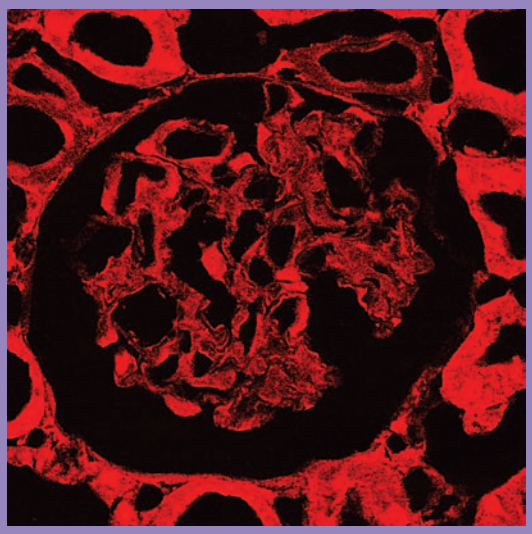
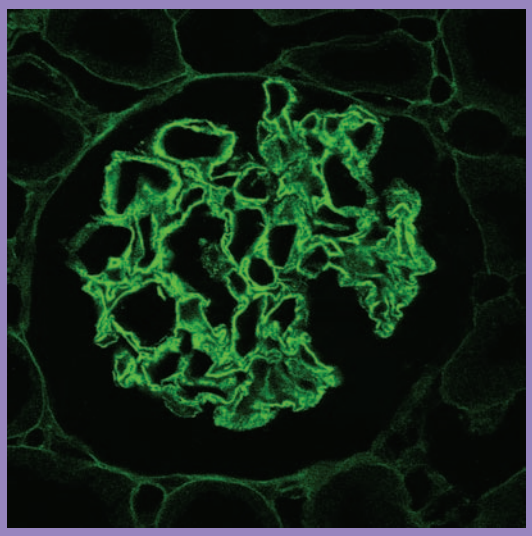
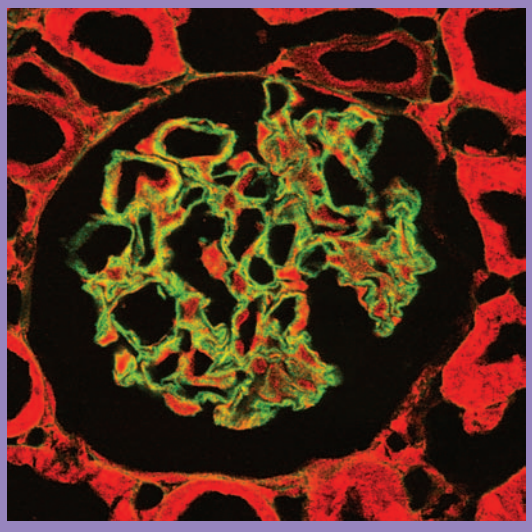






Using multiple antibodies linked to different fluorescent molecules, scientists can determine the location of various proteins with great specificity and high resolution. These three images show the pattern of expression of the protein TRPC6 in mouse kidney. The structure at the center of each image is one of the critically important filtering units of the kidneys, a glomerulus. Within these filtering units, TRPC6 is found primarily in a subpopulation of cells called podocytes. Red fluorescent antibodies (top) detect expression of TRPC6 in two types of cells in the glomerulus and in the surrounding tubules. Green fluorescent antibodies (middle) detect synaptopodin, a protein specific to podocytes. When the fluorescence of both antibodies is seen together (bottom), the combined fluorescent pattern is yellow, confirming that TRPC6 expression within the glomerulus is confined largely to podocytes.

Image courtesy of Dr. Martin R. Pollak and reprinted with permission from Reiser et al. Nat Genet 37: 739-744, 2005.

Kidney, Urologic, and Hematologic Diseases

Diseases of the kidneys, urologic system, and blood are among the most critical health problems in the U.S. They afflict millions of Americans, including children and young adults. The NIDDK is committed to enhancing research to understand, treat, and prevent these diseases.

Normal, healthy kidneys process about 200 quarts of blood a day to filter out about two quarts of waste products and extra water, excreting them as urine. In people with chronic kidney disease, the function of these life-sustaining organs is impaired. Kidney disease may progress to irreversible kidney failure, a condition known as end-stage renal disease (ESRD). People with ESRD require dialysis or a kidney transplant to live. Between 1990 and 2000, the number of people with kidney failure requiring dialysis or transplantation more than doubled, to 380,000. The leading cause of kidney disease is diabetes, with hypertension (high blood pressure) the second-leading cause. If unchecked, the recent increases in obesity and type 2 diabetes in the U.S. will have grave implications in several years, as more people begin to develop kidney complications of diabetes.

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

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

Urologic diseases affect men and women of all ages, result in significant health care expenditures, and—if misdiagnosed or improperly treated—may lead to substantial disability and impaired quality of life. The NIDDK's urology research portfolio includes basic and clinical research on the normal and abnormal development, structure, and function of the genitourinary (GU) tract. The NIDDK also supports studies of a number of noncancerous urologic diseases, including benign prostatic hyperplasia, prostatitis, urinary tract infections, urinary tract stone disease, interstitial cystitis, urinary incontinence, and congenital anomalies of the genitourinary tract.

Benign prostatic hyperplasia, or BPH, is a serious condition that is especially common among older men. Prostatitis—chronic inflammation of the prostate gland—is a painful condition that accounts for a significant percentage of all physician visits by young and middle-aged men for complaints involving the genital and urinary systems. The NIDDK is committed to enhancing research to understand, treat, and prevent these common and troubling disorders.

Infections of the urinary tract are extremely common in women, and many women suffer repeated urinary tract infections (UTIs). Interstitial cystitis (IC) is a debilitating, chronic, and painful bladder disease. The number of individuals suffering with IC is not known with certainty, but it has been estimated as many as 1 million Americans may have the disease, and of those, up to 90 percent are

women. Millions of Americans, most of them women, suffer from urinary incontinence. Kidney stones, a condition formally known as urolithiasis or urinary tract stone disease, is a frequent cause of visits to health care providers. One of the most common causes of kidney failure in children is vesicoureteral reflux. In fact, abnormalities of the genitourinary tract are among the most common birth defects.

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

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

CHRONIC KIDNEY DISEASE AND HEART DISEASE

Cardiovascular Mortality Risk in People with Chronic Kidney Disease: Elderly people with chronic kidney disease have a substantial risk of dying from cardiovascular disease (CVD). The Cardiovascular Health Study, involving a group of elderly men and women with a high prevalence of chronic kidney disease, has underscored the importance of combating "traditional" risk factors among this population. These factors include high blood pressure, diabetes, obesity, smoking, and left ventricular hypertrophy (enlargement of the lower left chamber of the heart, usually caused by high blood pressure). "Novel" risk factors for CVD, including markers of inflammation and prothrombotic factors (molecules that promote blood clotting) were also examined. Examining six traditional risk factors and six novel risk factors for CVD, researchers found that, in patients with chronic kidney disease, traditional risk factors were associated with the largest increases in CVD death and that the increases associated with the novel factors were smaller and not statistically significant. These findings suggest that interventions that target traditional risk factors—blood pressure control, blood sugar control, smoking cessation, and increased physical activity—may have the greatest potential to reduce CVD mortality in this high-risk population.

Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, and Psaty B: Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA *293: 1737-1745, 2005.*

MOLECULAR FACTORS UNDERLYING KIDNEY DISEASE

An Ion Channel Plays a Role in Kidney Disease: Focal segmental glomerulosclerosis (FSGS) damages the filtering units of the kidneys, thereby allowing protein and sometimes red blood cells to leak into the urine. Many patients with FSGS progress to end-stage renal disease. The ion channel encoded by the *TRPC6* gene is thought to be an important contributor to the kidney damage seen in this disease, but its role has been unclear. In one recent study, researchers studying a large family with hereditary kidney disease identified a mutation in the *TRPC6* gene, which results in a protein with altered subcellular distribution that is hypersensitive to stimulation. In a second study, researchers described in fine detail the subcellular localization of the normal protein encoded by the gene within the kidney filters and identified a number of important structural proteins with which the gene interacts. They then identified five families with hereditary kidney disease, and found each had a different mutation in this gene. When expressed in cultured cells, two of these five mutants resulted in increased ion flow across the cell membrane—suggesting that the mutant proteins may alter normal functions in the kidney filters. These

two advances identify a novel mechanism for the kidney damage seen in FSGS. The development of agents that target the mutated TRPC6 protein may be a useful strategy in the treatment of chronic kidney disease.

