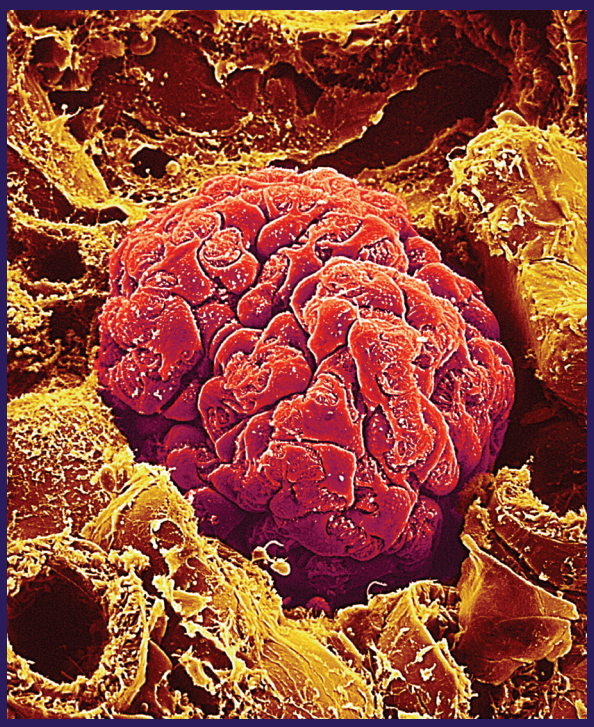

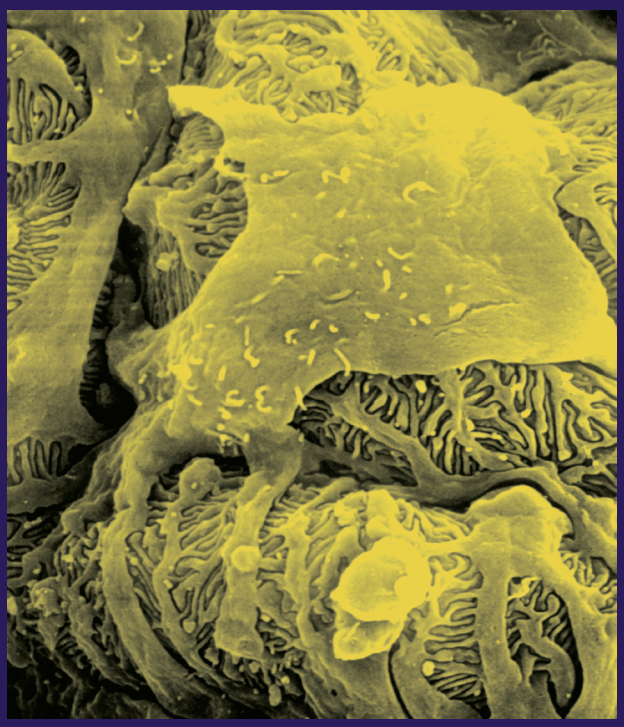

**The glomerulus, located in center of the image on the left, is a small ball of capillaries that, together with surrounding cells, comprises the basic filtering unit of the kidney. The glomerulus is composed of several cell types, including podocytes, which can be seen in the image on the right. Processes extend from neighboring podocytes and interdigitate with one another, like the interlocking fingers of two hands. Many forms of kidney disease involve damage to podocytes within the glomerulus. As described in this chapter, researchers have recently identified variations near the *MYH9* gene on chromosome 22 that correlate with increased susceptibility to non-diabetic kidney disease in African Americans. The MYH9 protein is found in kidney podocyte cells. This finding may have important implications for the treatment of the very large number of these individuals who bear a disproportionate burden of kidney disease.**

*Left image credit: Susumu Nishinaga/Photo Researchers, Inc.; Right image credit: Dr. Tobias B. Huber, University Hospital Freiberg.*

# Kidney, Urologic, and Hematologic Diseases

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

Normal, healthy kidneys process about 200 quarts of blood a day to filter out about two quarts of waste products and extra water from the blood, excreting them as urine. In people with chronic kidney disease, the function of these life-sustaining organs is impaired. Kidney disease may progress to irreversible kidney failure, a condition known as end-stage renal disease (ESRD). People with ESRD require dialysis or a kidney transplant to live. At the close of 2006, more than 500,000 patients were receiving treatment for ESRD.[1] An estimated 26 million Americans suffer from chronic kidney disease.[2] The leading cause of kidney disease is diabetes, with hypertension (high blood pressure) the second-leading cause. If unchecked, the recent increases in obesity and type 2 diabetes in the U.S. will have grave implications in several years, as more people begin to develop kidney and other 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.[1] Hispanics have a significantly increased risk for kidney failure as well.

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

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

Benign prostatic hyperplasia, or BPH, is a common, symptomatic condition that increases with age in men. Prostatitis—chronic inflammation of the prostate gland—is a painful condition that accounts for a significant percentage of all physician visits by young

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[1] *U.S. Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008.*

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

and middle-aged men for complaints involving the genital and urinary systems. To advance research in these areas, the NIDDK recently released a Prostate Research Strategic Plan which will serve as a guide for future scientific inquiry. The NIDDK is committed to enhancing research to understand, treat, and prevent these common and troubling disorders.

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

A conservative estimate is that approximately 12-13 million Americans, most of them women, suffer from urinary incontinence.[4,5] Many who have the disorder suffer in silence due to embarrassment and lack of knowledge about options available. The clinical field of urinary incontinence has changed dramatically in the last decade with the advent of new surgical procedures that have rapidly been introduced into the field. The NIDDK's Urinary Incontinence Treatment Network has recently completed a trial comparing two minimally invasive surgeries for the treatment of stress urinary incontinence and results are expected by the end of 2009.

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

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

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

## ELUCIDATING THE GENETICS OF KIDNEY DISEASE

**New Insights into a Common Form of Kidney Disease:** Two recent reports describe the development of new research tools and advances in our knowledge of the mechanisms underlying IgA nephropathy (IgAN). IgAN is a relatively common form of kidney disease arising from the accumulation of IgA—an antibody the body uses to fight infections—in the kidneys. The cause

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

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

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

of IgAN is unknown, although there is evidence that it runs in families. Over time, IgA deposits can damage the kidneys, and in severe cases patients require dialysis or a kidney transplant to live.

In most patients with IgAN, the sugar molecules that are normally attached to the IgA antibodies are aberrantly-formed, and this is thought to lead to IgA accumulation in the kidneys. Basic research on IgAN has been hampered by a dearth of experimental models. To advance research progress, scientists recently used a blood sample from a patient with IgAN to establish IgA-producing cells that can be grown in the laboratory. By analyzing these cells, they identified the specific step in the biologic pathway at which the addition of sugar molecules to the IgA antibodies goes awry. Such studies may identify new targets for future therapies.

