherapies.

As Dr. McConnell pointed out, data gathered during the recently completed MTOPS trial provide key examples of gaps in knowledge that need to be filled in both basic prostate biology and BPH. The MTOPs trial was a large randomized clinical trial of over 3,000 men with BPH comparing the efficacy of two drugs that are currently used to treat the disease. The two drugs, finasteride and doxazosin, target different aspects of BPH pathology. Finasteride stops growth of and sometimes even shrinks the prostate. Doxazosin, on the other hand, is a so-called "alpha blocker" that targets alpha adrenergic pathways in prostate smooth muscle, decreasing the tension around the bladder and urethra that can interfere with normal urination. The landmark MTOPs trial demonstrated that using the two drugs in combination is much more effective at reducing the risk of progression of BPH than using each drug singly. It also showed that administering doxazosin alone over time (up to 5 years) does not significantly reduce the risk of acute urinary retention, or the complete inability to urinate. This indicates that "the alpha adrenergic-mediated smooth muscle tone is not the only story when it comes to the development of problems with urethral resistance, which is why men go into urinary retention."

Furthermore, the use of finasteride and similar drugs to "androgen ablate" the prostate does not reduce prostate size more than 13 to 16 percent, because the cells that respond to this treatment do not constitute the majority of the cells in the overgrown prostate tissue. The non-responsive cells, stromal cells, take up significant volume, but their biology is not well understood. According to Dr. McConnell, "as of today, we have no understanding of how that population of cells can be targeted for therapeutic intervention, and I think if I had to pick a single high priority area of research it would be that."

Research Goals in Bladder

The bladder is a balloon-shaped organ made of smooth muscle with a protective inner lining of specialized epithelial cells and proteins. But rather than being a simple sack that fills with urine and empties when appropriate, it is actually quite a complex organ. The NIDDK-led Bladder Research Progress Review Group, of which Dr. McConnell was a member, recently issued a strategic plan that is meant to guide current and future endeavors in bladder research. Dr. McConnell referred to the strategic plan and its delineation of research goals (see sidebar, "The Bladder Research Progress Review Group: A Strategic Plan for Bladder Research"), but also offered a summary of research needs. These include understanding the normal developmental biology of the bladder and the role that innervation

plays in determining the activities of bladder smooth muscle. Understanding the activity of bladder smooth muscle is especially important in bladder disease because "the common final pathway…for bladder failure, whether it is related to congenital anomalies,…obstruction, or infection, is a switch in the smooth muscle phenotype that leads these normally contractile cells to express large amounts of extracellular matrix (molecules)"—an inappropriate, pathological phenotype.

Other bladder research areas needing attention include understanding the normal biology of the epithelial cells lining the inner bladder wall; the impact of obstruction, aging, and inflammatory conditions on sensory pathways in the bladder that influence urination and contribute to pain; the development of mouse models for bladder disease and development—accompanied by the development of techniques and expertise that can be more readily applied to studying bladder function in such a small animal; and comparative studies of bladder function between men and women over the age spectrum to tease out problems common to aging versus problems due to differences in male and female anatomy. Finally, a high priority research need that affects all of these areas is the need for refinement and validation of tools and techniques used to assess the function of the lower urinary tract in humans.

Other Research Needs and Opportunities

In closing remarks, Dr. McConnell briefly touched on the role of advanced imaging technologies in the detection of urological disorders, noting that many people "go into urology actually because they have an interest in imaging," but also want to continue with direct patient care. In exciting new work, advanced imaging techniques such as magnetic resonance (MR) spectroscopy and positron emission tomography (PET) are being applied to looking at metabolic function of the bladder, detecting the presence or absence of prostatic disease, and to a variety of other lower urinary tract disorders.

He re-emphasized the need for research on urological organ replacement or substitution—primarily the bladder—as the best means to successfully combat congenital abnormalities and other pediatric and adult urological conditions. Tissue engineering, genomics, and stem cell research are all areas that hold promise for enabling clinicians to move beyond the limitations of reconstructive surgical repairs currently used for these conditions. The Bladder Research Progress Review Group has made specific recommendations in these areas as part of its strategic plan for bladder research.

Finally, he brought up androgen replacement—specifically, the administration of testosterone to men. The growing use of testosterone by men needs to be more closely examined for its long-term impact on health, as well as its true value as a therapeutic approach for men with borderline serum testosterone values. According to Dr. McConnell, "This really needs to be addressed. I think it will shortly become a major health issue."

"Push Complex Systems in the Right Directions"

Ultimately, Dr. McConnell proposed that in trying to "steer the future to some degree," it is useful to view the current state of the urology field as a complex system. If the "starting conditions" in such a system are appropriately adjusted and tweaked, down the road, the most positive outcomes may be realized. Thus, the NIDDK and its advisors may best influence the future of urology research by assessing the state of research and research needs, setting goal(s), providing research tools and funding, guiding the complex system of research relationships and research training in urology to obtain maximum productivity, and—perhaps most importantly—providing leadership. In this way, the NIDDK can continue to meet the challenge of ensuring an optimistic future in urology research and its ensuing clinical benefits for Americans suffering from urological disorders.

The Bladder Research Progress Review Group: Generating a Strategic Plan for Bladder Research

Diseases and conditions affecting the bladder and associated structures of the lower urinary tract are a leading cause of urinary incontinence, pelvic pain, and kidney failure, and they often contribute to poor quality of life. It has been estimated that 35 million Americans of all ages suffer from bladder disease and most have chronic conditions. Bladder problems have been reported to cost Americans more than $16 billion per year in health-related expenses, and this estimate does not take into account the associated physical and emotional disabilities that are considered "unmentionable" by many men, women, and children.

Significant basic and clinical advances in bladder disorders have been emerging more slowly than in other fields with similar disease burdens, such as diabetes and chronic kidney disease. Responding to this research gap, the NIDDK formed the Bladder Research Progress Review Group (Bladder Research PRG) in early 2000. This independent group of advisors consisted of scientists and medical professionals prominent in clinical and basic research and professional and lay organizations related to the bladder. They were asked to evaluate the research portfolios of NIDDK and NIH, identify research opportunities, and define unmet needs in bladder research The ultimate objective of the Bladder Research PRG was to develop a national "strategic plan" for bladder research—a document outlining goals and recommendations for future research and its implementation, to be used by the NIDDK, the NIH, and other entities as a guide for future initiatives.