Reiser J, Polu KR, Moller CC, Kenlan P, Altintas MM, Wei C, Faul C, Herbert S, Villegas I, Avila-Casado C, McGee M, Sugimoto H, Brown D, Kalluri R, Mundel P, Smith PL, Clapham DE, and Pollak MR: TRPC6 is a glomerular slit diaphragm-associated channel required for normal renal function. Nat Genet 37: 739-744, 2005.

Winn MP, Conlon PJ, Lynn KL, Farrington MK, Creazzo T, Hawkins AF, Daskalakis N, Kwan SY, Ebersviller S, Burchette JL, Pericak-Vance MA, Howell DN, Vance JM, and Rosenberg PB: A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. Science 308: 1801-1804, 2005.

Signaling Pathways in Kidney Fibrosis: New research clues could lead to prevention strategies for a major cause of kidney damage—the scarring of kidney tissue (fibrosis). Insights are emerging about bone morphogenic proteins (BMPs), which not only induce bone formation, but also play an important role in embryonic development. One of these proteins, BMP-7, is key to the development of the kidney. Signaling by BMPs is mediated through cell surface receptors. Their activity is known to be inhibited by proteins, such as chordin and noggin, that prevent them from binding to their receptors. Scientists have now identified another BMP-binding protein, called KCP, which is similar in structure to chordin, but which enhances BMP-7 activity. Found in embryonic brain, limb buds, and kidney, this protein seems to have its enhancing effect by promoting the binding of BMP-7 to its receptor. Using two animal models of kidney damage, researchers found that mice lacking KCP were more susceptible to kidney damage. In one model, these mice also had a significantly higher death rate and a more problematic recovery compared to normal mice. Kidney fibrosis is a common clinical feature of many forms of chronic kidney disease, and it can contribute to irreversible kidney failure. Thus, enhancing BMP signaling with KCP-like agents may have important clinical implications.

Lin J, Patel SR, Cheng X, Cho EA, Levitan I, Ullenbruch M, Phan SH, Park JM, and Dressler GR: Kielin/chordin-like protein, a novel enhancer of BMP signaling, attenuates renal fibrotic disease. Nat Med 11: 387-393, 2005.

COSTS OF KIDNEY STONES

Kidney Stones: A Growing Health and Economic Burden: Researchers are gathering data about the natural history and economic impacts of kidney stones, also known as urolithiasis, which are solid masses formed from minerals that are dissolved in urine. Kidney stones are an increasing problem in the U.S., and the recurrence rate of kidney stones has been estimated to be as high as 50 percent at 5 years. Treatment of kidney stones may require physician visits, hospitalizations or surgical interventions. Between 1994 and 2000, the number of hospitalizations and the average length of hospital stays for urolithiasis decreased 15 percent. However, due to the emergence of less invasive treatment options, the number of outpatient visits increased by 40 percent and physician office visits increased 43 percent between 1992 and 2000. Overall, kidney stone-related expenditures rose 50 percent from 1994 to 2000, with an annual total cost of $2.1 billion, despite a shift from costly inpatient procedures to less expensive outpatient procedures.

Pearle MS, Calhoun EA, and Curhan GC: Urologic diseases in America project: urolithiasis. J Urol 173: 848-857, 2005.

KEY EVENTS IN PROPER URINARY TRACT DEVELOPMENT

Insights into the Development of the Urinary Tract: Congenital malformations of the urinary tract are among the most common of all birth defects, and can cause renal failure and the need for dialysis or transplantation. Researchers have identified a previously unknown key event in urinary tract development that will aid in understanding the developmental process. Complete and efficient removal of toxic substances from the blood depends on tight connections among the kidneys, bladder, and interconnecting tubules called ureters. During embryonic development, one end of the ureter is attached to the nascent kidney and the other end is joined to the developing bladder through a structure called the common nephric duct (CND). The CND disappears during development. Previous models of ureter development posited that the CND underwent tissue remodeling and became a different structure. Scientists have now found that the CND is in fact lost during urinary tract development through a process of programmed cell death. The death of CND cells is dependent on signaling by vitamin A. Loss of the

CND is critical for the formation of the essential tight connection between the ureter and the bladder. This novel finding, which contradicts the previous model of ureter development, provides a new way to approach the biology and genetics of urogenital tract formation.

Batourina E, Tsai S, Lambert S, Sprenkle P, Viana R, Dutta S, Hensle T, Wang F, Niederreither K, McMahon AP, Carroll TJ, and Mendelsohn CL: Apoptosis induced by vitamin A signaling is crucial for connecting the ureters to the bladder. Nat Genet 37: 1082-1089, 2005.

UNDERSTANDING HEMATOLOGIC DISEASE

Insights into Hereditary Hemochromatosis: An important connection has been identified between two molecules involved in maintaining the delicately balanced metabolism of iron. Hemochromatosis is a disease in which abnormal iron metabolism results in the accumulation of toxic iron levels—termed iron overload—that eventually damages the liver, heart and other organs. Recent studies to combat this problem have focused on the hormone hepcidin, which is known to be a key player in the regulation of iron metabolism. Although deficiency in hepcidin has been implicated in some forms of hereditary hemochromatosis, the precise mechanism for hepcidin regulation of iron levels was not known. Scientists recently identified the protein ferroportin (Fpn), an iron exporter on the surface of some cells, as a receptor for hepcidin. In cell cultures, the binding of hepcidin to Fpn resulted in internalization and degradation of the complex, thereby preventing iron export by Fpn. Because Fpn exports iron absorbed by intestinal cells into the circulation, hepcidin-mediated destruction of Fpn may be key to regulating the dietary iron equilibrium. Researchers then studied several mutations in the Fpn gene that are linked to one type of hereditary hemochromatosis, and found that they either produced a protein that never arrives at the cell surface or one that does not internalize and degrade in the presence of hepcidin. Taken together, these findings suggest that loss of hepcidin regulation of Fpn levels—caused either by Fpn mutations or by deficiency in hepcidin—could explain, at least in part, the abnormal iron accumulation observed in hemochromatosis patients. A fuller understanding of the hepcidin-Fpn pathway in iron regulation will help to provide the foundation for future research aimed at treating or preventing iron overload disorders.

De Domenico I, Ward DM, Nemeth E, Vaughn MB, Musci G, Ganz T, and Kaplan J: The molecular basis of ferroportin-linked hemochromatosis. Proc Natl Acad Sci U S A 102: 8955-8960, 2005.

Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, and Kaplan J: Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 306: 2090-2093, 2004.

U.S. Kidney Failure Rates Stabilize, Ending a 20-Year Climb, but Troubling Racial Disparities Persist

According to new data released by the NIDDK-supported United States Renal Data System (USRDS), rates for new cases of kidney failure have stabilized after 20 years of five to ten percent annual increases. Decreases have been noted each year for the last four years, and epidemiologists are now convinced these trends reflect consistent changes in the rate of disease. The good news is accompanied by bad news, however, since racial disparities in the rates of end-stage renal disease persist.

In 2003, the rate for new cases of kidney failure was 338 per million people, down slightly from 2002 and continuing a four-year trend. This has permitted researchers to be cautiously optimistic that rate decreases have not happened by chance. The average annual increase has been less than one percent since 1999, compared to five percent or more each year in the previous two decades.

Diabetes and high blood pressure remain the leading causes of kidney failure, accounting for 44 percent and 28 percent of all new cases, respectively. The most striking trends are seen in diabetes, where rates for new cases in Caucasians under age 40 were the lowest since the late 1980s, in stark contrast to rates for their African American counterparts, which have not changed.

The recent stabilization in kidney failure rates is likely attributable, at least in part, to better preventive care. The aging of the population and the increased numbers of diabetic patients are all trends tending to increase, not decrease, the number of people at risk of kidney disease. In the last two decades, however, clinical research, funded in part by NIDDK, has established the effectiveness of preventive strategies. The Diabetes Control and Complications Trial (DCCT) established the importance for patients with diabetes of good control of blood sugar and the value of monitoring for protein in the urine to detect early disease.