In a second study, researchers measured aberrant IgA levels in patients with IgAN, their relatives, and other volunteers as controls. High levels of aberrant IgA were detected in blood from patients with IgAN compared to controls. Somewhat surprisingly, approximately half of the family members of IgAN patients had elevated levels of the aberrant IgA but did not display symptoms of IgAN. The study suggested that the defect in sugar addition to IgA antibodies is an inherited trait, but that additional factors—either genetic or environmental—are required for kidney disease to develop. The study also showed clustering of abnormal IgA within some of the families, a result that suggested that there may be different subtypes of IgAN.

The new cultured cell line will facilitate future studies of the mechanism of the disease, may identify new targets for therapy, and could help scientists test possible approaches to treatment. The discovery that IgAN arises at least in part due to a genetic component helps scientists understand how the disease is transmitted, and the observation that some people with elevated abnormal IgA do not display symptoms suggests that additional, unknown factors may be contributing to the disease. These and future studies may allow physicians to predict which at-risk patients are likely to develop IgAN, and to personalize treatment depending on an individual's disease subtype.

*Gharavi AG, Moldoveanu Z, Wyatt RJ, Barker CV, Woodford SY, Lifton RP, Mestecky J, Novak J, and Julian BA: Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol 19: 1008-1014, 2008.*

*Suzuki H, Moldoveanu Z, Hall S, Brown R, Vu HL, Novak L, Julian BA, Tomana M, Wyatt RJ, Edberg JC, Alarcón GS, Kimberly RP, Tomino Y, Mestecky J, and Novak J: IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. J Clin Invest 118: 629-639, 2008.*

**Rare Mutations in Kidney Salt Handling Genes Confer Reduced Blood Pressure:** While studying three genes (*SLC12A3*, *SLC12A1*, and *KCNJ1*) known to cause severe inherited blood pressure disorders, scientists identified rare mutations which clinically lower blood pressure and protect individuals from developing hypertension (high blood pressure). While there is known inherited variability in blood pressure, it has been difficult to identify the genes involved.

For this study, researchers analyzed DNA from 3,125 participants in the well-characterized Framingham Heart Study offspring cohort. People have two copies of most genes, and either copy can be normal or contain a mutation that affects the function of the gene (or the protein it encodes). The blood pressure disorders caused by mutations in *SLC12A3*, *SLC12A1*, or *KCNJ1*, genes that affect salt reabsorption by the kidneys, were known to result from inheritance of two mutant copies of any of these genes. For example, two mutant copies of *SLC12A1* results in severe low blood pressure and a greatly enhanced risk of death at a young age.

In the present study, researchers sought to investigate whether there is an effect on blood pressure in people who have only one mutant copy of any of these genes, with the other copy being normal. Approximately 1.6 percent of the tested participants had both a mutation that led to a single defective copy of one of the three salt handling genes, and also a normal copy of the gene. Researchers studied the 49 people with only one mutation. When present in only one copy, these mutations were found to be associated with significantly reduced blood pressure compared to the blood pressure of control participants who had two copies of the more common gene sequence. Of the mutations, 10 had been previously proven to be mutations that cause the protein to malfunction, with the remaining 20 suspected to cause similar loss of protein function. While mutations in both of a person's copies of any of these genes

result in clinically significant lower blood pressure, this new research interestingly identified a beneficial effect—protection from hypertension—conferred by rare mutations when present in only one copy of the gene. The scientists hypothesized that in such cases, the mutations may lower blood pressure by affecting salt reabsorption, although perhaps not to the extent seen with two mutant gene copies. This study contributes to overall understanding of the genetic basis of blood pressure variation in the general population.

*Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, Newton-Cheh C, State MW, Levy D, and Lifton RP: Rare independent mutations in renal salt handling genes contribute to blood pressure variation. Nat Genet 40: 592-599, 2008.*

**Genome-wide Scan Identifies Genetic Regions Linked to Diabetic Kidney Disease:** Researchers have recently reported the identification of four chromosomal regions associated with the development of diabetes-related kidney disease and three chromosomal regions linked to the presence of protein in the urine, a sign of impaired kidney function. These results confirm and extend previous searches for genetic links to kidney disease in people with diabetes, and will allow for more detailed studies that may identify individual genes linked to this serious health problem.

The NIDDK established the Family Investigation of Nephropathy and Diabetes (FIND) consortium to identify genes that confer susceptibility to diabetes-related kidney disease, a life-threatening complication of diabetes. The consortium has focused its research efforts on four ethnic groups: European Americans, African Americans, Mexican Americans, and American Indians. Using genome-wide scans of samples collected from over 1,200 people with diabetes-related kidney disease and their relatives, the FIND researchers identified four regions on chromosomes 7, 10, 14, and 18 where subtle variations correlated with an increased risk of diabetic kidney disease. Similar scans identified three regions on chromosomes 2 and 15 and a different part of 7 associated with elevated protein in the urine. The strength of the linkages varied with the ethnic background of participants. For diabetic kidney disease, the linkage to chromosome 7 was strongest in African American families, while the linkage to chromosomes 10 and 14 was driven primarily by American Indians. For protein in the urine, the linkage on chromosome 2 was strongest in American Indians, on 7 for European Americans, and on 15 for African Americans.

These findings confirm earlier studies implicating regions of chromosomes 7, 10, and 18 in increased risk of diabetic kidney disease, and identify a new region of interest on chromosome 14. The next step is to perform more detailed analyses of these chromosomal regions to identify candidate genes that may confer susceptibility to diabetic kidney disease. Identification of such genes could greatly improve understanding of the disease process as well as provide targets for novel therapeutic strategies.

*Iyengar SK, Abboud HE, Goddard KA, Saad MF, Adler SG, Arar NH, Bowden DW, Duggirala R, Elston RC, Hanson RL, Ipp E, Kao WH, Kimmel PL, Klag MJ, Knowler WC, Meoni LA, Nelson RG, Nicholas SB, Pahl MV, Parekh RS, Quade SR, Rich SS, Rotter JI, Scavini M, Schelling JR, Sedor JR, Sehgal AR, Shah VO, Smith MW, Taylor KD, Winkler CA, Zager PG, and Freedman BI on behalf of the Family Investigation of Nephropathy and Diabetes Research Group: Genome-wide scans for diabetic nephropathy and albuminuria in multiethnic populations: the Family Investigation of Nephropathy and Diabetes (FIND). Diabetes 56: 1577-1585, 2007.*

**Genetic Link to Kidney and Eye Complications of Diabetes:** Scientists have identified a gene associated with risk of kidney and eye complications of diabetes. Proliferative diabetic retinopathy, or PDR, is a serious form of diabetic eye disease and the most common cause of new cases of legal blindness in working age adults in the U.S. Similarly, diabetes is the leading cause of irreversible kidney failure, also called end-stage renal disease (ESRD), in this country. People who develop PDR and ESRD usually develop them both, rather than developing one condition or the other. This observation suggests that there is a shared genetic factor(s) underlying susceptibility or resistance to developing these complications, but until recently, no causal gene had been conclusively identified.