From early 2000 to July 2001, the members of the Bladder Research PRG held discussions and intensive meetings to examine all areas of bladder-related problems categorized by diseases and by organ or tissue. Fourteen subcommittees focused their attention on specific bladder-related problem areas, including diabetes, muscle, development, inflammation/infection/interstitial cystitis, and clinical trials. The discussions and assessments performed by the Bladder Research PRG culminated in the report released in August 2002, *Overcoming Bladder Disease: A Strategic Plan for Research.* (http://www.niddk.nih.gov/fund/other/brprg_book.pdf).

In the report, the Bladder Research PRG identified four crosscutting priority areas in which strategic planning in bladder research will make important contributions to basic scientific knowledge and to the improved management and potential prevention of bladder diseases and conditions:

- **New technology-driven basic and clinical research,** to integrate advanced biotechnologies, such as gene microarray technology, into bladder research as has been successfully done for other organ systems and diseases.

- **Focused research for basic systems and disease,** to both improve management of and prevent bladder disorders and their complications, and to learn more about basic and abnormal bladder biology.

- **Epidemiology, outcomes evaluation, prevention, and bioethics,** to ensure the effective translation of basic research advances into clinical research to improve the diagnosis, treatment, and management of bladder disease.

- **Research infrastructure,** to provide greater support for programs, manpower training and technology (including information technology) in the area of the bladder.

These crosscutting strategic priorities emerged from the coordinated review of three overarching research areas: the basic science of the lower urinary tract, common clinical conditions, and methodologies and technologies for future research. The report presents a comprehensive summary of these areas, with specific goals and recommendations for each. The strategic plan will thus be invaluable in the development of research initiatives and in shaping the future of bladder research as a whole. Already, the NIDDK has responded to recommendations of the Bladder Research PRG in its development of two new research solicitations, one for basic research on the biology of the bladder, the other for basic research studies related to interstitial cystitis.

The work of the Bladder Research PRG will play an important part in efforts to reduce morbidity and mortality among those suffering from bladder-related diseases and disorders. As noted by Dr. Linda Shortliffe in the Letter from the Chair that introduces the report, "Advances in biomedical science and technology have opened the door for rapid and significant advances in bladder research that will improve the diagnosis, management, and prevention of bladder problems for many Americans."

PATIENT PROFILE

Kara Fishbein Goldman

Interstitial Cystitis

From left, Kara Fishbein Goldman and her twin sister, Beth. Both sisters are living with the bladder disease interstitial cystitis.

In 1994, when she was barely 20 years old and a student at the University of Pennsylvania, Kara Fishbein Goldman was diagnosed with interstitial cystitis or IC. She did not have too many symptoms of IC at that time, she says, but she had vulvodynia, chronic pain in the vulva, a symptom often associated with IC.

While Goldman was under anesthesia during treatment for the vulvodynia, her doctor dilated the bladder with sterile saline solution and used a cystoscope to visualize the bladder wall. He found areas of inflammation and pinpoint bleeding called glomerulations, which are characteristic of IC. Eventually, Goldman developed other symptoms of the disease—urinary frequency, urgency, and a burning sensation in the bladder—symptoms that she has experienced constantly for the past eight years.

Goldman describes her pain as feeling as though she has a bad bladder infection—a burning type pain that gets worse as her bladder becomes full—but "antibiotics don't cure it and other medications provide little relief," she says. "I feel like I have to (urinate) all the time, and it gets worse when the bladder is full. The pain is constant, but the severity varies."

Symptoms of IC vary from patient to patient, but they generally cluster around an urgent need to urinate; frequent urination both day and night; reduced bladder capacity; and feelings of pressure, tenderness, and pain around the bladder, pelvis, and genital area that may increase as the bladder fills.

"With IC, everybody is different. The pain presents in different ways in different people," Goldman explains. "Some have sharp pain, some have a burning sensation all the time where the inside of your body feels like it's on fire." She believes IC is more like a syndrome, a collection of symptoms. "Some people have some symptoms from the syndrome. Some people have other symptoms from the syndrome." In fact, Goldman's identical twin, Beth Fishbein, who developed IC a year after she did, has had milder symptoms. Currently in medical school, Fishbein is stabilized on a low dose of medication.

In some ways, Goldman and her sister were lucky. Their IC was diagnosed in the early stages, obviating the need to search for a diagnosis, a frustrating journey most people with IC are forced to undertake because many physicians are unfamiliar with the condition or because symptoms are often confused with other illnesses such as urinary tract infections. Even after IC has been diagnosed, many patients still have to search for new or different treatments that may help with their particular symptoms. In the year after her diagnosis, Goldman instilled a weekly "cocktail" of medications prescribed by

KARA FISHBEIN GOLDMAN

her physician into her bladder through self-catheterization. The bladder instillation included a local anesthetic, an antibiotic, and a steroid to reduce inflammation. This regimen kept her symptoms under control for about a year, but then the "cocktail" ceased to be effective, Goldman says, so she stopped it. Her pain gradually got worse, and became difficult to manage in the year before her wedding. She tried numerous oral medications, including tricyclic antidepressants, drugs that relax the bladder muscle, block pain, and have some effect on the body's allergic response, which appears to be involved in IC. Other drugs prescribed for her condition include a drug to relieve nerve pain; a drug that appears to augment the bladder lining; several pain medications; and drugs to relieve the bladder spasms that often accompany and worsen urinary urgency, frequency, and pain. All of the medications helped for only a little while, Goldman says, and a neurostimulation device implanted in the epidural space of her sacrum did not provide any relief.

Interstitial cystitis has no cure and no universal treatment; therefore, physicians must try several treatments to relieve symptoms. People with IC have responded to various therapies, but even so, a particular treatment may work only temporarily. Flare-ups and remissions also occur.

"The (pain medicine) doesn't ever make my pain go away," she says, "It just makes me tired and sleepy and less aware of myself." This creates a dilemma. She either works in pain or takes off and sleeps. During the workday, Goldman forgoes the pain medicine, but when the pain is severe, she takes off from work, takes the medicine, and sleeps. She says she's lucky because some people wake up from the pain; she does not. "There's nothing much I can do to make myself feel better," she says. "I'm either working or sleeping. I don't want to sleep the rest of my life." Goldman has tried to explain her illness to her students, co-workers, and friends to help them understand why she cannot function as well as she would like. She has had varying degrees of success. "People don't understand chronic pain," she says. "I look absolutely fine, and people can't see that I'm in pain. I'm not limping and I don't look particularly bad." In October 2001 and last spring, Goldman's pain was so severe she had to take quite a number of days off from her teaching job. "That year was really bad. I missed a lot of days of school, and I'm taking a leave of absence (this school term). This illness has affected my life in a big way," Goldman says, adding that she and her husband, Steve, had hoped to have children by now, but can't because of all the medications she's on.