Other studies performed in the 1990s demonstrated that angiotensin-converting enzyme inhibitors (ACE-inhibitors) and angiotensin receptor blockers (ARBs) significantly delay or prevent kidney failure, particularly in patients with protein in the urine. Both types of drug decrease the amounts of protein in the urine. While ACE-inhibitors and ARBs are still underutilized, there has been a dramatic increase in their use. In the past decade, the use of these medications doubled among people over age 60 with chronic kidney disease, from 16 percent to 32 percent of patients, and they were also used by nearly half of those who also had diabetes or hypertension or congestive heart failure.

Still, despite incremental successes in preventing kidney failure and in improving health and survival of people who have it already, the increasing and aging U.S. population means that more people than ever before are living with the disease. The NIDDK has launched a program to increase awareness about kidney disease, the National Kidney Disease Education Program (NKDEP). The NKDEP encourages early diagnosis and management by increasing awareness about the connection between diabetes, high blood pressure and kidney disease; strategies proven to prevent or delay kidney failure; estimating kidney function to detect kidney disease earlier; and efforts to standardize testing for kidney disease and encourage more laboratories to automatically report estimated kidney function. Because of the higher rates of kidney disease seen in minority populations, the NKDEP has developed the "You Have The Power To Prevent Kidney Disease" campaign for African American adults and the *"¡Cuidado! La diabetes y la presión arterial alta pueden causar enfermedades de los riñones. Aprenda a proteger sus riñones"* ("Caution! Diabetes or High Blood Pressure Can Cause Kidney Disease! Learn how to protect your kidneys") campaign for Hispanics. Both programs are intended to increase awareness of kidney disease and the importance of

early detection in these minority populations who are disproportionally affected by the disease. "You Have The Power To Prevent Kidney Disease," was pilot-tested in 2003 in four cities—Atlanta, GA; Baltimore, MD; Cleveland, OH; and Jackson, MS—before being launched nationally in 2004. *"¡Cuidado! La diabetes y la presión arterial alta pueden causar enfermedades de los riñones. Aprenda a proteger sus riñones"* is a new NKDEP initiative, and was launched in January 2006. For more information about the NKDEP, see the accompanying sidebar, "National Kidney Disease Education Program (NKDEP)."

USRDS research depends on collaborations with other agencies of the U.S. Department of Health and Human Services (HHS), including the Centers for Medicare and Medicaid Services, the United Network for Organ Sharing, and the Centers for Disease Control and Prevention. Patient registries for other countries also contribute data for analyses.

Increasing Awareness of Interstitial Cystitis

Experiencing symptoms of pain around the bladder or pelvic area, and increased urge or frequency of urination, can disrupt normal life. Not knowing what is causing these symptoms—or what can be done about it—makes a difficult situation even harder. Interstitial cystitis (IC) is a painful and often debilitating bladder illness characterized by this syndrome of symptoms. Both IC and the related "painful bladder syndrome" (PBS) are currently diagnosed only by excluding other possible causes of these symptoms, such as infections or bladder cancer. Thus, IC is difficult to identify. Moreover, many patients and physicians are not familiar with these syndromes, and this lack of knowledge can delay diagnosis and possible treatment even further.

The NIDDK is helping to increase awareness of IC and PBS in order to help hasten patient diagnosis and access to information about treatment options. The Institute developed and launched an Interstitial Cystitis Awareness Campaign under the auspices of its National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). Throughout 2005, the campaign targeted messages about IC to three audiences—the public, urologists, and general practitioners. For example, to increase awareness among urologists, the Clearinghouse developed and mailed an information package to members of the American Urological Association that included:

- A cover letter to AUA members from the NKUDIC
- Copies of the IC/Painful Bladder Syndrome fact sheet (available at *http://www.kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis/index.htm*)
- A "Hope Through Research" fact sheet, "NIDDK: Solving the Puzzle of Interstitial Cystitis." This new publication was developed specifically for this mailing.

To reach primary care providers, the Clearinghouse provided information about IC at several broad-based professional meetings, including the annual conference of the American Academy of Family Physicians and the meeting of the American Academy of Physician Assistants. Finally, to increase awareness in the general public, the Clearinghouse developed and distributed a feature article about IC nationwide in 30 newspapers and weeklies, with a cumulative circulation of more than 500,000.

Many questions remain about which individuals develop IC and why, as well as how many people are affected in the U.S. and abroad. The NIDDK is supporting studies to obtain more precise answers to these questions, which will, in turn, assist in efforts to target information to patients and physicians. However, IC/PBS does appear to be far more common in women than in men. In the future, the IC Awareness campaign will become part of a new, multifaceted women's urologic health outreach program that is currently under development by the NIDDK.

The National Kidney Disease Education Program (NKDEP)

An estimated 20 million Americans currently suffer from chronic kidney disease (CKD), and millions more do not realize they are at risk. Treating the number of people with irreversible kidney failure, also called end-stage renal disease (ESRD), now costs the U.S. health care system more than $25 billion every year for dialysis and kidney transplantation. Although recent data from the NIDDK-supported USRDS indicate that ESRD rates are stabilizing after twenty years of annual five to ten percent increases, ESRD remains an enormous public health problem that disproportionately affects minority populations. Because the leading causes of kidney disease are diabetes and high blood pressure, the increasing prevalence of obesity and type 2 diabetes in the U.S. could fuel future rates of ESRD.

The NKDEP aims to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk—those with diabetes, high blood pressure, cardiovascular disease, or a family history of kidney disease—and the availability of treatment to prevent or slow kidney failure.

The NKDEP emphasizes that effective treatments and management strategies for kidney disease exist, yet are being inadequately utilized. The progression from chronic kidney disease to kidney failure can be prevented or delayed if it is detected and treated early enough. Yet only a small number of the people who need proper screening or treatment receive it.

The NKDEP uses a multipronged approach to help achieve its goals. Toward this end, it is implementing public education and awareness initiatives; creating tools and programs for healthcare providers who play a key role in diagnosing and treating chronic kidney disease and its complications; and spearheading systemic change to improve the accuracy and automatic reporting of estimated glomerular filtration rate (GFR), a measure of kidney function.

Some current and recent activities of the NKDEP include:

Creatinine Standardization Program: The NKDEP's Laboratory Working Group is leading an effort to reduce bias in the measurement of serum creatinine, which is used to calculate GFR, and thereby estimate kidney function. GFR measures how well the kidneys are filtering waste, and is based on measurements of creatinine in the blood. Creatinine is a waste product, and healthy kidneys remove it from the blood and excrete it in urine. When the kidneys are not working well, creatinine builds up in the blood.

The standardization program encourages manufacturers of *in vitro* diagnostic equipment to recalibrate routine serum creatinine methods and to coordinate this recalibration with the introduction of a revised equation to estimate GFR.

Through information materials, the Laboratory Working Group also is encouraging laboratories to routinely report estimated GFR when serum creatinine is ordered. The NKDEP is in the process of developing a laboratory survey to gather baseline data that will be used to evaluate the success of this initiative.

Health Care Provider Outreach: NKDEP information is encouraging provider interactions with health systems, disease management companies, professional associations and others to encourage testing of at-risk patients and use of estimated GFR to increase early detection of kidney disease.

Communicating about Risk Factors—Family Reunion Initiative: The NKDEP conducted a pilot program to encourage African Americans to discuss the connection between diabetes, high blood pressure, and kidney disease at large family reunions. The "Kidney Connection Toolkit," the centerpiece of the initiative, provided kidney disease background information and guides to facilitate communication about risk factors for kidney disease and the steps people can take to prevent or delay kidney failure.

Hispanic Outreach: The NKDEP recently launched an effort to raise awareness in Hispanic/Latino audiences about risk factors for chronic kidney disease by developing and disseminating a new Spanish-language brochure, creating new Spanish pages on the NKDEP website, and distributing public service announcements to Spanish radio stations nationwide.

USRDS Data: The NKDEP publicized new data from the NIDDK U.S. Renal Data System (USRDS) that showed that kidney failure rates appear to have stabilized in the past four years. Ongoing promotion of the findings will demonstrate the importance—and benefit—of early detection and proper treatment of chronic kidney disease and the value of programs such as NKDEP.