Researchers sought to identify possible genetic factors contributing to these severe diabetes complications by comparing 11 genes in people with type 2 diabetes who either had or did not have PDR and ESRD. These genes were chosen because they were involved in regulating new blood vessel growth. Although new

blood vessel growth is an important part of healthy development, problems with this process are known to play a role in the development of diabetic eye and possibly diabetic kidney disease. One of the genes the researchers examined codes for the hormone erythropoietin, a potent stimulator of new blood vessel growth. The researchers found that variation in a region of DNA near the erythropoietin gene—a region that influences how much of the hormone is made—was associated with PDR and ESRD. They also analyzed genes of people with type 1 diabetes and found the same result, suggesting even more strongly a link between this genetic variation and diabetic eye and kidney disease in people of European American ancestry, who comprised the study groups. Additional analysis suggested that the risk variant may lead to the production of too much erythropoietin, which in turn could promote excessive new blood vessel growth and contribute to the development of PDR and ESRD in people with diabetes. This study identifies a genetic region influencing susceptibility to serious kidney and eye complications of diabetes, and also points to new targets for prevention and therapy. Further study is needed to determine if this genetic variant raises the risk of these complications across racial and ethnic groups. Identifying people at high risk for developing PDR and ESRD could also lead to personalized therapies.

*Tong Z, Yang Z, Patel S, Chen H, Gibbs D, Yang X, Hau VS, Kaminoh Y, Harmon J, Pearson E, Buehler J, Chen Y, Yu B, Tinkham NH, Zabriskie NA, Zeng J, Luo L, Sun JK, Prakash M, Hamam RN, Tonna S, Constantine R, Ronquillo CC, Sadda S, Avery RL, Brand JM, London N, Anduze AL, King GL, Bernstein PS, Watkins S; Genetics of Diabetes and Diabetic Complication Study Group, Jorde LB, Li DY, Aiello LP, Pollak MR, and Zhang K: Promoter polymorphism of the erythropoietin gene in severe diabetic eye and kidney complications. Proc Natl Acad Sci USA 105: 6998-7003, 2008.*

## DEVELOPING NEW TREATMENTS FOR KIDNEY DISEASE

**Novel Mechanism of Action of a Drug Used To Treat Kidney Disease:** A recent report describes a previously unknown direct effect on kidney cells of a drug used to treat various forms of kidney disease. Physicians use cyclosporine A (CsA) to treat people with a variety of kidney diseases, including focal segmental glomerulosclerosis, that are characterized by proteinuria (large amounts of protein in the urine). One cause of proteinuria is injury and damage to specialized cells in the kidneys called podocytes. Damaged podocytes cannot maintain close contact with each other and surrounding membranes, and this disruption allows protein to leak from the bloodstream into the urine. CsA has generally been effective at reducing proteinuria in patients, though its precise mechanism of action was previously unknown. It has been widely assumed that CsA's beneficial effect in kidney disease was due to its suppression of the immune system. However, researchers have recently discovered a direct effect of CsA in the kidney: the drug acts on the podocyte's cytoskeleton, a three-dimensional structure within the cell that is important in cell adhesion and motility and that helps the cell maintain or change its shape. CsA inhibits the degradation of synaptopodin, a podocyte cytoskeletal protein, thereby stabilizing the podocyte's three-dimensional structure and helping to maintain tight cell-cell contact. Experiments in mice indicate that the introduction of genetically-modified forms of synaptopodin that are resistant to degradation protects the animals against experimentally-induced proteinuria. Conversely, activation in podocytes of the enzyme that breaks down synaptopodin causes proteinuria. Together, these results establish a key role for cytoskeletal stability in proper podocyte function, and have important clinical implications. The findings may open new opportunities for the development of drugs to treat proteinuria that directly and selectively act on the podocyte. This avenue of research is particularly important because long-term CsA treatment is associated with serious side effects, which might be avoided with specific podocyte-targeting therapies.

*Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang J-M, Choi HY, Campbell KN, Kim K, Reiser J, and Mundel P: The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. Nat Med 14: 931-938, 2008.*

*(For more information about how possible changes in cellular cytoskeletal components might play a role in kidney disease, see the accompanying Story of Discovery, "Newly-identified Genetic Variations Account for Much of the Increased Burden of Kidney Disease among African Americans.")*

**Reducing Blockage Fails To Improve Access to the Bloodstream for Kidney Dialysis:** Reducing early blockages in bloodstream access in patients with kidney failure (also called end-stage renal disease, or ESRD) by using a drug that inhibits blood clotting does not increase the likelihood that the access will function adequately for long-term treatments, an NIDDK-funded study has found.

Most Americans with ESRD depend on hemodialysis for survival. Hemodialysis, which removes waste products and excess fluid from the bloodstream, requires a vascular access—a surgically-created site that allows blood to be removed from and returned to the body. A fistula is a type of access that is preferred by many physicians because it is less likely to clot or become infected and is less expensive than other types of vascular access sites. However, maintaining an access site represents a significant clinical challenge, and blood clots at the fistula are the most frequent cause of early fistula failure. The Dialysis Access Consortium (DAC) enrolled almost 900 patients with ESRD and fistulas for vascular access, and randomly assigned them to receive either placebo or the anti-platelet drug clopidogrel, which inhibits blood clotting. After 6 weeks, only 12 percent of patients developed blood clots in the fistula when treated with clopidogrel, compared to nearly 20 percent of patients treated with placebo. In order for a fistula to be used for dialysis, however, it must mature and undergo remodeling in order to accommodate increased blood flow. Despite the improvement in short-term outcomes in the group receiving clopidogrel, about 60 percent of the new fistulas in both groups were unsuitable for long-term dialysis.

The DAC Fistula Trial was the largest multi-center clinical trial to examine the effectiveness of approaches to prevent blood clots in new fistulas, and was the first to test whether a prevention strategy would allow more fistulas to function for long-term dialysis. Because vascular access is critical for delivering life-sustaining care to people with ESRD, these results highlight the compelling need for research into novel therapies to reduce or prevent access failure in these patients. The results also underscore the continuing importance of preventing kidney disease in people at risk, preempting the need for hemodialysis in the first place.

*Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, Himmelfarb J, Vazquez MA, Gassman JJ, Greene T, Radeva MK, Braden GL, Ikizler TA, Rocco MV, Davidson IJ, Kaufman JS, Meyers CM, Kusek JW, and Feldman HI for the Dialysis Access Consortium Study Group: Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA 299: 2164-2171, 2008.*

**Chronic Kidney Disease Substantially Worsens in a Fourth of African Americans Despite Recommended Therapy:** Recent findings from a follow-up study to the landmark African American Study of Kidney Disease and Hypertension (AASK) clinical trial show that recommended treatment for chronic kidney disease (CKD) due to high blood pressure did not keep the disease from substantially worsening in about a quarter of the study participants. On a positive note, however, about one-third of participants in the study experienced only a slow decline in kidney function, about what is generally observed with aging.

The AASK clinical trial found that initial drug therapy with an angiotensin converting enzyme (ACE) inhibitor—which targets the renin-angiotensin hormone system that regulates blood pressure and fluid balance—was more effective than either initial therapy with either a calcium channel blocker or beta-blocker in slowing kidney disease progression in African Americans with CKD attributed to high blood pressure. The ACE inhibitor also significantly reduced the risk of kidney failure and death in these patients. No beneficial effect was observed in the trial of a lower than usual blood pressure goal (less than 130/80 mm Hg). However, little data were available regarding the long-term effects of an ACE inhibitor and a low blood pressure goal. Therefore, upon completion of the study in 2001, participants were invited to enroll in the follow-up cohort study, which examined whether a low blood pressure level (less than 130/80) and the use of an ACE or a similar drug, an angiotensin receptor blocker (ARB), would confer long-term benefits. About one-fourth of the AASK Cohort Study had substantial loss of kidney function or developed end-stage renal disease.

The results of the AASK Cohort Study highlight the continuing importance of research into better ways to treat CKD once it occurs, in order to preserve kidney function and prevent progression to end-stage renal

disease. These findings are particularly important because uncontrolled high blood pressure, an increase in the number of people with diabetes, and the aging of the U.S. population—all risk factors for impaired kidney function—will result in more people with CKD. These results also underscore the importance of preventing kidney disease through education of patients and health care providers, increased awareness of the seriousness of the problem, and careful monitoring of people at risk.

*Appel LJ, Wright JT Jr, Greene T, Kusek JW, Lewis JB, Wang X, Lipkowitz MS, Norris KC, Bakris GL, Rahman M, Contreras G, Rostand SG, Kopple JD, Gabbai FB, Schulman GI, Gassman JJ, Charleston J, and Agodoa LY for the African American Study of Kidney Disease and Hypertension Collaborative Research Group: Long-term effects of renin-angiotensin system-blocking therapy and a low blood pressure goal on progression of hypertensive chronic kidney disease in African Americans. Arch Intern Med 168: 832-839, 2008.*

## PREVALENCE OF CHRONIC KIDNEY DISEASE

**Ominous Findings in Study of Chronic Kidney Disease:** A recent study found that a growing number of Americans have chronic kidney disease, but that most of them are unaware of their condition. An estimated 26 million people—about 13 percent of the U.S. population—now have chronic kidney disease, a 30 percent increase in prevalence since 1994. A rather alarming finding of this study was that most people who have impaired kidney function are not aware of their condition and are therefore not receiving treatment. Only 11.6 percent of men and 5.5 percent of women with moderate (stage 3) kidney disease knew it. Awareness was highest among people with severe (stage 4) kidney disease, but even in this group only 42 percent of people knew of their condition. (Stage 5 disease is complete kidney failure, in which patients require either dialysis or a transplant to live.)

People with kidney disease have an increased risk of heart attack, stroke, high blood pressure, and early death. Kidney disease is often silent until its late stages. Once kidney function is lost, patients must undergo kidney dialysis or receive a kidney transplant. But if detected early there are interventions that can preserve kidney function or slow its decline. Patients at risk for kidney disease—those with diabetes, high blood pressure, and/or a family history of kidney problems—should be screened for kidney damage with routine blood and urine tests.

*Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, and Levey AS: Prevalence of chronic kidney disease in the United States. JAMA 298: 2038-2047, 2007.*

## POLYCYSTIC KIDNEY DISEASE RESEARCH

**Genetic Predisposition, Cell-cell Signaling, and Cyst Development in Polycystic Kidney Disease:** Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous fluid-filled cysts, primarily in the kidneys. PKD cysts can profoundly enlarge the kidneys while replacing much of the normal structure, resulting in reduced kidney function and leading to kidney failure. Mutations in two genes, *PKD1* and *PKD2*, are associated with the most common form of the disease, autosomal dominant PKD (ADPKD). The proteins encoded by these genes, polycystin-1 and polycystin-2, form an ion channel on the surface of kidney cells. This channel regulates the flow of calcium into and out of the cell. Mutation of either gene inhibits the activity of the channel, thus disrupting calcium-dependent intracellular signaling pathways. Evidence suggests, however, that additional factors play a role in cyst development.

Scientists have reported that the inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) may play a role in cyst development seen in ADPKD. Expression of this protein is increased in patients with high blood pressure and kidney injury, two conditions often seen in patients with ADPKD. Treatment of cultured mouse kidney cells with TNF-alpha disrupted the ability of polycystin-2 to properly localize to the cell surface. TNF-alpha treatment of cultured whole mouse kidneys led to cyst formation, and this effect was greater in kidneys taken from mice lacking one of the normal two copies of the *PKD2* gene ($PKD2^{+/-}$). Furthermore, in contrast to $PKD2^{+/-}$ mice, which have been shown to develop cysts, $PKD2^{+/-}$ mice treated with an inhibitor of TNF-alpha did not develop cysts in their kidneys. These results connect an inflammatory

response, mediated through TNF-alpha signaling, and a reduction in polycystin-2 function as part of a critical pathway toward cyst formation. Unraveling of both the genetic and nongenetic factors that contribute to cyst formation may identify new targets for therapies to treat ADPKD.

*Li X, Magenheimer BS, Xia S, Johnson T, Wallace DP, Calvet JP, and Li R: A tumor necrosis factor-alpha-mediated pathway promoting autosomal dominant polycystic kidney disease. Nat Med 14: 863-868, 2008.*

## UROLOGY RESEARCH

**"Intracellular Bacterial Communities" Detected in Urinary Tract Infections in Women:** Scientists have shown that some human urinary tract infections (UTIs) are associated with intracellular bacterial communities (IBCs). Infections of the urinary tract are common in women—about one-third of all women in the U.S. are diagnosed with a UTI by the time they reach 24 years of age—and many women suffer repeated UTIs. While antibiotic treatments are available, better prevention and treatment strategies are needed. Most UTIs are caused by a common type of *Escherichia coli* (*E. coli*) bacterium. An acute UTI begins when bacteria attach to cells lining the inside of the bladder. This provokes a defense response in the infected individual including activation of the immune system and sloughing off of bladder cells into the urine in an attempt to rid the body of offending bacteria.