Goldman says she feels fortunate to have an extremely supportive and caring spouse and parents, who have been very helpful in her often frustrating search for therapy that will ease her symptoms. In 1997, after realizing that scientists knew very little about IC, Goldman's parents, Bob and Laurie Fishbein, established the Fishbein Family Interstitial Cystitis Research Foundation, which endows pilot studies of IC. Goldman also acknowledges great support from the Interstitial Cystitis Association, which has provided her with information about IC and treatment options and has put her in touch with other people with IC.

So far, Goldman's search for effective treatment and pain relief has taken her to six gynecologists, three urologists, and two pain specialists in two states. She hopes that her yearlong leave from teaching will lead to better health and perhaps to the fulfillment of a long-delayed goal. "I want to be free to go wherever I need to go in the country to see consultants," she says. "I'll take it easy and try to feel better. Maybe if I can get off the drugs, I'll try to get pregnant…. I'll revise as I go. I'll keep trying different things."

STORY OF DISCOVERY

Cardiovascular Disease and Kidney Disease: Teasing Out the Link

Are two diseases related or just coincident? Sometimes the answer comes through careful analyses of large sets of numbers—numbers of patients and their associated risk factors. In the case of kidney disease and cardiovascular disease, such epidemiologic studies have pointed to a connection between end-stage renal (kidney) disease and risk of cardiovascular disease. Now researchers are faced with teasing out answers to the question: why?

The United States Renal Data System (USRDS), established in 1987, is a national data system that collects, analyzes, and distributes information about end-stage renal disease in the U.S., and is supported by the NIDDK in conjunction with the Federal Centers for Medicare and Medicaid Services. End-stage renal disease (ESRD) is a state of irreversible kidney failure in which a person requires either dialysis or a kidney transplant in order to stay alive. The USRDS has collected comprehensive data on over 92 percent of Americans with ESRD and releases an Annual Data Report every year; researchers can then analyze these data to discover emerging trends in both causes of ESRD and causes of death in ESRD patients.

A connection between ESRD and death due to cardiovascular disease (CVD) in a small number of patients on hemodialysis was noted nearly three decades ago. However, it is the careful analysis of patient data available in the USRDS database that has enabled researchers to recognize the enormity of the connection between patients requiring dialysis and their subsequent deaths from CVD. According to the latest Annual Data Report (2002), CVD (primarily coronary artery disease, left ventricular hypertrophy, atherosclerotic heart disease, and congestive heart failure) is the leading cause of death in ESRD patients. Studies using recent USRDS data revealed that death rates from CVD in dialysis patients are 20 to 40 times higher than in the general population, and an extensive retrospective study showed that 73 percent of dialysis patients who suffer a heart attack die within two years.

The figures for mortality due to CVD in ESRD are striking—and ominous. Groups at highest risk for developing ESRD include the estimated 17 million Americans with diabetes, the elderly, and ethnic and racial minorities, as well as people with hypertension, genetic renal disease, or a family history of renal disease. Determining the underlying relationship between kidney disease and CVD is not simple, however. The population at risk for developing CVD—independent of ESRD—is very similar to the population at risk for ESRD. In fact, some of the risk factors for CVD are indistinguishable from those for ESRD. Furthermore, researchers recently reported a higher prevalence of many traditional CVD risk factors in ESRD patients than in the general population.

Studying the USRDS numbers, epidemiologists realized that rates of pre-existing CVD in people initiating dialysis are very high, approximately 40 percent. This led researchers to suspect that CVD is developing during pre-ESRD states. Before ESRD, there is a prolonged state of progressive loss of renal function, referred to as chronic kidney disease. The degree of chronic kidney disease is established by measuring how efficiently the kidneys can filter out toxins from the blood, known as the glomerular filtration rate. When glomerular filtration rate decreases, bloodstream levels of a number of waste products increase. Small studies recently indicated that, just as

in ESRD, there are higher rates of death from CVD in people with chronic kidney disease. A recently launched prospective study, the "Chronic Renal Insufficiency Cohort," will assess risk factors for both the progressive decline in kidney function and the development of CVD in a large study population with chronic kidney disease. Through careful data analysis, the scientists aim to determine whether chronic kidney disease causes CVD or is simply associated with it.

Although defining the link between chronic kidney disease and risk factors for developing CVD awaits the outcome of large prospective studies, researchers can still test ideas as to how factors traditionally associated with decreasing kidney function—uremia-related factors—might in fact also lead to CVD. Basic research studies have contributed significantly to a number of hypotheses about how observed uremia-related factors might increase the risk of developing CVD, including the following:

Uric Acid: Uric acid is a waste product of nitrogen metabolism. It is normally present in the bloodstream, where it is thought to act beneficially as an antioxidant. However, impaired renal function can lead to uric acid levels that are too high, causing health problems such as gout. Elevated blood levels of uric acid may also be associated with a greater risk of heart disease, although the epidemiologic data are still under debate. A recent study in rats suggests a possible mechanism for uric acid's proposed role in CVD, showing that elevation of uric acid increases blood pressure and causes kidney injury. The human gene encoding the uric acid transporter responsible for uric acid recovery from the kidney tubules was recently identified by researchers in Japan; now, its activity in chronic kidney disease and ESRD can be tested.

Salt-sensitive Hypertension: There is evidence in animal models that subtle renal injury, induced by local inflammation and vasoconstriction, may interfere with normal salt excretion from the kidneys. Sodium dysregulation in particular may, in turn, raise blood pressure and further damage the kidney, initiating a vicious cycle, resulting in permanent salt-sensitive hypertension that promotes CVD.

Homocysteine: Homocysteine is a modified form of the essential amino acid methionine. Normal blood levels of homocysteine are maintained primarily by the activities of folic acid, vitamin B12, and vitamin B6. Deficiency in these vitamins can lead to hyperhomocysteinemia (high levels of homocysteine)—as can decreased glomerular filtration rate. Mild to moderate hyperhomocysteinemia appears to contribute to CVD outcomes in both the general population and persons with ESRD. Although successful in the general population, B-vitamin supplementation is not effective in lowering homocysteine in ESRD patients; however, it does normalize homocysteine levels in both renal transplant patients and mild chronic kidney disease patients. A study called FAVORIT is now testing whether high-dose supplementation with folic acid, vitamin B12, and vitamin B6 will improve CVD outcomes in chronic kidney disease patients and stable renal transplant patients.

As scientists develop testable hypotheses about how chronic kidney disease might induce CVD, they will be able to shore up epidemiologic data with mechanistic data to explain any observed link between these two conditions, and move towards possible prevention and treatment of CVD induced by chronic kidney disease. Through these efforts, future analysis of data from the USRDS will hopefully become the more optimistic task of documenting a steady reduction in cardiovascular disease-related mortality in patients with end-stage renal disease.