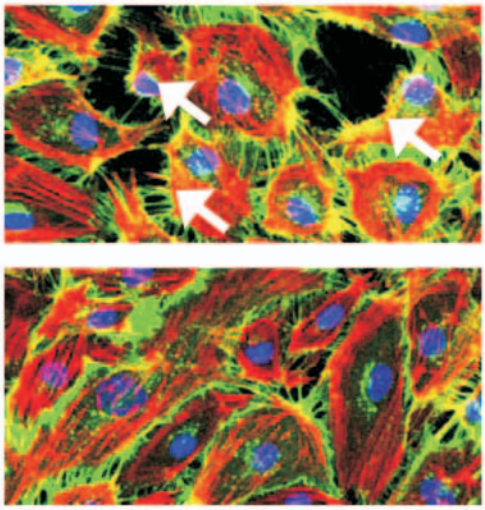
More information about the NKDEP can be found at *http://www.nkdep.nih.gov*

Vignettes in Vascular Biology: Working Across Borders

Dr. Vikas Sukhatme

Dr. Vikas Sukhatme is a leading researcher in the field of vascular biology and kidney disease. His research team focuses on kidney physiology and disease, the mechanisms of cancer growth and spread, the development of preeclampsia and eclampsia, and the regulation of blood vessel growth. Dr. Sukhatme is the Chief of the Renal Division of Beth Israel Deaconess Medical Center and Victor J. Aresty Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center. The following are scientific highlights based on a scientific presentation Dr. Sukhatme gave to the Institute's National Advisory Council in September 2005.

Dr. Vikas Sukhatme shared several vignettes of "translational vascular biology research in action" to illustrate the insights and advances that can be achieved when scientists work across disciplines when conducting research. Dr. Sukhatme told the Council that previous conceptions of translational research focused primarily on moving research advances from the laboratory into improvements in clinical practice, so-called "bench-to-bedside" translation. In recent years, however, physicians and scientists have come to appreciate that observations and data obtained in a clinical setting have the potential to inform and enrich basic laboratory studies. With this evolution in thinking, translational research can now be envisioned as "bedside-to-bench-and-back" as well. It is thus a bi-directional, dynamic process that is central to the research enterprise and requires close collaboration between basic and clinical researchers. This bi-directional paradigm also highlights the important role that patients play as partners in the biomedical research enterprise.



Sepsis is a bacterial infection that has entered the bloodstream, and can lead to fluid accumulation in the lungs. Normally, the tight association between cells prevents this leakage, but these junctions weaken in patients who have sepsis. Serum from a patient with severe sepsis causes gaps to form between cultured cells (top; black spaces and white arrows). Serum from this patient does not damage the cells if a factor called angiopoietin 2 is first neutralized (bottom).

Image courtesy of S. Parikh and T. Mammoto (Sukhatme Laboratory).

Fundamentals of Vascular Biology

The circulatory system provides nourishment to, and removes wastes from, all the cells of the body. Arteries carry oxygenated blood away from the heart and lungs, while veins return blood laden with carbon dioxide. Arteries and veins are basically long, branching tubes that gradually narrow as distance from the heart

increases. These vessels are connected by a web-like structure of much smaller, narrower vessels called capillaries. It is in the capillaries that oxygen and carbon dioxide are exchanged inside tissues.

In the filtering units of kidneys, capillary beds also unload many other waste products to be excreted in urine. Thus, proper function of the vasculature is critical to obtaining oxygen and removing potentially harmful substances from the body.

Key players in vascular biology are endothelial cells that line the blood vessels, smooth muscle cells that surround the vessels, and circulating cells within the vessels. Dysfunction among any of these cell types can cause disruption of the circulation and its many important functions. Dr. Sukhatme noted that a person who weighs 70 kg—about 150 lbs.—has about 1 kg of endothelial cells in his body. Although this may not sound like a lot, if lined up end-to-end, a person's endothelial cells would stretch 100,000 miles; if laid flat, they would cover over 1000 square meters. Clearly, the vasculature represents a vast system of critical importance in the maintenance of health, and endothelial cells play critical roles in hemostasis, vascular permeability, angiogenesis (sprouting of new vessels from existing ones) and blood pressure control.

The Puzzle of Preeclampsia

During a normal pregnancy, arteries in the mother's uterus undergo changes, or remodeling, in order to ensure an adequate blood supply to the placenta and fetus. In preeclampsia, the pregnant mother's arteries fail to remodel appropriately, resulting in diminished blood supply to the growing fetus. Patients with preeclampsia have high blood pressure and protein in the urine, a sign of kidney damage. However, the underlying causes of preeclampsia have been largely unknown.

Using gene profiling techniques, Dr. S. Ananth Karumanchi, who had previously trained in Dr. Sukhatme's lab and had assumed a faculty appointment in Dr. Sukhatme's division, identified several products that were expressed at high levels in placentas from mothers with the disease. The protein encoded by one of these genes, *sFlt-1*, binds vascular endothelial growth factor (VEGF), a powerful promoter of blood vessel growth. However, sFlt-1 is not capable of transducing the signal carried by VEGF, and thus limits the amount of VEGF available to stimulate cell-bound VEGF receptors. Dr. Karumanchi shared this data with Dr. Sukhatme, who was becoming aware—because of his interest in tumor angiogenesis—that trials of VEGF inhibitors as anti-angiogenic therapy for cancer were producing hypertension and proteinuria as side effects. He suggested to Dr. Karumanchi that sFlt-1 might be involved in preeclampsia, because it would mimic the actions of a VEGF inhibitor. Using a number of animal studies and analyses of patient samples, the researchers showed that diminished VEGF levels, resulting from elevated levels of the sFlt-1 protein, correlated with high blood pressure and kidney damage. Strategies to enhance VEGF signaling, through manipulation of sFlt-1 protein levels, may therefore be a useful avenue to pursue for therapies to prevent or treat preeclampsia. (*For more information about recent advances in preeclampsia research, including Dr. Sukhatme's and Dr. Karumanchi's work, see the Story of Discovery in this chapter.)*

Zebrafish and Endothelial Cell-Target Discovery

The circulatory system appears early in embryonic development. In order to identify potential future targets for therapies of circulatory problems, Dr. Sukhatme and his collaborators looked for genes involved in the development of the vasculature. For these studies, the scientists chose as a model system the zebrafish. This organism is particularly well-suited for several reasons. First, it develops its internal organs over two to five days, allowing rapid screening of a large number of organisms in a relatively short period of time. Second, at early stages of development, it is transparent, allowing developmental progress or problems to be readily observed. To discover genes involved in vasculogenesis, the researchers screened for genes that were expressed

specifically in vessels and then proceeded to use an approach to knock down their expression. Some of animals so treated exhibited defects in blood vessel formation. Several novel genes have been identified by this process and their function and mechanisms of action, as well as their role in human vascular disorders, are under investigation. One gene encoded a protein that seems to be important in embryonic vascular development and, interestingly, this gene is also active at sites of active blood vessel growth in adults. While the size and simplicity of zebrafish impose some limits on these types of studies, this model system represents a useful way to identify potential targets for later, more in-depth investigation.

Vascular Leak—From the Kidney to the Lung

Sepsis is a bacterial infection that has entered the bloodstream, and can lead to excessive fluid in the lungs. If the tiny air sacs within the lungs fill with fluid, the lungs cannot exchange blood-borne carbon dioxide for oxygen. This in turn leads to acute respiratory distress, which can, in extreme cases, result in death.

Normally, the tight association between the cells lining blood vessels prevents leakage of fluid or blood cells from within the vessels into the surrounding tissue. Dr. Sukhatme's team of researchers has identified proteins important to maintaining this leak barrier in the lungs. These proteins are angiopoietin 1 and angiopoietin 2 and their common receptor, TIE-2. Their studies suggest that angiopoietin 1 promotes vessel stability, while angiopoietin 2 promotes vascular permeability in the lung. Vascular leak may therefore be a consequence of an imbalance between angiopoietin 1 and angiopoietin 2.

Support for this hypothesis comes from the observation that acute respiratory distress is often accompanied by a three- to five-fold increase in angiopoietin 2, and that angiopoietin 2 levels return to normal when patients recover. Furthermore, in cultured cells, addition of angiopoietin 2 to the growth medium caused gaps to form in an otherwise tightly associated layer of cells. These findings point to a disturbance in the delicate balance between angiopoietin 1 and 2 as a key factor in the development of vascular leak and respiratory distress. Investigators are examining strategies to block angiopoietin 2 action as potential treatments for sepsis-related vascular leak in humans.

Dialysis Vascular Access: Combating Stenosis

Patients receiving hemodialysis to treat their kidney failure undergo a surgical procedure to create an easily accessible site at which blood will be removed and returned. The creation of this "vascular access graft" facilitates the repeated insertions of relatively wide-diameter needles, because large volumes of blood must be processed to remove toxins no longer filtered out by the patient's kidneys.