Over the past several years, scientists studying UTIs in a mouse model found that UTI-causing *E. coli* are able to invade cells lining the bladder and form so-called IBCs, which appear to help promote sustained infection. Following up on these intriguing findings in mice, the researchers recently turned their attention to determining whether IBCs play a role in human UTIs. To do so, they looked for evidence of IBCs in urine samples from 100 women, 80 of whom had been recently diagnosed with an acute UTI, and 20 of whom had a history of UTI but did not have symptoms of an active infection. Using a variety of microscopic techniques, the investigators found that urine samples from 14 of the 80 women with UTIs (18 percent) contained IBCs. None of the asymptomatic women with a history of UTI showed evidence of IBCs.

Urine samples were also analyzed for the presence of filamentous bacteria—a form of the UTI-causing *E. coli* bacteria that can evade the host immune response. While nearly half of the urine samples from women with a UTI had filamentous bacteria, none were detected in the asymptomatic group. Filamentous bacteria were detected in all of the IBC-containing urines, compared to 29 percent of samples with no detectable IBCs. This study demonstrates, for the first time, that filamentous bacteria and IBCs do occur in some women with UTIs. Additional studies need to be done to determine whether IBCs contribute to recurrent infections in women as they do in mice. However, these results already suggest that new treatment strategies that address the host-evading nature of IBCs and filamentous bacteria may be beneficial for women who test positive for UTIs.

*Rosen DA, Hooton TM, Stamm WE, Humphrey PA, and Hultgren SJ: Detection of intracellular bacterial communities in human urinary tract infection. PLoS Med 4: 1949-1957, 2007.*

**Common Gut Bacteria May Reduce Risk of Kidney Stone Formation:** The presence of a particular kind of bacteria in the intestinal tract may protect against the formation of the most common kind of kidney stone, according to a recent report. Kidney stone disease is a common and painful health problem in the U.S. It is estimated that between 5 and 15 percent of people will form a stone at some point during their lives, and that 30 to 50 percent of these people will suffer from recurrent stones over the ensuing 5 years. Most kidney stones mainly consist of crystallized calcium oxalate and small amounts of other compounds. Both calcium and oxalate are components of a normal diet, and high levels of oxalate in the urine correlate with increased risk of stone formation. However, decreasing dietary intake of oxalate has not been demonstrated to be effective in preventing kidney stone formation.

A recent report suggests that the common gut bacterium, *Oxalobacter formigenes* (*O. formigenes*), can metabolize and break down oxalate in the digestive tract, thereby reducing the likelihood of oxalate entering the body and forming a kidney stone. Researchers studied nearly 250 people who suffered from recurrent calcium oxalate stones and compared them to 250 people who did not form stones. They found that, among patients who formed stones, 17 percent had the bacterium *O. formigenes* in their intestinal tracts;

among those who did not form stones, the fraction with *O. formigenes* was 38 percent. *O. formigenes* presence in the intestinal tract was associated with a 70 percent reduction in risk for being a recurrent calcium oxalate stone former. Surprisingly, urinary oxalate levels did not differ with the presence or absence of *O. formigenes* colonization. Nevertheless, these results suggest that future therapies could involve introduction of *O. formigenes* or similar agents into the intestinal tracts of individuals who are at risk of recurrent stone formation. Such approaches may significantly reduce the likelihood of calcium oxalate stone formation in such individuals.

*Kaufman DW, Kelly JP, Curhan GC, Anderson TE, Dretler SP, Preminger GM, and Cave DR: Oxalobacter formigenes may reduce the risk of calcium oxalate kidney stones. J Am Soc Nephrol 19: 1197-1203, 2008.*

**Brain Reacts to Bladder Disease:** Overactive bladder is a prevalent condition which negatively impacts the quality of life. Partial bladder obstruction is the common cause of overactive bladder in males. Although many studies have characterized the structural and functional changes associated with the partially obstructed bladder, little is known regarding the impact of overactive bladder on brain function. The researchers determined that a portion of the brain, including the locus ceruleus, displayed altered activity as a result of the partial bladder obstruction. These findings might have potential implications for overactive bladder in people, in that altered activity in this region of the brain might cause disordered sleep, anxiety, and difficulty in concentrating. The findings of this study suggest that pharmacological interventions which target the locus ceruleus may be beneficial in patients with bladder dysfunctions.

*Rickenbacher E, Baez MA, Hale L, Leiser SC, Zderic SA, and Valentino RJ: Impact of overactive bladder on the brain: Central sequelae of a visceral pathology. Proc Natl Acad Sci USA 105: 10589–10594, 2008.*

## HEMATOLOGY RESEARCH

**New Insights into Gene Regulation During Blood Cell Development:** A recent study shows that there is an inherent spatial organization that relates to how genes are regulated within the cell. Different types of cells require different proteins in order to perform their specialized functions, and thus must activate different arrays of genes. For example, red blood cells, infection-fighting white blood cells, and early-stage progenitor cells (that can develop into multiple types of blood cells) all need to turn on different sets of genes as they mature. But how are genes and chromosomes organized in the cell to achieve the co-regulation of specific sets of genes required for the development of specific types of blood cells?

In a recent report, scientists analyzed the arrangement of co-regulated genes along chromosomes and determined their organization during blood cell development in the mouse. By assessing the extent to which different genes are expressed (active or inactive) during blood cell development, as well as the chromosome locations of the genes, the researchers were able to demonstrate that coordinately-regulated genes, or gene sets, are clustered within individual chromosomes and that chromosomes are positioned in a cell's nucleus such that co-regulated gene clusters on separate chromosomes touch one another. These experiments determined that active genes associated with blood cell development are found within a particular part of the cell nucleus, the cellular compartment which houses most of the genes. The results indicated that active genes are localized to the inner portion of the nucleus and also that each duplicate pair of chromosomes—one from each parent—tend to associate and that this organization is related to the distribution of co-regulated genes along chromosomes. Thus, this study indicates that the proximity of chromosomes to the inner portion of the nucleus and the positioning of duplicate pairs of chromosomes in the cell nucleus has an important role in coordinating gene regulation during blood cell development.