The National Kidney Disease Education Program (NKDEP)

Early in 2002, the NIDDK launched the National Kidney Disease Education Program (NKDEP), whose mission 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 10 to 20 million Americans suffer from reduced kidney function, also called chronic kidney disease, and nearly 400,000 must have either dialysis or a kidney transplant to stay alive. The number of people developing kidney failure has doubled each decade for the last two decades, and disease statistics indicate that this trend is likely to continue. One of the most common causes of kidney disease is diabetes, and the rates of both diabetes and kidney disease are increasing simultaneously.

Fortunately, kidney failure can be slowed, if not prevented. Evidence demonstrates that good control of blood sugar and blood pressure can reduce the risk of developing kidney disease. Low protein diets can also consistently lessen kidney disease progression. In spite of these advances in treatment and prevention, only a small number of those who most need it are receiving proper screening or treatment. NKDEP's mission is to get information on prevention and treatment to those who can most benefit from it.

Racial and ethnic minorities suffer a far higher incidence and prevalence of kidney failure than Caucasians. Rates of kidney failure 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 kidney failure in all of the aforementioned minority groups except for African Americans. High blood pressure-induced kidney damage is the primary cause of kidney failure in African Americans, with diabetic kidney disease running a close second.

The NKDEP message is targeted at doctors and other primary healthcare providers, at people at high risk for kidney disease—especially those with diabetes, hypertension and/or a family history of kidney failure—and at insurers and others responsible for paying for healthcare. Currently in its first phase, the NKDEP is recruiting volunteers to conduct educational campaigns for at-risk African Americans and health care providers in four pilot sites. The message focuses on identifying risk factors for kidney disease, screening those at risk, and providing appropriate treatment for those who are diagnosed with kidney disease. The four pilot sites are Baltimore, MD; Atlanta, GA; Jackson, MS; and Cleveland, OH. After completing campaigns in these sites, the NKDEP will be able to identify and refine successful strategies and launch a broader national campaign. In its next phase, NKDEP will target its message to American Indians, Hispanics and Latinos. The ultimate goal of this educational campaign is to reduce complications and death due to kidney disease and kidney failure among all Americans.

VISION STATEMENT

Robert Schrier, M.D.

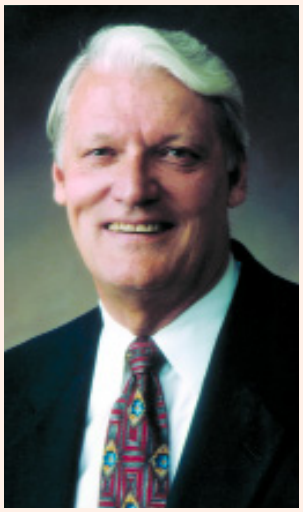
Kidney Disease Research: A Vision of the Future

Dr. Robert Schrier is Professor of Medicine at the University of Colorado School of Medicine. He has dedicated his research career to the study of both basic and clinical aspects of disease. Dr. Schrier has conducted extensive investigations of the molecular origins and causes of renal (kidney) failure and the mechanisms and pathways responsible for cell damage in this condition. His clinical research portfolio includes work examining the mechanisms responsible for kidney damage in people with diabetes, specifically on the role played by hypertension, the clinical term for high blood pressure. Additionally, Dr. Schrier is involved in a multi-institutional research project investigating hypertension in people with polycystic kidney disease, a particularly devastating genetic form of kidney disease. Dr. Schrier spoke at the September 2002 NIDDK National Advisory Council meeting about his vision of the future for kidney disease research.

Diabetes, Hypertension, and Kidney Disease

Type 2 diabetes affects about 8 percent of the U.S. population aged 18 and older and is strongly associated with obesity. Type 2 diabetes is also associated with aging, affecting 20 percent of Americans over 65 years of age. The current epidemic of obesity among Americans, coupled with the aging of the population, dramatically expands the number of people at risk of developing type 2 diabetes and its debilitating—and life-threatening—complications. This trend, if left unchecked, threatens to become a significant burden on the health care system in coming years.

Up to 65 percent of people with diabetes also have high blood pressure (hypertension), a condition that is associated with cardiovascular disease. Blood pressure is the force the blood exerts against the walls of arteries as it is pumped by the heart. High blood pressure is dangerous because it makes the heart work too hard and contributes to atherosclerosis (hardening of the arteries). It increases the risk of heart disease and stroke, as well as congestive heart failure, kidney disease, and blindness. Blood pressure is expressed as two values—the systolic pressure (as the heart beats) over the diastolic pressure (as the heart relaxes between beats). Blood pressure is measured in millimeters (mm) of mercury (abbreviated as its chemical symbol, Hg). "Normal" blood pressure is less than 135-140 mm Hg systolic and less than 85-90 mm Hg diastolic. "Optimal" blood pressure, which is associated with a reduced risk of heart disease, is less than 120 mm Hg systolic and less than 80 mm Hg diastolic. Blood pressure is usually presented as systolic/diastolic; for example, optimal blood pressure would be written 120/80 mm Hg and read as "120 over 80."



Dr. Robert Schrier

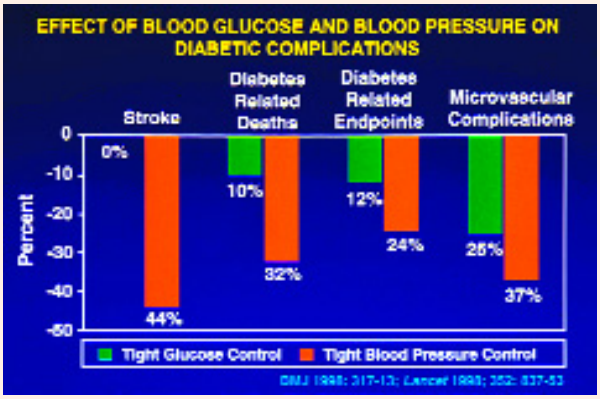
It is the vascular complications of diabetes that are responsible for the increased risk of heart disease, stroke, blindness, kidney failure, amputations, and premature death associated with the disease. Furthermore, both diabetes and hypertension are independent risk factors for cardiovascular disease, which is the leading cause of death in people with diabetes. Prolonged diabetes, in the presence or

absence of hypertension, is also associated with kidney disease, which can, if left unchecked, progress to irreversible kidney failure, a condition known as end-stage renal disease (ESRD). Once kidney function diminishes to less than 10 to 15 percent of normal, ESRD patients require regular dialysis or a kidney transplant to survive.