Unfortunately, repeated needle punctures often lead to the development of smooth muscle-like lesions in the vascular access grafts. These lesions can cause the graft to narrow, a phenomenon known as "stenosis," and ultimately to fail. They can be treated, but often unsuccessfully.

To try to prevent or treat vascular-access stenosis, Dr. Sukhatme's research team used a pig model to study the molecular factors involved in this process. They found that receptors for platelet-derived growth factor (PDGF) were activated in these lesions, suggesting that agents that block PDGF receptor action might be a valid therapeutic approach. Several such medications are already on the market, though they are not being used currently to treat this condition. One challenge is to devise ways to use such agents locally in relatively high doses, where their activity could be concentrated at the site of the stenosis. Dr. Sukhatme and his colleagues are currently working to address this limitation to current therapy.

Conclusion

Dr. Sukhatme closed by reviewing the long and often arduous path of drug development. This path ranges from the early identification of possible targets, through pre-clinical testing and compound design and development, onward to clinical trials to show effectiveness, and finally, to regulatory approval. He estimated that for every single drug approved for use in patients, 5,000 to 10,000 initial compounds are screened. Studies such as Dr. Sukhatme's vascular development work in zebrafish might help identify potentially beneficial compounds early, and thereby allow researchers to focus their initial studies on the most promising biological targets. Dr. Sukhatme's work on preeclampsia and sepsis illustrates the importance of identifying molecular factors that may play a role in predicting or diagnosing a condition, as they may also be valuable therapeutic targets. Finally, his work on vascular access stenosis illustrates how uncovering a new molecular role for a pathway already targeted in other disease processes may permit the use of existing agents to jump-start research into new therapies. By casting his net widely, Dr. Sukhatme showed how working across scientific borders can strengthen and enlighten all aspects of research.

Helping Women Have a Safer Pregnancy — Advances in Detecting Preeclampsia

A series of research findings may help women avoid a common and sometimes serious complication of pregnancy called toxemia or preeclampsia. This condition usually involves a combination of high blood pressure and persistent swelling, as well as protein in the urine—a sign of impaired kidney function. Preeclampsia can impede blood flow to the baby and result in low birth weight and even graver problems for mother and child. Insights into this condition have been gained by recruiting patients as research partners and combining cutting-edge technology with careful laboratory studies. Moving from the "bench-to-bedside-and-back," investigators used patient samples to design laboratory studies, and then returned to patient data to confirm hypotheses. In doing so, they identified a perturbation in a signaling pathway that may play a central role in preeclampsia. In addition, they developed an assay that may predict preeclampsia with a greater degree of precision than previously. This research has also identified potential targets for new prevention-oriented strategies.

Preeclampsia is a relatively common complication of pregnancy, especially in first pregnancies or in twin pregnancies. The central lesion in preeclampsia is the failure of maternal arteries at the uterus/placenta interface to remodel appropriately. This results in diminished blood supply to the placenta and fetus. Preeclampsia is characterized by high blood pressure and kidney damage resulting in proteinuria, or protein in the urine. It appears in 2.5 to 3.0 percent of pregnancies. Unaddressed, it may progress to eclampsia—violent seizures that can result in the death of the mother and developing child. Children of mothers with preeclampsia may be born prematurely and/or may be small for their age. Treatment for preeclampsia is often not satisfactory. It is managed by close observation of the mother and the administration of anti-hypertensive drugs to lower blood pressure. If the condition progresses, the only effective therapy is urgent delivery of the fetus. Doctors have long believed that placental factors are central to the development of preeclampsia, because the presence of a placenta is an absolute requirement for preeclampsia, and the condition markedly and rapidly improves after delivery.

To investigate possible genetic factors involved in preeclampsia, a research team looked for changes in gene expression in the placentas of women with this condition. They found increased expression of the gene *sFlt-1*, a finding that was interesting for a number of reasons. First, the protein encoded by the *sFlt-1* gene can bind two important growth factors, placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). VEGF and PlGF are powerful promoters of new blood vessel growth, and they play an important role in ensuring the maintenance and survival of the endothelial cells lining blood vessels. Swollen, damaged endothelial cells are one consequence of preeclampsia. Second, the sFlt-1 protein is not anchored in the cell membrane, but circulates in the blood. Although this protein is produced locally in the placenta, it has the potential to act systemically throughout the body. Thus, this protein's ability to bind VEGF and PlGF diminishes the amount of VEGF and PlGF available to endothelial cells. The scientists hypothesized that depletion of VEGF and PlGF due to *sFlt-1* overexpression by the placenta in affected women is a potential explanation for the systemic blood vessel dysfunction that is a hallmark of preeclampsia.

In order to determine whether excessive *sFlt-1* expression might contribute to the vascular derangement seen in preeclampsia, the investigators used laboratory studies to determine the effect of serum from normal and preeclamptic women on the growth of blood vessel cells. Serum from normal women promoted the development of vessel-like tubules in culture, but serum collected from preeclamptic women before delivery inhibited formation of these structures. Intriguingly, when the cells were incubated with serum collected from preeclamptic women 48 hours after delivery, tubules did form. This rapid loss of the unknown factors causing inhibition of tubule formation strongly suggested the involvement of circulating, placenta-derived factors. Furthermore, when researchers induced overexpression of the *sFlt-1* gene in pregnant and non-pregnant rats, both developed hypertension and proteinuria, and their kidneys showed damage remarkably similar to that seen in humans with preeclampsia. Together, these observations pointed strongly toward the involvement of the sFlt-1/VEGF/PlGF signaling pathway in the vascular and kidney complications of preeclampsia.

Going from the "bench-to-the-bedside," the scientists next compared their laboratory results with patient data. They analyzed blood samples from 120 preeclamptic women and 120 normal controls, which had been collected as part of an earlier study. They found that circulating levels of the sFlt-1 protein increased and PlGF levels decreased late in pregnancy in normal women. These changes occurred earlier and were greater in the women in whom preeclampsia developed, and the increase in levels of the sFlt-1 protein preceded the onset of preeclampsia by about five weeks. Building on this finding, researchers turned to urine samples from the same patients. The sFlt-1 protein cannot be measured in urine because the molecule is too large to be excreted intact. Moreover, deducing circulating levels of VEGF in blood using urine samples is problematic, because kidney cells normally secrete VEGF. The researchers therefore measured PlGF protein levels as a surrogate marker of sFlt-1 and VEGF signaling activity because all three share the same pathway. They reported that PlGF protein levels in urine were similar and rising in both groups early in pregnancy. Women who would go on to develop preeclampsia saw this increase slow at around 25 weeks. After the onset of preeclampsia, PlGF protein levels in affected women plummeted to just one-seventh those seen in normal women. Thus, low urinary PlGF protein levels early in pregnancy may be an early warning sign of subsequent preeclampsia.

The ability to measure a factor in urine that may predict preeclampsia represents a significant advance as a diagnostic tool, because no such test previously existed and because urine can be sampled more easily than blood. The VEGF/PlGF signaling pathway also presents multiple potential new targets for developing therapies aimed at preventing or treating preeclampsia. The rapid pace of recent progress in this area gives hope to at-risk women and their children that, through continued research, they may be able to avoid the perils of preeclampsia.

Frankie Cervantes

Battling Focal Segmental Glomerulosclerosis: A Little Boy With a Big Wish

Six-year-old Frankie Cervantes awoke extra early the morning he was scheduled for his kidney transplant. He simply could not contain his excitement and joy. "It's kidney day. It's kidney day," Frankie laughingly kept telling his mother and father. "He was so happy," his father says.

And Frankie had every right to be.

At just 18 months of age, Frankie was diagnosed with nephrotic syndrome—symptoms of kidney malfunction—caused by focal segmental glomerulosclerosis (FSGS), a serious kidney disease. By the time he was three years old, the disease had become so severe that Frankie's kidneys failed and needed to be removed to prevent life-threatening complications. Three years later, in August 2005, Frankie was transplanted with a kidney donated by his mother. Despite the successful transplant, the last several years have been extremely hard on the Cervantes family, and Frankie's medical future remains uncertain.