*Kosak ST, Scalzo D, Alworth SV, Li F, Palmer S, Enver T, Lee JSJ, and Groudine M: Coordinate gene regulation during hematopoiesis is related to genomic organization. PLoS Biol 5: 2602-2613, 2007.*

**Genetic Cause Identified for Iron Deficiency in Individuals Unresponsive to Oral Iron Supplementation:** A recent study implicates mutations of the gene *TMPRSS6* as causing a particular form of iron deficiency anemia. *TMPRSS6* encodes a cell membrane-bound protein produced in the liver that controls levels of a critically important iron-regulatory protein called

hepcidin. In the U.S., most people with iron deficiency are easily treated with oral iron therapy; however there exists a small subset of children who don't respond to oral iron therapy—a condition termed iron-refractory iron-deficiency anemia (IRIDA). Investigators identified five families in which IRIDA was present in siblings. Because the siblings' parents did not have iron deficiency, the scientists thought that each parent may have one mutant and one normal copy of the causative gene, and that perhaps the children inherited only mutant copies of the gene, resulting in the disorder. Once identified as a likely candidate gene for this form of iron deficiency, analysis of this gene derived from the five families revealed several different types of genetic mutations.

Although not fully understood, mutations in the TMPRSS6 protein cause the body to over-produce hepcidin. Hepcidin controls iron concentrations in the body by regulating the recycling of iron from old red blood cells, and also by controlling intestinal iron absorption. The over-production of hepcidin effectively shuts down absorption of dietary iron from the intestine and traps the body's existing iron within the cells (called macrophages) that attempt to recycle it, thereby limiting the availability of iron to be used for new red blood cell production. These findings demonstrate the importance of TMPRSS6 to normal iron regulation in humans. Additionally, this study raises the possibility that delivery of functional TMPRSS6 into patients with IRIDA may reduce hepcidin levels and timely improve iron absorption from the intestine and release of iron from internal iron stores. Because other iron metabolism disorders are also associated with abnormal hepcidin levels, the development of strategies to modulate TMPRSS6 activity could potentially have even broader clinical implications in the future.

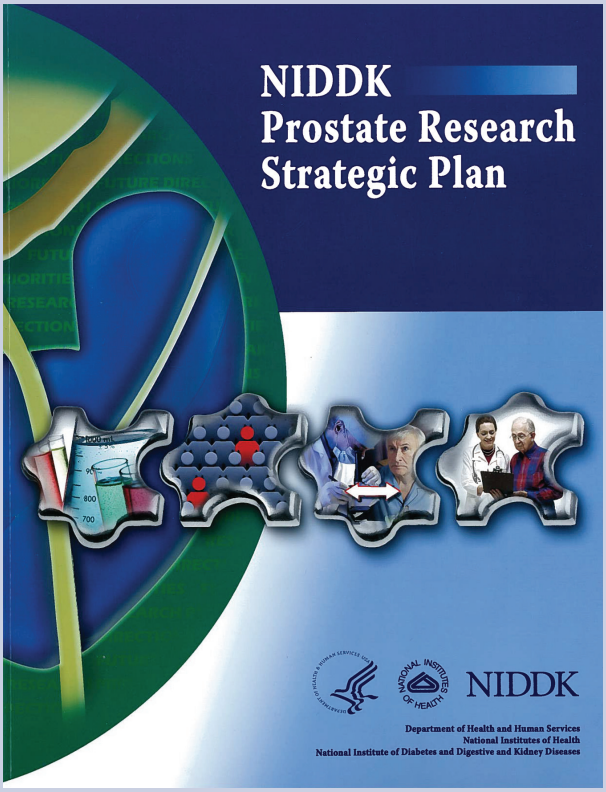
*Finberg KE, Heeney MM, Campagna DR, Aydinok Y, Pearson HA, Hartman KR, Mayo MM, Samuel SM, Strouse JJ, Markianos K, Andrews NC, and Fleming MD: Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). Nat Genet 40: 569-571, 2008.*

**"Nix"-ing Mitochondria as Part of Red Blood Cell Maturation:** NIDDK-supported researchers have determined that a protein called "Nix" plays a vital role in the normal maturation of red blood cells by targeting the cells' mitochondria for destruction. While mitochondria are cell components typically used for energy production, they can also be detrimental to cell survival by producing reactive oxygen species that can lead to cell death. In red blood cells, the removal of mitochondria through autophagy (self digestion) within so-called "autophagosomes" is a natural part of maturation, which also helps to prolong cell life. In people with defects in this process, disorders such as anemia can result. The Nix protein is a member of a family of proteins that regulate a pathway the body can use to get rid of cells—a cell death pathway. During differentiation of cells into mature red blood cells, the Nix protein is increased and is thus well positioned to influence this process.

In this series of studies, researchers studied mice that were unable to produce Nix in order to evaluate the role that this protein plays in a cell's digestion of its mitochondria as part of normal red blood cell maturation. In the absence of Nix, the mice developed both anemia associated with a reduced number of circulating red blood cells, and an expanded population of immature red blood cell precursors. The circulating red blood cells that were present retained mitochondria and had a shorter lifespan which was associated with an inability of the mitochondria to undergo autophagy. These studies enrich understanding of key molecular events in red blood cell maturation and how these events can be disturbed to result in anemia and other disorders. Based on these findings, novel therapeutic approaches could be developed in the future to treat certain forms of anemia.

*Sandoval H, Thiagarajan P, Dasgupta SK, Schumacher A, Prchal JT, Chen M, and Wang J: Essential role for Nix in autophagic maturation of erythroid cells. Nature 454: 232-235, 2008.*

# *A Strategic Plan for Prostate Research*




**The *NIDDK Prostate Research Strategic Plan* will guide the development of future research efforts targeting benign prostate disease cause, prevention, and treatment.**

The *NIDDK Prostate Research Strategic Plan*, published in May 2008, was developed under the Institute's auspices with the contributions of external experts in benign urologic disease. The Plan identifies questions of highest significance and provides recommendations for research to address them. The NIDDK will use the recommendations and insights in the *Plan* to guide the development of future research efforts targeting benign prostate disease cause, prevention, and treatment.

The research area of benign prostate disease includes two of the most significant non-cancerous disorders affecting men—benign prostatic hyperplasia (BPH) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). BPH, an enlargement of the prostate gland, is often associated with lower urinary tract symptoms (LUTS). LUTS, which can include symptoms such as overactive bladder, restricted or excessive urination, and sensations of urgency, affects men of all races and ethnic groups and can become severe over time. An estimated 50 percent of men in their 50s have BPH, and 26 to 46 percent of men between the ages of 40 and 79 have moderate to severe symptoms. CP/CPPS is generally described as inflammation of the prostate gland and is sometimes associated with urinary symptoms, pain, and sexual dysfunction. The source of the pain in this syndrome is unknown and there are no generally effective methods for preventing or treating the condition.