Clinical Trials of Blood Pressure Control in Diabetes and Kidney Disease

The growing epidemic of obesity, coupled with the aging of the population, taken together with the toxic combination of diabetes and hypertension, bodes ill for the future. "There is an epidemic of (type 2) diabetes, not just in this country but in the world," noted Dr. Schrier. The leading cause of death among people with diabetes is cardiovascular disease. However, Dr. Schrier pointed out that several major clinical trials have shown that tight blood pressure control can be very effective in preventing cardiovascular complications in people with type 2 diabetes. The challenge now is translating these basic and clinical research findings into effective therapies, and defining and meeting the new challenges of the future.

Dr. Schrier reviewed a number of large-scale clinical trials that examined the consequences of lowering blood pressure levels in people with diabetes. Many of these trials compared the difference between lowering blood pressure to certain levels versus lowering it further. The United Kingdom Prospective Diabetes Study (UKPDS) found that tight blood pressure control (144/82mm Hg) was more effective in preventing vascular complications than either less tight blood pressure control (154/87 mm Hg) or tight control of blood glucose (sugar) levels. Reviewing the results, Dr. Schrier notes that tight blood pressure control had a more positive impact on "stroke, diabetes-related death, diabetes-related end points, and even microvascular (complications)" than tight blood sugar control.



Results from the United Kingdom Prospective Diabetes Study demonstrate a greater beneficial effect of tight blood pressure as compared to tight blood sugar control on diabetes complications.

Similarly, the Hypertension Optimal Treatment (HOT) trial found that aggressive control of blood pressure (less than or equal to 80 mm Hg diastolic) was particularly beneficial in patients with diabetes. The Appropriate Blood Pressure Control in Diabetes (ABCD) study showed that diabetes patients with hypertension had significantly higher rates of kidney disease than patients with normal blood pressure, and that drug therapy with an angiotensin-converting enzyme (ACE) inhibitor was more effective in reducing cardiovascular events than a calcium channel blocker. Similar results were seen in the Heart Outcomes Prevention Evaluation (HOPE) study. All of these trials indicate that tight blood pressure control in people with diabetes can significantly reduce the likelihood of cardiovascular complications and death. They also suggest that improved blood pressure control may be more important as blood sugar control in reducing complications and death in people with diabetes.

Several trials have focused specifically on the role of blood pressure control in the development of kidney disease. As Dr. Schrier noted, "Nearly 50 percent of all ESRD is due to diabetes, and (this value) continues to climb." In the hypertensive cohort of the ABCD trial, patients with diabetes and high blood pressure, but no signs or minimal signs of

kidney damage, maintained their starting level of kidney function over a 5-year follow-up period. In contrast, patients with overt diabetic nephropathy (kidney disease), in whom there was clear evidence of kidney damage, steadily lost kidney function over 5 years irrespective of whether their blood pressure was normally or tightly controlled. According to Dr. Schrier, this finding underscores the importance of identifying these patients early, when prevention measures can still be effective at halting degeneration. "You have to get there early, if we're talking about prevention (of ESRD)," he says. "Otherwise, you may be just delaying the need for transplant and dialysis for two or three years."

Polycyctic Kidney Disease and Blood Pressure

Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous large, fluid-filled cysts in the kidneys. Over time, PKD cysts can slowly replace much of the mass of the kidneys, crowding and damaging the tissue and reducing kidney function, which can ultimately lead to ESRD. In the U.S., about 500,000 to 600,000 people have PKD and it is the fourth leading cause of kidney failure. There are two major, inherited forms of PKD: autosomal dominant PKD and autosomal recessive PKD. The autosomal dominant form accounts for nearly 90 percent of all PKD cases. Symptoms usually develop between the ages of 30 and 40, but they can begin earlier, even in childhood. About one-half of people with this form of the disease progress to ESRD. The autosomal recessive form of the disease is relatively rare, with symptoms beginning in the earliest months of life, even in the womb. "PKD is the fourth most common cause of ESRD," Dr. Schrier says, but "until 15 years ago, there was virtually no research on polycystic kidney disease." He adds, "Until the NIH focused on this disease."

As in patients with diabetes, people with PKD are particularly at risk for complications and progression to ESRD if they also have high blood pressure. In a study at the Heidelberg Outpatient Clinic, the percentage of patients with high blood pressure was significantly higher in those with the dominant form of PKD than in the general population, suggesting a correlation between PKD and hypertension. Furthermore, there is a correlation between the number and size of the cysts in the kidneys and the decline in renal function. PKD patients with hypertension progress to ESRD at a faster rate that those with normal blood pressure. Taken together, all of these factors add up to an ever-accelerating spiral, according to Dr. Schrier. "The larger the cysts, the larger the kidneys, the more hypertension, and the faster the progression to end-stage renal disease." Unfortunately, many patients with PKD are not treated until kidney damage has become irreversible.

But why do people with PKD have higher blood pressure to begin with? The answer to this question comes from insights into the molecular pathways cells use to "talk" to each other in the kidney. Researchers hypothesized that the ever-enlarging cysts in PKD stretch the blood vessels that line the cavities of the cysts. The compression of the blood vessels and resultant reduced blood flow result in damage to the kidney tissue. This damage activates a hormonal signaling system—the renin-angiotensin-aldosterone system—that has the end result of raising blood pressure. Studies led by Dr. Schrier have shown that this hormonal pathway is elevated in people with PKD, and that it correlates with the decline in kidney function over time, heart damage, and high blood pressure. Fortunately, aggressive control of blood pressure using ACE inhibitors (drugs that block the renin-angiotensin system) can reduce the progression of many of these complications.

However, recent clinical studies have suggested that "optimal" blood pressure (120/80 mm Hg) as opposed to blood pressure closer to normal values (in the range of 135 to 140 over 85 to 90) can have a dramatic effect on slowing the progression of patients with PKD to ESRD. "Focusing on research and education, we can do a better job controlling blood pressure," Dr. Schrier noted. The results of this recent focus have been dramatic: if one compares the period from 1985-1992 with the period from 1992-2001, the median age at which people with PKD progressed to ESRD rose from 53 to 63 years for men and from 57 to 61 years for women. This delay in the onset of ESRD means improvement in the quality of life of people with PKD. Dr. Schrier credited this improvement to better blood pressure control and the development of new drugs, such as ACE inhibitors, that make this control possible.

The Future of Basic and Clinical Kidney Research

As valuable as these clinical studies are, the importance of basic research—which lays the foundation of molecular knowledge upon which these trials stand—is also critically important. The NIH has an important role to play in both processes, Dr. Schrier says. "I think the NIH has had a major impact with respect to clinical studies and I would encourage the NIH to continue to do that."