Since his diagnosis, Frankie has experienced several long-term hospitalizations; been through at least two life-threatening experiences; taken numerous medications; and been on extremely restrictive diets. Prior to his transplant, he underwent invasive medical treatment at home every day for more than two and a half years to substitute for lost kidney functions. Then, he experienced a relapse of nephrotic syndrome just days after he received his mother's healthy kidney. Yet Frankie remains a joyful, playful child who loves dinosaurs and toy racing cars—while his parents remain hopeful.

Frankie Cervantes

This is the story of a little boy whose kidneys may have failed him, but not his heart nor spirit, nor the heart, spirit and tenacious love of his mother and father who are counting on medical research to help their son and others like him.

About the Kidneys and Kidney Damage

The kidneys are two bean-shaped organs, located below the ribs toward the middle of the back. The kidneys perform several critical functions in the body. They remove extra water and wastes from the blood, converting them to urine. At the same time, they must ensure that critical blood components (such as blood proteins) do not leak into the urine. The kidneys also keep a stable balance of salts (primarily

sodium and potassium salts) and other substances in the blood, and produce hormones that help build strong bones and help form red blood cells.

If the kidneys become damaged by disease, patients can develop a condition called nephrotic syndrome. Nephrotic syndrome is marked by several symptoms: high levels of protein in the urine (proteinuria); low levels of protein in the blood; swelling (edema), especially around the eyes, feet, ankles, and hands; and high cholesterol. When a patient develops nephrotic syndrome, physicians need to determine what is causing the kidney damage—for example, a chronic disease or an infection—so that they can take appropriate steps in order to halt these potentially life-threatening symptoms.

What is FSGS?

FSGS, or focal segmental glomerulosclerosis, is a medical term that describes scarring in scattered regions of the kidneys. Patients with FSGS experience damage and eventual scarring in the tiny filtering units of the kidneys, called glomeruli. Each kidney has about one million glomeruli, which filter the blood repeatedly—the equivalent of about 200 quarts of blood a day—to remove waste products and extra water to form urine. When the glomeruli are damaged in FSGS, the filters no longer work properly, and blood proteins begin to leak into the urine. If there is heavy loss of protein, a patient develops nephrotic syndrome. The extensive loss of protein in the urine leads to low blood protein levels. This protein loss then, in turn, causes buildup of fluid outside the circulatory system, resulting in excessive swelling in the face, hands, feet or ankles. FSGS also interferes with the kidneys' ability to clear waste products, which begin to build up to toxic levels in the blood.

In some cases, FSGS leads to end-stage renal disease (ESRD), or irreversible kidney failure. ESRD means that in order for a patient to live, he or she needs help to replace kidney functions that are critical for survival. This help comes either in the form of dialysis or a kidney transplant. Dialysis is a medical treatment that mimics the cleansing activities of the kidneys, and their regulation of salt balance. Patients on dialysis are also commonly treated with medications to reduce health problems associated with irreversible kidney failure, such as anemia and bone loss. They also are given guidance on dietary restrictions and meal planning to help reduce the dangerous build-up of wastes in the blood.

First described in 1957, FSGS is an irreversible disease whose cause is often unknown. It appears to be more prevalent and more severe in African American and, perhaps, in Hispanic American children. Frankie's father is Mexican; his mother is Panamanian. Although steroid therapy is commonly used to treat children with FSGS, approximately 75 percent do not respond to therapy, relapse while on therapy, or relapse when therapy is stopped. In short, no current treatment for nephrotic syndrome caused by FSGS is completely satisfactory. As a result, many children and young adults with this condition are at high risk for kidney failure.

Frankie's Story

Aside from being born during his mother's eighth month of pregnancy, Frankie was a perfectly healthy, bouncy, baby boy. Like all young children, he had his bouts with fevers and colds. When he was 18 months old and began running a fever, accompanied by a cough and runny nose, his mother brought him to a pediatrician. The doctor discovered Frankie also had an ear infection, and treated it with penicillin.

That same night, Frankie's cries woke his parents. Their son's eyes, lips and cheeks were extremely swollen. It was obvious Frankie was in great pain, so Mr. and Mrs. Cervantes rushed him to the nearest hospital emergency room. There, they were told that Frankie had likely suffered an allergic reaction to the penicillin. He was given another antibiotic for the infection and an additional medication to reduce the swelling. However, the swelling got worse, so Frankie's parents took him back to the hospital.

PATIENT PROFILE

After numerous tests, including a biopsy of his kidneys, Frankie was diagnosed with FSGS. He was immediately put on the steroid, prednisone, which helped to reduce the swelling and seemed to stabilize his kidney function. Steroids, such as prednisone, as well as other immunosuppressive drugs, appear to help some FSGS patients by decreasing proteinuria and improving kidney function. However, these medications can also produce severe side effects. These side effects include, but are not limited to, increased blood sugar; bone, muscle and eye problems; increased hair growth; and an inability to fight off infection (immunosuppression). Consequently, these drugs can be used for a limited time only. In addition, such treatments are beneficial to only a minority of those in whom they are tried.

Because of the immunosuppressive nature of prednisone, "every time Frankie passed someone on the street with a cough or a cold, he'd get it," says his father. Frankie was on prednisone for a year. However, as physicians began to reduce his dosage, Frankie's swelling increased again, as did his pain.

The Cervantes family struggled to find treatments that could help alleviate Frankie's symptoms, including alternatives to standard medical therapies, such as acupuncture. Frankie's condition only worsened. Mr. and Mrs. Cervantes relate how, one morning, Frankie woke up crying in such pain that he began pulling at his mother's hair and pleaded to be brought back to the hospital. He was immediately treated again with prednisone and remained in the hospital for three months. This time, however, he did not respond to the prednisone treatment.

Blood tests and a kidney biopsy showed that Frankie was suffering from a severe case of FSGS, and his kidneys were shutting down. He was dialyzed to clear waste products. Because his kidney disease was so severe, then-three-year-old Frankie had his kidneys removed to prevent catastrophic loss of blood proteins and save his life. To stay alive until a kidney donor could be identified and Frankie's body was mature enough to accept a transplant, his mother was trained to perform one type of dialysis procedure, called peritoneal dialysis, at home. The procedure required her to administer this 11-hour blood-cleansing procedure seven days a week to her 3-year-old, hard-to-sit-still son, mostly at nighttime, when Frankie was asleep. Moreover, Frankie had to take medications that could help substitute for some of the other kidney functions he had lost. For example, with his family's approval, Frankie was given a medication to try to control hyperparathyroidism (high parathyroid hormone). This condition develops as a result of kidney failure and causes bone loss. Frankie's father understates it when he says, "It's been hard."

The painstaking task of almost daily dialysis went on for two years and seven months. In that time, Frankie contracted an infection that landed him in the hospital yet again, this time for a month, two weeks of which were spent in the intensive care unit. "We almost lost him," says an emotional Mr. Cervantes.

The good news was that also during this time it was discovered that Mrs. Cervantes was eligible to donate one of her kidneys to her son. "I could not have been happier to learn that we matched," she says with a big smile, as she holds her son on her lap.

The Transplant

The family needed to wait nearly a year before Frankie's body matured enough to accept his mother's kidney. During that time, Frankie remained on a strict diet in order to control his blood pressure and cholesterol levels. "No milk, no fruit, no salt, no potassium, no nothing," says Mr. Cervantes. "Frankie would see kids eating ice cream and chips. It was very hard for us to always tell him 'no'."

When the day finally came for Frankie to receive his mother's kidney, Frankie, who had been through so much so young, was joyful. When he walked by the hospital security station he cheerily said to the guard on duty, "I'm getting my new kidney today."

The new kidney worked perfectly for three days. Then, tests began to show the return of excessive amounts of protein in Frankie's urine, a sign that his FSGS was recurring and inducing nephrotic syndrome. He was plasmapheresed, a medical treatment whereby the blood is treated outside the body to remove harmful factors, and then returned to the patient. Fortunately, Frankie responded well to the treatment. But after all they've been through, Mr. and Mrs. Cervantes feel they are living with a "time bomb." "We never know when this disease will explode again," says Mr. Cervantes.

Hope Through Research

The NIDDK is seeking to defuse the time bomb of disease for Frankie and other children with FSGS. Working with the American Society of Pediatric Nephrology, the NIDDK has formed a collaborative network of research centers to conduct a clinical trial for treatment of FSGS in children and young adults. The goal of the trial is to compare the effectiveness of two treatment regimens in reducing proteinuria in patients who, like Frankie, have steroid-resistant FSGS of unknown cause, but who have not yet had a kidney transplant. Moreover, NIDDK scientists are committed to studying possible causes of various forms of FSGS. These researchers are conducting clinical studies of therapeutic approaches that may prevent recurrence in transplant patients, as well as additional studies of treatments for FSGS in patients.