*The NIDDK Prostate Research Strategic Plan* addresses four major research areas judged critical for advancing the field. These include basic science, epidemiology and population-based studies, translational research, and clinical sciences. Selected high priority recommendations from the *Plan* include:

- Promote interdisciplinary research that focuses on how benign prostate diseases are influenced by other organ-specific diseases and systemic conditions, such as obesity, high blood pressure, high cholesterol, cardiovascular disease, diabetes, and erectile dysfunction. For example, the possible influence of high blood pressure on BPH/LUTS is a previously unexplored area of research.
- Study the primary prevention of benign prostate diseases, including possible benefits of lifestyle changes such as avoidance of alcohol and caffeine, frequency of sexual practice, pelvic massage therapy, stress reduction, and diet modulation for relief of CP/CPPS.
- Develop data and human tissue resources from patients of various ages to derive information useful in investigating risk factors, underlying causes and natural history of disease progression, quality of life, quality of care, and decision making regarding treatment of benign prostate disease.
- Develop imaging approaches and other biomarker studies to assess severity and risk of progression based on physical and cellular findings.
- Develop targeted medical therapies based on new insights into disease-relevant cellular pathways and physiological events.

- Develop standardized, clinically significant benign prostate disease syndrome definitions and classifications based on measurable phenotypic features.
- Train and mentor epidemiologists, health services researchers, clinical investigators, and students interested in the study of benign prostate disease.

The *Plan* is designed for researchers, clinicians, professional organizations, and patients. Each major section includes a mission statement, a lay summary, an overview of current knowledge, and high-priority recommendations for future research.

The Plan is online at *http://www2.niddk.nih.gov/NR/rdonlyres/318606D2-A9D1-4CAD-B9BF-8EB3009C83BE/0/NIDDKProstateStrategicPlan.pdf* and can be purchased online in print or compact disc format at *http://catalog.niddk.nih.gov/PubType.cfm?Type=182&CH=NKUDIC*

## STORY OF DISCOVERY

# *Newly-identified Genetic Variations Account for Much of the Increased Burden of Kidney Disease among African Americans*

For the first time, researchers have identified variations near a single genetic locus that are strongly associated with kidney diseases disproportionately affecting African Americans. Two research teams independently studied kidney diseases arising from causes other than diabetes. Kidney disease can lead to kidney failure, requiring long-term dialysis or a kidney transplant to sustain life. Using a type of genome-wide association technique that relies on differences in the frequency of genetic variations between populations, the researchers identified several variations in the region of the *MYH9* gene on chromosome 22 as major contributors to excess risk of non-diabetic kidney disease among African Americans. Somewhat surprisingly, both research teams found no association between the *MYH9*-area variants and diabetes-related kidney failure in this population, a finding that suggests the mechanisms leading to chronic kidney disease and then to kidney failure may be different depending on the underlying cause. This insight may have important implications for the treatment of the very large number of individuals with kidney disease.

**Kidney Disease: A Heavy Burden for Some Populations**

Early-stage kidney disease often has no symptoms. Left unchecked, however, it can silently progress to kidney failure, a condition in which the kidneys are no longer able to filter waste and excess fluids from the blood. As many as 26 million U.S. adults over the age of 20 are estimated to have some degree of impaired kidney function,[1] and over a half million Americans were receiving life-sustaining kidney dialysis or were living with a kidney transplant at the end of 2006[2] (the most recent year for which complete data are available). Despite recent advances in preserving kidney function in individuals with early-stage kidney disease, serious health complications are common. In fact, roughly half of the people with kidney disease will die from cardiovascular disease before their kidney function further deteriorates and they progress to full-blown kidney failure.[3]

The two most common causes of kidney failure are diabetes and hypertension (high blood pressure), which together account for about 70 percent of all new cases.[2] Both conditions are seen more frequently in members of ethnic minorities, and African Americans bear an especially heavy burden of kidney disease. African Americans are nearly 3 times as likely as whites to develop kidney failure from any cause.[4] One such cause is a form of kidney disease called focal segmental glomerulosclerosis (FSGS), in which the glomeruli—the tiny filtering units of the kidneys—are damaged and scarred.[5] Most FSGS arises from unknown causes and is termed "idiopathic" FSGS. African Americans are approximately 5 times more likely to develop idiopathic FSGS compared to individuals of other racial backgrounds. The health disparity increases with HIV infection: African Americans are 18 to 50 times more likely than whites to develop FSGS related to infection with HIV, the virus that causes AIDS.[6,7] These rather striking disparities represent a serious public health problem, not only because of the kidney disease itself, but also because people who have even mild- to moderately-severe kidney disease typically have high blood pressure and other risk factors for serious complications such as cardiovascular disease.[2]

What accounts for this dramatically increased risk of severe kidney disease in African Americans? Scientists and physicians have long known that kidney disease tends to run in families and cluster in ethnic groups. These observations indicate that

kidney disease is likely to have a genetic component. It is also almost certain that environmental factors play a role in disease susceptibility as well. However, studies that have attempted to identify genes that confer susceptibility to kidney disease and kidney failure have not generally been successful.

Furthermore, it is not clear that all forms of kidney disease originate from a common starting point or progress through a shared pathway. For example, while patients with diabetes or those with hypertension are at increased risk of developing kidney disease and kidney failure, not all patients at risk go on to develop kidney disease. In addition, it is not clear that the underlying disease mechanisms which initiate injury and facilitate progression in diabetic and hypertensive kidney disease are the same. If, in fact, these two conditions cause kidney disease through different pathways, then treatment strategies for people whose kidney disease is a consequence of diabetes could be very different from those for people whose kidney disease is attributed to hypertension. Because of these considerations, it is especially important to identify the genetic contribution to disease development and progression and characterize the biological pathways that lead to diminished kidney function.

**New Techniques Allow Researchers To Ask New Questions**

For some conditions, mutations in a single gene are sufficient to cause disease, and careful analysis of inheritance patterns in families can often readily identify the gene responsible. These diseases are termed "simple" genetic diseases, because their underlying cause, while not always easy to uncover, tends to lead to disease in a straightforward way.

However, many diseases likely arise not from mutations in a single gene but from the interplay of complex genetic susceptibility—resulting potentially from multiple genes, each of which may have only modest effects—and environmental influences. In the case of these "complex" genetic diseases, identifying the genetic contribution of multiple, widely-spaced chromosomal regions to disease development and progression can be quite difficult.