Also of importance is the translation of these basic and clinical insights into changes in patient and physician behavior. To foster the translation of research advances into real-life improvements in the lives of patients, the NIDDK supports a number of education campaigns and information clearinghouses. The National Kidney and Urologic Diseases Information Clearinghouse increases knowledge and understanding about diseases of the kidneys and urologic system among people with these conditions and their families, health care professionals, and the general public. Pilot efforts of the National Kidney Disease Education Program aim to reduce morbidity and mortality from kidney disease by raising awareness about the seriousness of the problem and the importance of prevention, early diagnosis, and appropriate management (see sidebar, "The National Kidney Disease Education Program").

However, Dr. Schrier acknowledged that the expense of clinical trials—and translation of the results—can sometimes be an impediment to progress. In concluding remarks, he stressed the importance of building partnerships between the public and private sectors. "Given the cost of these trials and the industry interest in this area—with appropriate guidelines—this relationship can be supported and progress made," he said.

DR. WILLEM KOLFF AND DR. BELDING SCRIBNER

Two Pioneers in Dialysis Share the 2002 Albert Lasker Award for Clinical Medical Research

Willem J. Kolff, M.D., Ph.D., currently is Distinguished Professor Emeritus at the University of Utah School of Medicine in Salt Lake City. He previously was Head of the Division of Artificial Organs, and was Professor of Surgery, Research Professor of Engineering, and Director, Institute of Biomedical Engineering, at the University of Utah. Dr. Kolff invented the artificial kidney and dialysis technique in his native Holland before emigrating to the United States in 1950. In the course of his research on dialysis at the Cleveland Clinic in the early 1950s, he became involved in development of an artificial heart. Under his leadership in the late 1960s, the University of Utah's Division of Artificial Organs developed and tested an improved artificial kidney system that included the dialyzer and ancillary components. The major goal of the new design, developed under an NIAMD contract (see following text), was to produce an artificial kidney system that was efficient, easy, and safe to operate, and whose cost of manufacture was lower than the available systems. Under Dr. Kolff's leadership, the University of Utah developed as one of the world's leading artificial organ research centers. In 1982, under his supervision, the first fully artificial heart was implanted in a human patient, Dr. Barney Clark.

Belding Scribner, M.D., Professor Emeritus of Medicine at the University of Washington, pioneered the use of dialysis for patients suffering from kidney disease by inventing, in 1960, a shunt that could be hooked up to a dialysis machine. Also, through Dr. Scribner's investigations, the minimum level of adequate dialysis was established, lowering dialysis times previously standardized at 24-27 hours per week to 15-16.5 hours per week. In addition, Dr. Scribner established that dialysis schedules in the future would need to be individualized, taking into consideration clinical parameters such as body size, residual renal function, and dialysis frequency.

In 2002, Drs. Willem Kolff and Belding Scribner were the honored recipients of the Albert Lasker Award for Clinical Medical Research for their pioneering research on development of hemodialysis as treatment for acute and chronic kidney failure. Dr. Scribner was a grantee of National Institute of Arthritis and Metabolic Diseases (NIAMD), a forerunner to the present NIDDK, and Dr. Kolff was awarded numerous research and development contracts from the NIAMD.

When the NIDDK was established in 1950, medicine lacked any proven treatments to control end-stage renal disease (ESRD), and individuals with ESRD faced certain death. With the advent of effective kidney dialysis and transplantation, however, most chronically ill kidney patients no longer are confronted with such a dire prognosis. In fact, kidney dialysis alone has saved hundreds of thousands of lives.

Recipients of NIDDK awards have contributed significantly to the developments in kidney hemodialysis that have produced substantial benefits for ESRD patients. The earliest of these was Dr. Scribner's discovery in 1960 that a "no-stick" Teflon shunt—an artery-penetrating device that connects a vein to an artery—prevents the development of blood clots during dialysis. This was the first major breakthrough in hemodialysis. This simple but revolutionary idea provided the basis for regular and safer kidney dialysis, because without the threat of clotting a shunt could be left in place for multiple uses. Before this, patients received dialysis infrequently, because minor surgery was required before each treatment to re-

DR. WILLEM KOLFF AND DR. BELDING SCRIBNER

attach the necessary devices to veins and arteries. Although the shunt would later be replaced with the arteriovenous fistula* and synthetic graft, this reusable vascular access technique made it possible for the first time to keep patients with ESRD alive indefinitely.

Dr. Kolff reported the first successful dialysis to treat kidney failure in 1945. This was an extraordinary achievement and established the principle that cleansing the blood by passing it over a semi-permeable membrane could replace the function of failing kidneys. In its first applications, its use was limited to people who had temporary kidney failure, in part because punctures to remove and cleanse the blood irreparably damaged the vessels after fewer than a dozen times. Subsequently, with support from the NIAMD, Dr. Kolff and his colleagues designed a more-efficient, safer, and less expensive dialysis machine.

"Studies by Kolff and Scribner, funded by NIDDK, were pivotal in developing technologies that transformed dialysis from the realm of experimental possibility to effective and accepted clinical practice," said Josephine P. Briggs, M.D., Director of the NIDDK's Division of Kidney, Urologic, and Hematologic Diseases. "We are delighted that their critical contributions have been recognized."

Although kidney dialysis is an extremely successful therapy, it is of course no substitute for the healthy kidneys with which most individuals are born. For this reason, NIDDK scientists and grantees continue to explore the basic mechanisms of kidney function and disease with the aim of learning how to prevent ESRD. But, until the day that our understanding of abnormal kidney function dictates that no one ever need lose a kidney to disease, most of the millions of Americans who today suffer from irreversible kidney disease can rest assured that because of biomedical research, their disease does not mean certain death.

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

NIDDK Contributions to Dialysis

Dialysis as a practical treatment for kidney failure has evolved over centuries and continents. Many have played a role in developing this medical technology, starting with Thomas Graham of Glasgow, who first presented the principles of solute transport across a semipermeable membrane in 1854. Nearly 100 years later, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), originally called the National Institute of Arthritis and Metabolic Diseases (NIAMD), was established as part of the National Institutes of Health (NIH). Almost from the start, the NIDDK was committed to supporting research to combat kidney failure. Recently, investigators responsible for early advances in hemodialysis research were recognized with a major national award.

Willem J. Kolff, M.D., Ph.D., and Belding H. Scribner, M.D., shared the 2002 Albert Lasker Award for Clinical Medical Research for their pioneering work on chronic hemodialysis, a life-saving treatment for kidney failure. Their studies were funded in the late 1960s and early 1970s by the NIAMD.