Because of the immunosuppressant medications Frankie is currently taking to help prevent his body's rejection of his new kidney, he must limit his exposure to germs. For now, Frankie—who is a first-grader—is being taught by a teacher who comes to his home. Like all little boys his age, Frankie loves to play video games, ride his bike and watch family movies. When asked what his one big wish is, Frankie says "to swim in the ocean"—a dream that has been difficult to attain for the past few years because of his peritoneal dialysis treatment. Now, with his new kidney, Frankie may one day be granted his wish.

For more information on the FSGS Clinical Trial, see *http://www.clinicaltrials.gov/ct/show/NCT00135811?order=8*

Frankie Cervantes

Una Lucha contra la Glomeruloesclerosis Focal y Segmentaria: Un Chiquitín con un Gran Deseo

Frankie Cervantes, un niño de seis años, se despertó mucho más temprano de lo habitual la mañana en que su trasplante de riñón estaba programado. Simplemente no podía contener su entusiasmo y alegría. "Es el día del riñón. Es el día del riñón," Frankie reía al decírselo una y otra vez a su madre y a su padre. "Estaba tan contento," comenta su padre.

Realmente, Frankie tenía todo el derecho a estar feliz.

A tan sólo 18 meses de edad, a Frankie se le diagnosticó síndrome nefrótico, un cuadro de insuficiencia renal, causado por la glomeruloesclerosis focal y segmentaria, una grave enfermedad del riñón. Cuando Frankie cumplió tres años, la enfermedad había empeorado tanto que los riñones de Frankie dejaron de funcionar y fue necesario extirparlos para prevenir complicaciones potencialmente mortales. Frankie sobrevivió durante este periodo gracias al uso de diálisis renal. Varios años más tarde, en agosto de 2005, a Frankie se le trasplantó un riñón donado por su madre. A pesar del éxito del trasplante, los últimos años han sido extremadamente difíciles para la familia Cervantes, y el futuro médico de Frankie es todavía incierto.

Desde su diagnóstico, Frankie ha sido hospitalizado muchas veces por largos períodos; ha tenido por lo menos dos experiencias que amenazaron su vida; ha tomado un sin fin de medicamentos y ha participado en regímenes alimenticios extremadamente complejos. Antes de su trasplante, se le administró diariamente en su casa, por más de dos años y medio, un tratamiento médico agresivo para sustituir las funciones renales perdidas. Luego, él experimentó una

Frankie Cervantes

recaída cuando el síndrome nefrótico se presentó tan sólo unos cuantos días después de haber recibido el riñón sano de su madre. Aún así, Frankie continúa siendo un niño juguetón y feliz, que ama a los dinosaurios y a los cochecitos de carreras, mientras que sus padres no pierden la esperanza que su condición médica mejore.

Esta es la historia de un chiquitín cuyos riñones fallaron, pero no su corazón ni su espíritu, ni el corazón ni el espíritu y el firme amor de su madre y su padre, quienes tienen fe en que las investigaciones médicas podrán ayudar a su hijo y a otros que padecen esta enfermedad.

Información sobre los Riñones y el Daño Renal
Los riñones son dos órganos en forma de frijol (habichuela), ubicados en el abdomen debajo de las costillas hacia la parte media de la espalda. Los riñones desempeñan varias funciones vitales en el cuerpo. Extraen el exceso de agua y los desechos de la sangre para convertirlos en orina. Al mismo tiempo, deben asegurar que los componentes vitales de la sangre (tales como las proteínas que residen en ella) no pasen a la orina. Los riñones también mantienen un equilibrio estable de sales (principalmente las sales de sodio y potasio) y de otras sustancias en la sangre, y producen hormonas que ayudan a formar huesos fuertes y también glóbulos rojos (eritrocitos).

Si alguna enfermedad daña a los riñones, los pacientes pueden contraer una enfermedad denominada síndrome nefrótico. El síndrome nefrótico se caracteriza por varios síntomas: altas concentraciones de proteína en la orina (proteinuria); bajas concentraciones de proteína en la sangre; hinchazón (edema), especialmente alrededor de los ojos, los pies, tobillos y manos; y alto colesterol. Cuando un paciente padece un síndrome nefrótico, los médicos necesitan determinar qué es lo que está causando el daño a los riñones, por ejemplo, una enfermedad crónica o una infección, de manera que puedan tomar los pasos adecuados para detener estos síntomas que son potencialmente mortales.

¿Qué es la Glomeruloesclerosis Focal y Segmentaria?
La glomeruloesclerosis focal y segmentaria (FSGS, siglas en inglés) es un término médico que describe la cicatrización que ocurre en distintas regiones de los riñones. Los pacientes con FSGS experimentan daños y posteriormente cicatrización en las minúsculas unidades de filtración de los riñones, denominadas glomérulos. Cada riñón tiene aproximadamente un millón de glomérulos, los cuales filtran la sangre repetidamente (el equivalente a 180 litros o 50 galones de sangre cada día) para extraer los desechos y el exceso de agua para formar la orina.

Cuando los glomérulos se dañan en la FSGS, los filtros dejan de funcionar correctamente, y las proteínas de la sangre empiezan a pasar a la orina. Si ocurre una gran pérdida de proteínas, el paciente contrae el síndrome nefrótico. La abundante pérdida de proteínas en la orina resulta en bajas concentraciones de proteínas en la sangre. Esta pérdida de proteínas, a su vez, causa una acumulación de líquido fuera del sistema circulatorio, lo que resulta en una hinchazón excesiva de la cara, manos, pies o tobillos. La FSGS también interfiere con la capacidad de los riñones de retirar los desechos, los cuales empiezan a acumularse en cantidades tóxicas en la sangre.

En algunos casos, la glomeruloesclerosis focal y segmentaria es causa de la nefropatía terminal (ESRD, siglas en inglés) o insuficiencia renal irreversible. La nefropatía terminal significa que, para que un paciente pueda vivir, él o ella necesita ayuda para sustituir las funciones renales que son fundamentales para la supervivencia. Esta ayuda se proporciona en forma de diálisis o de un trasplante de riñón. La diálisis es un tratamiento médico que imita las actividades de limpieza de los riñones, así como también su regulación del equilibrio de las sales. Los pacientes sometidos a diálisis también son tratados comúnmente con medicamentos para disminuir los problemas de salud relacionados con la insuficiencia renal irreversible, tales como la anemia y la osteopenia (debilitamiento de los huesos) y la hipertensión (alta presión sanguínea). Además, se les brinda orientación respecto a restricciones alimenticias y planificación de comidas para ayudarlos a reducir la peligrosa acumulación de desechos en la sangre y limitar la ingesta de sal.

La glomeruloesclerosis focal y segmentaria, que fuera descrita por primera vez en 1957, es una enfermedad irreversible cuya causa es con frecuencia desconocida. Parece ser más común y más grave en niños afroamericanos y, quizás también, en niños hispanos. El padre de Frankie es de México, y su madre es de Panamá. Aunque el tratamiento con medicinas llamadas esteroides se utiliza comúnmente para tratar a

niños con FSGS, aproximadamente el 75 por ciento de ellos no reacciona favorablemente al tratamiento, recae durante el tratamiento o recae cuando se detiene el tratamiento. En pocas palabras, no se cuenta actualmente con un tratamiento para el síndrome nefrótico causado por la FSGS que sea completamente satisfactorio. Como resultado, muchos niños y adultos jóvenes que padecen esta enfermedad corren un gran riesgo de desarrollar insuficiencia renal.

La Historia de Frankie

A pesar de haber nacido durante el octavo mes de embarazo de su madre, Frankie era un bebé lleno de vida y perfectamente sano. Como todos los niños pequeños, tuvo sus episodios de fiebres y resfriados. Cuando a los 18 meses de edad se le presentó una fiebre acompañada con tos y goteo nasal, su madre lo llevó a un pediatra. El médico determinó que Frankie también tenía una infección del oído y le dió tratamiento con penicilina.

Esa misma noche, los llantos de Frankie despertaron a sus padres. Los ojos, labios y mejillas de su hijo estaban extremadamente hinchados. Era obvio que Frankie tenía mucho dolor, así que los Cervantes lo llevaron rápidamente a la sala de emergencias del hospital más cercano. Ahí, les informaron que Frankie muy probablemente había tenido una reacción alérgica a la penicilina. Le administraron otro antibiótico para la infección y un medicamento más para disminuir la hinchazón. Sin embargo, la hinchazón empeoró, así que los padres de Frankie lo llevaron de regreso al hospital.

Tras numerosas pruebas, entre ellas una biopsia de los riñones, a Frankie se le diagnosticó glomeruloesclerosis focal y segmentaria. Inmediatamente se le administró prednisona, un esteroide, que lo ayudó a disminuir la hinchazón y que aparentemente estabilizó la función de sus riñones. Como mencionáramos previamente, los esteroides, tales como la prednisona, así como otros medicamentos inmunodepresores, parecen ayudar a algunos pacientes que padecen FSGS al disminuir la proteinuria y mejorar el funcionamiento de los riñones. No obstante, estos medicamentos pueden también producir efectos secundarios graves. Entre estos efectos secundarios se incluyen, por ejemplo, aumento de azúcar en la sangre (hiperglucemia); problemas de los huesos, músculos y ojos; aumento en el crecimiento de vello corporal; e incapacidad para luchar contra las infecciones (inmunodepresión). Por consiguiente, estos medicamentos sólo pueden utilizarse por un tiempo limitado. Además, dichos tratamientos son beneficiosos solamente para un pequeño porcentaje de aquellos que los reciben.

Debido a la naturaleza inmunodepresora de la prednisona, “cada vez que Frankie pasaba junto a alguien en la calle que tuviera tos o un resfriado, él se contagiaba,” relata su padre. Frankie fue tratado con prednisona por un año. Sin embargo, a medida que los médicos empezaron a reducir su dosis, la hinchazón de Frankie y su dolor aumentaron nuevamente.

La familia Cervantes luchó para encontrar tratamientos que pudieran ayudar a aliviar los síntomas de Frankie, entre ellos, tratamientos distintos a los tratamientos médicos normales, como por ejemplo la acupuntura. La enfermedad de Frankie sólo empeoró. El Sr. y la Sra. Cervantes cuentan como una mañana, Frankie se despertó llorando con tanto dolor que empezó a jalarle el cabello a su madre y le rogó que lo llevara de regreso al hospital. Fue tratado nuevamente con prednisona, y permaneció hospitalizado durante tres meses. En esta ocasión, sin embargo, no reaccionó favorablemente al tratamiento con la prednisona.

Los análisis de sangre y una biopsia renal mostraron que Frankie padecía un grave caso de glomeruloesclerosis focal y segmentaria, y que sus riñones estaban dejando de funcionar. Fue sometido a diálisis para eliminar los desechos. Debido a que su caso de nefropatía era tan grave, a Frankie, quien apenas tenía tres años de edad, se le extirparon sus riñones para prevenir una pérdida catastrófica de proteínas de la sangre y salvar su vida. Para mantener vivo a Frankie

hasta que se pudiera identificar un donante de riñón y que su cuerpo estuviera lo suficientemente maduro para aceptar un trasplante, se capacitó a su madre para realizar en casa un tipo de procedimiento de diálisis, llamado diálisis peritoneal. Se requería que siete días a la semana ella administrara a su hijo inquieto, de tres años de edad, este procedimiento de limpieza de sangre de 11 horas, casi siempre en la noche, mientras Frankie estaba dormido. Además, Frankie tuvo que tomar numerosos medicamentos para ayudarlo a sustituir algunas de las otras funciones renales perdidas. Por ejemplo, con la aprobación de su familia, a Frankie se le administró un medicamento para intentar controlar el hiperparatiroidismo (producción excesiva de la hormona paratiroidea). Esta enfermedad se presenta como resultado de la insuficiencia renal y es causa de fragilidad en los huesos (osteopenia). Las palabras del padre de Frankie no reflejan plenamente la realidad cuando él dice, "ha sido una experiencia difícil."

La tarea meticulosa de la diálisis casi diaria fue realizada por casi tres años. En ese entonces, Frankie contrajo una infección que lo forzó a ser hospitalizado una vez más, en esta ocasión por un mes, de la cual dos semanas las pasó en una unidad de cuidados intensivos. "Casi lo perdimos," cuenta sentimentalmente el Sr. Cervantes.

La buena noticia es que también durante ese tiempo se determinó que la Sra. Cervantes era una persona apta para donar uno de sus riñones a su hijo. "No pude haber estado más contenta cuando me enteré de que era un donante adecuado para mi hijo," cuenta con una gran sonrisa, con su hijo sentado en sus piernas.

El Trasplante

La familia necesitaba esperar casi un año antes de que el cuerpo de Frankie estuviera lo suficientemente maduro para aceptar el riñón de su madre. Durante ese tiempo, Frankie permaneció en un régimen alimenticio estricto a fin de controlar su presión arterial y las concentraciones de colesterol. "Nada de leche, fruta, sal, ni potasio; nada de nada," dice el Sr. Cervantes. "Frankie veía a otros niños comer helado y papitas fritas. Era muy difícil para nosotros tener que decirle siempre que 'no'."

Cuando finalmente llegó el día en el que Frankie recibiera el riñón de su madre, Frankie, quien había padecido tanto siendo tan pequeño, estaba feliz. Al pasar por la estación de seguridad del hospital le dijo entusiasmado al guardia de turno, "hoy me van a dar mi riñón nuevo."

El riñón nuevo funcionó perfectamente durante tres días. Luego, las pruebas empezaron a mostrar la recurrencia de cantidades excesivas de proteína en la orina de Frankie, una señal de que la glomeruloesclerosis focal y segmentaria estaba presentándose nuevamente y causando síndrome nefrótico. Se le administró un procedimiento de plasmaféresis, es decir, un tratamiento médico mediante el cual se trata la sangre fuera del cuerpo para retirar de ella factores perjudiciales para luego regresarla al paciente. Afortunadamente, Frankie reaccionó bien al tratamiento. Pero después de todo lo que han sufrido, los Cervantes sienten que están viviendo con una "bomba de tiempo." "Nunca sabemos cuándo va a explotar nuevamente esta enfermedad," dice el Sr. Cervantes.

Esperanza que Nace de la Investigación

El Instituto Nacional de la Diabetes y Enfermedades Digestivas y del Riñón (National Institute of Diabetes and Digestive and Kidney Diseases, NIDDK) está interesado en desactivar la bomba de tiempo de enfermedad de Frankie y de otros niños que padecen la glomeruloesclerosis focal y segmentaria. Con ayuda de la Sociedad Estadounidense de Nefrología Pediátrica (American Society of Pediatric Nephrology), el NIDDK ha formado una red de colaboración de centros de investigación para realizar un estudio clínico sobre el tratamiento de FSGS en niños y adultos jóvenes. El objetivo del estudio clínico es comparar la eficacia de dos tratamientos para disminuir la proteinuria en pacientes que, como Frankie, padecen una forma de FSGS de causa desconocida que es

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resistente a los esteroides, pero quienes todavía no han tenido un trasplante de riñón. Asimismo, los científicos del NIDDK están comprometidos a estudiar las posibles causas de otras formas de la FSGS. Estos investigadores están realizando estudios clínicos de enfoques terapéuticos que pudieran prevenir la recurrencia en pacientes que han recibido trasplantes, así como también otros estudios de tratamientos para la FSGS en estos pacientes.

Debido a los medicamentos inmunodepresores que Frankie está tomando actualmente para ayudar a prevenir que su cuerpo rechace su nuevo riñón, él debe limitar su exposición a microbios. Por ahora Frankie, que es un estudiante de primer grado, recibe instrucción de un maestro que lo visita en casa. Como todos los niños de su edad, a Frankie le encanta jugar videojuegos, andar en bicicleta y ver películas. Cuando le preguntan cuál es su mayor deseo, Frankie contesta "nadar en el océano," un sueño que ha sido difícil de lograr durante los últimos años debido a su tratamiento de diálisis peritoneal. Ahora, con su nuevo riñón, es posible que algún día se cumpla el deseo de Frankie.

Para obtener mayor información sobre el estudio clínico de la glomeruloesclerosis focal y segmentaria (FSGS), visite la página *http://www.clinicaltrials.gov/ct/show/NCT00135811?order=8*