Kolff reported the first successful dialysis to treat kidney failure in 1945. This was an extraordinary achievement and established the principle that cleansing the blood by passing it over a semi-permeable membrane could replace the function of failing kidneys. In its first applications, its use was limited to people who had temporary kidney failure, in part because punctures to remove and cleanse the blood irreparably damaged the vessels after fewer than a dozen times. But subsequent research by Kolff and Scribner led to a number of further advances that revolutionized the treatment, broadening its use to people who had permanent kidney failure. Funded by NIDDK, Kolff and his colleagues designed a more-efficient, safer, and less expensive dialysis machine, and Scribner and his team invented the first permanent device, made from Teflon, that allowed repeated, long-term access to the blood stream without piercing the vessels each time. Through his NIDDK-supported work on the diffusion of molecules through dialysis filters, Dr. Scribner also established minimum dialysis times and developed data needed to tailor treatment to the needs of individual patients.

The United States Renal Data System

Continuing its commitment to advance knowledge about ESRD, the NIDDK, in cooperation with the then Health Care Financing Administration, established the United State Renal Data System (USRDS) in 1987 to provide more extensive epidemiologic and demographic information for scientific purposes. The original mandate of the USRDS included four goals: (1) characterize the total population of renal patients and describe their distribution by sociodemographic variables across treatment modalities; (2) report on incidence, prevalence, and mortality rates and trends over time; (3) develop and analyze data on the effect of various treatment modalities by disease and patient group; and (4) identify problems and opportunities for more focused special studies of renal concerns. In 1992, two more goals were added: (5) conduct cost-effectiveness studies and other economic studies of ESRD and (6) support investigator-initiated projects to conduct biomedical and economic analyses of patients with ESRD. The USRDS has published an *Annual Data Report* every year since 1989 and has conducted a large series of special studies.

Beyond invaluable trend data, USRDS has had practical clinical implications, such as comparisons of outcomes of hemodialysis *vs.* peritoneal dialysis patients, peritonitis incidence by CAPD (chronic ambulatory peritoneal dialysis) connection technique, the role of dialysis efficiency on mortality risk in hemodialysis patients, and the role of histocompatibility antigen matching on kidney graft survival, to name only a few examples.

NIH Consensus Conference on the Morbidity and Mortality of Dialysis

In 1993, NIDDK sponsored a consensus conference on the morbidity and mortality of dialysis. Experts in general medicine, nephrology, pediatrics, biostatistics, and nutrition reviewed the available scientific data to develop a series of recommendations addressing several issues, specifically predialysis therapy, quality of life for patients with ESRD, quantitative evaluation of dialysis dose and adequacy, reasons for underdialyzing, cardiovascular complications, malnutrition, and research opportunities. The recommendations included a call for a minimum adequate dose of dialysis (a recommendation that would be repeated a few years later by the National Kidney Foundation's Dialysis Outcomes Quality Initiative) and clinical trials to explore whether a higher dialysis dose would result in even more favorable outcomes.

The HEMO Study

Following the consensus conference, the NIDDK initiated the multi-center HEMO clinical trial testing whether a higher hemodialysis dose or high-flux membranes or both would reduce mortality and morbidity, a hypothesis that evolved from Willem Kolff's work of nearly 60 years ago. The full-scale phase of the trial began in July 1994 with a data center and 15 participating clinical centers. The final results of this trial have just been reported; based upon the results, the investigators have concluded that these more intensive dialysis treatments do not, on average, provide any more benefit to patients as measured by patient survival.

The Hemodialysis Vascular Access Clinical Trials Consortium

The NIDDK has launched a new initiative that relates directly to Belding Scribner's early work on the Teflon shunt for vascular access. In 1998, NIDDK sponsored a workshop on Critical Issues in the Care of the Dialysis Patient. The workshop focused on nutrition and vascular access, which is often called the Achilles heel of hemodialysis because vascular access problems can lead to treatment failure. One recommendation that emerged from the workshop was to support basic investigations and clinical trials that explore ways to prolong the life of two types of vascular access ports, arteriovenous grafts and fistulas. In September 2000, NIDDK awarded grants to a consortium of institutions to conduct vascular access clinical trials. The consortium will conduct a series of multi-center, randomized, placebo-controlled clinical trials of drug therapies to reduce the failure and complication rate of arteriovenous grafts and fistulas in hemodialysis. Recently developed antithrombotic agents and drugs to inhibit cytokines will be rigorously evaluated in these large clinical trials.

Clinical Trial on Frequent Dialysis

A strong interest has developed throughout the renal community in the potential of intensified dialysis regimens, either slow nocturnal or short daily dialysis, to improve patient outcomes—a further refinement of Willem Kolff's original concept of improving the efficiency and effectiveness of dialysis treatment. Increasing dialysis frequency has a number of theoretical advantages as a strategy to improve dialysis dose, since clearance of accumulated toxins is greatest early in a dialysis run. In a small number of sites, with highly selected patient groups, markedly improved patient rehabilitation, better control of plasma phosphate and reduced erythropoietin requirements have been reported with more frequent dialysis.

In collaboration with the former Health Care Financing Administration, now the Centers for Medicare and Medicaid Services, the NIDDK organized an intensive two-day planning meeting in 2001 of dialysis experts to explore the feasibility of a randomized trial or observational studies of these new treatment strategies. Experts at the meeting were in general strongly supportive of the need for careful evaluation of these new therapeutic approaches. The feasibility of a randomized trial was discussed extensively; most meeting participants were strongly supportive of the need for the kind of rigorous evaluation only possible with randomized participants.

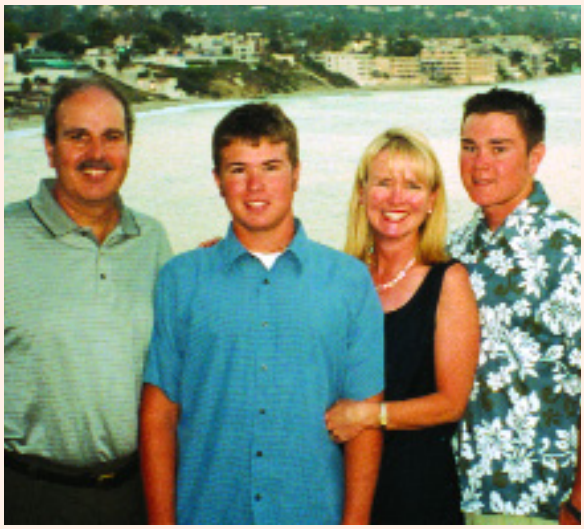
In December 2002, the NIDDK issued a Request for Applications (RFA) for cooperative agreement applications for a Data and Analysis Coordinating Center and two Coordinating Clinical Centers to design, develop and implement clinical treatment trials of frequent hemodialysis for patients with ESRD. The centers will propose trial designs for the studies. It is anticipated that two trials will be initiated, one comparing short daily hemodialysis with conventional dialysis and one comparing long nocturnal dialysis with conventional dialysis. The goal of the RFA is to test the feasibility of randomizing a representative sample of dialysis patients into either (a) conventional three times per week dialysis, or (b) slow nocturnal or short daily dialysis, and to obtain preliminary data on the impact of these modalities on patient well-being. It is expected that patients will be followed for a minimum of six months and that intermediate outcomes will be tracked, such as anemia, nutritional status, blood pressure, left ventricular hypertrophy, exercise tolerance, medication use, and hospitalizations. Based on the results of these trials, NIDDK will determine the advisability of continuing with a large scale trial of daily dialysis, powered to measure the impact of more frequent dialysis on hard endpoints, such as mortality and/or cardiovascular outcomes.

Advances in the treatment of kidney failure have come from many sectors, including private industry, educational institutions, and hospitals. The NIDDK has provided support and direction for much of the research that has led to incremental improvements and major breakthroughs in dialysis, and continues to look for ways to improve treatment and enhance quality of life for people with chronic kidney failure.

PATIENT PROFILE

Timothy Hawkins

Vesicoureteral Reflux



The Hawkins family (Tim, second from left). Tim has undergone two major surgeries to treat vesicoureteral reflux. Describing life since his surgery as "fairly normal," Tim is now attending college in California.

At the age of 18, Timothy Hawkins doesn't remember much about the pain and discomfort he experienced as a little boy, when he was frequently sick. His mother, Mary Pat, says he suppresses that memory because "he went through a lot." What Tim does remember is as follows: Going to the bathroom and seeing "all these lumps of things in my urine." Having high fevers and going in to the doctor's office and hospital for numerous tests—"ultrasounds and a VCUG" or voiding cystourethrogram, a diagnostic test that involves threading a catheter through the urethra, filling the bladder to maximum capacity with a radiographic dye solution, and following the flow of urine on x-ray as the child voids. Taking antibiotics every day between the ages of three and five to prevent kidney infection and to preserve kidney function. Going into the hospital with his parents for surgery when he was five years old for the removal of his right kidney. And having bad dreams after surgery that he thinks were caused by "the pain killers I took."

"My right kidney was deteriorating because I had reflux," Tim says. "The urine backed up into both my kidneys, but the right one was worse. When I was in kindergarten the right kidney had to be removed." Vesicoureteral reflux is the abnormal flow of urine from the bladder back into the ureter(s) and kidney(s). It is the most common cause of kidney failure in children and is usually diagnosed when a urinary tract infection or UTI occurs.

About one-third of children with UTI have reflux, which can occur from primary or secondary causes. Primary reflux occurs during fetal development when the tunnel in the bladder wall where the ureter inserts fails to grow long enough, thereby preventing the valve that forms at that juncture from closing properly. This permits backflow of urine and bacteria into the ureter(s) and even the kidney(s). Secondary reflux occurs as the result of conditions such as posterior urethral valves which obstruct the urethra, or bladder infection that causes swelling.

Tim's mother has more vivid memories of those years. She describes Tim's fevers, which were also caused by ear infections, as "raging" and frequent, and remembers putting him in a tub of tepid water to bring them down. She remembers her son telling her at the age of three that "sometimes poop comes out from where I pee" and the horror she felt when she saw dark lumps in the bottom of the toilet bowl after he urinated standing up. She remembers the anger and frustration she felt toward Tim's pediatrician when he told her over the phone that she was probably over-reacting and that she should give her son cranberry juice.

TIMOTHY HAWKINS

"Neither Tim's pediatrician nor the emergency room physicians took a urinalysis to see if the problem was caused by a urinary tract infection, a sign of reflux," Mary Pat says "A urinalysis is now done routinely when a child has a high fever."

She also remembers her father, a physician, urging her to ask Tim's doctor to perform an ultrasound to visualize Tim's urinary tract, and she remembers making an urgent phone call to her sister-in-law, a radiologist, to ask her to find someone who would do this when Tim's physician said it was unnecessary.

Mary Pat and her husband Jim soon decided that they needed to consult a pediatric urologist at a major medical center. "She placed Tim on continuous antibiotic therapy to see if his kidneys would heal," Mary Pat explains. Antibiotic therapy usually corrects secondary reflux caused by infection, and it prevents further damage if the cause is primary, that is, genetic.

Many children also outgrow reflux. During a period of "watchful waiting" to see if this would occur, Tim was monitored at intervals with urinalyses, ultrasounds, and VCUGs. However, when he was five years old, it became obvious that the right kidney was not going to heal, and it had to be removed.

By age nine, Tim's urologist determined that his reflux was primary and that it had not improved in the left ureter. Re-implantation of the ureter was now necessary because his urologist feared that in time it would cause further damage to his remaining kidney. The surgery involved lengthening the canal in the bladder wall where the left ureter inserts and then re-implanting the ureter.

Tim describes his life since his surgery as "fairly normal." He graduated from high school last June and is currently enrolled at Santa Clara University in California. Although he has not been able to play contact sports since his first surgery because of the risk of injury to his remaining kidney, he has found other outlets for his interest in sports. He played Little League baseball for a few years, learning to bat left handed so that if he were hit by a wild pitch, the side that doesn't have a kidney would absorb the impact. But when the pitches got faster, he decided it was time to drop out. In high school, he took up golf, which he has grown to love, and has played on his school team. "I sometime wish I could play football, though, but that's not an option," he adds.

Tim has been monitored with ultrasounds periodically to see if his remaining kidney is growing. "It grows larger to make up for the kidney that was removed," he explains. He recently had an MRI to check on scarring in that kidney. "Everyone has a little scarring. It can occur when you hold back going to the bathroom," he says. "But I'm more susceptible to it because of the reflux."

Recently, one of Tim's younger cousins was discovered to have reflux after he developed bladder control problems and side pain. At the age of six, the cousin's ureter was reimplanted. Because of the familial implications, Tim has begun to think about what a genetic disease will mean for his children.

"My doctor says that some reflux is genetic and there's a good chance that my kids would have the same problem with reflux," he says. "Maybe by doing research, doctors could test my kids before they develop problems or even before they're born so that they don't develop scarring and high blood pressure or lose a kidney."