Recently, a new technique, termed admixture mapping, has been developed to search for genes that cause complex genetic diseases. Admixture mapping is particularly useful in examining the underlying genetic causes of complex diseases in which the frequency of disease is very different between two populations. Using admixture mapping, scientists examine haplotypes—groups of genes spanning multiple chromosomal loci that are transmitted together. These haplotypes are inherited; therefore, haplotypes tend to be similar among members of the same population but to differ between members of different populations. Admixture mapping takes advantage of the fact that genetic variants that are not linked to one another tend to dissociate from one another rather rapidly—within a few generations—while those that are linked tend to stay together longer. The relatively recent (anthropologically speaking) mixing of European and African populations is referred to as "admixture": the formation of a new population with a heterogeneous mixture of African- and European-derived haplotypes.

**A New Window into the Genetics of Kidney Disease**

Because of the striking difference in kidney disease and kidney failure rates between whites, who are largely of European ancestry, and African Americans, researchers had speculated that admixture mapping might be an effective way to try to identify which chromosomal regions are associated with the development of kidney disease. The rationale behind these experiments was that chromosomal regions that confer an increased risk of kidney disease would be more common in individuals of African ancestry than in those of European ancestry. At least two groups of scientists hypothesized that, by using admixture mapping, they could identify genetic variants that tracked closely with disease development.
In the fall of 2008, the two research teams reported

## STORY OF DISCOVERY

the identification of genetic variants more common in African Americans that seemed to explain a large proportion of the excess burden of FSGS and HIV-associated and other non-diabetic kidney disease in African Americans. In addition, the contribution of this genetic variation to an individual's risk of developing kidney disease is higher than that observed for nearly all previously described genetic factors discovered by genome-wide scans, including those for prostate cancer, diabetes, cardiovascular disease, breast cancer, and hypertension.

One research team, which included members of the NIDDK Intramural Research Program's Kidney Disease Branch and other researchers, studied individuals with FSGS, HIV-associated FSGS, and hypertensive end-stage kidney disease. The other team, consisting of researchers working as part of the NIDDK-funded Family Investigation of Nephropathy and Diabetes Consortium, was led by researchers at The Johns Hopkins University and included collaborating scientists at other institutions. They examined patients with kidney failure arising from multiple causes, including diabetes, hypertension, FSGS, and HIV infection. Using admixture mapping, both groups of scientists identified a genetic variant in a region of chromosome 22 that correlated strongly with susceptibility to certain kidney diseases.

Fine mapping of this chromosomal region revealed that the gene *MYH9* was located in the identified area. *MYH9* encodes the protein "non-muscle myosin heavy chain 9," which is part of non-muscle myosin IIA. Myosin is a protein made up of several subunits and serves as a cellular motor, providing the force for cell movement, cell tension, and cell division. The most common form of myosin is found in skeletal muscle and is involved in muscle contraction. Non-muscle myosin IIA is a form of myosin found in many tissues, including—despite its name—muscle. The *MYH9* gene is expressed in podocytes, specialized cells within kidney glomeruli that play an important role in the filtering of waste and excess fluid. Podocyte damage is a hallmark of FSGS and other kidney diseases that can lead to reduced kidney function and/or kidney failure. However, it is not known how variations in the *MYH9* region might impact podocyte function.

The degree to which these genetic variants increase risk of developing kidney disease in African Americans from certain causes is truly striking. *MYH9* risk variants account for nearly all of the increased risk for idiopathic FSGS and HIV-associated FSGS among African Americans compared to European Americans and a portion of the increased risk for hypertensive kidney disease. Surprisingly, however, these variants were not associated with kidney failure arising from diabetes.

The risk of developing kidney disease is strongest when an individual has two copies of the risk variant. Nonetheless, even among individuals with two risk variants, kidney disease is uncommon. Thus 36 percent of African Americans have two copies of the risk variant but only approximately 1 in 50 of these individuals will develop FSGS during the course of a lifetime. It is likely other factors, possibly additional genes or environmental influences, are important in triggering FSGS. Future research efforts will focus on the identification and characterization of these additional factors.

It is important that it is the presence of the variant that confers the increased risk of kidney failure, not African ancestry *per se*. However, these variants were much more frequently seen among people of African ancestry than among those of European ancestry—60 percent of alleles among African Americans are the risk variant (84 percent of African Americans carry one or two copies of the risk allele), while only 4 percent of alleles among European Americans are the risk variant (8 percent of European Americans carry one or two copies of the risk allele).

## STORY OF DISCOVERY

**Implications and Future Directions**

Although both studies described here implicate variations in the chromosomal region surrounding *MYH9* as important risk factors for kidney disease, scientists have not identified specific mutations in the *MYH9* gene that might suggest a causal mechanism. One possibility is that the critical genetic variations lie not within the coding sequence of the *MYH9* gene, but in the surrounding chromosomal regions. The nature of these hypothetical variations, and the ways they might alter cellular metabolism or function so as to confer greater risk of non-diabetic kidney disease, are the subject of ongoing investigations. Future studies will aim to characterize the exact nature of the variations in the *MYH9* region and how these variations may influence susceptibility to non-diabetic kidney disease. Additional future studies will focus on the pattern of *MYH9* expression across tissues, and investigation into the role played by *MYH9* in podocyte function, and how this might be disrupted in individuals carrying the risk variant.

One of the central questions facing researchers who study kidney disease is whether all kidney disease is created equal: although many different conditions—diabetes, hypertension, and FSGS were among the ones studied by these investigators—put people at increased risk for chronic kidney disease and kidney failure, it is not known whether these conditions share a common disease pathway or each have unique characteristics that define them. This distinction is important, because current approaches to therapy are aimed at preserving kidney function and addressing the underlying health problem, not at addressing specific processes that may damage the kidneys. The discovery that a particular genetic variation confers susceptibility to kidney failure by some mechanisms—such as hypertension and FSGS—and not by others—such as diabetes—indicates that there are likely at least two pathways to kidney failure.

These findings also validate the use of admixture mapping to perform genome-wide scans to identify susceptibility genes for complex diseases. Insights gained from the studies have important implications for improved patient care and for understanding the basic biology of kidney disease and kidney failure.

Finally, this story highlights the importance of collaborations between scientists at the NIH and NIH-funded investigators at outside research institutions. Government-academic collaborations of this kind are one way to move translational research forward, from the bench to the bedside and beyond, and provide the knowledge base for developing new therapies for chronic health disorders such as kidney disease and kidney failure.

*The investigators in the NIDDK Intramural Research Program, who first identified the* MYH9 *gene as contributing to kidney disease, have been conducting basic and clinical research studies of kidney disease, focusing on focal segmental glomerulosclerosis, at the NIDDK since 1995. Scientists at the National Cancer Institute's Center for Cancer Research also contributed to this study. The Johns Hopkins-led research team, that confirmed and extended the MYH9 findings, is part of the NIDDK-funded Family Investigation of Nephropathy and Diabetes (FIND) Consortium. First funded in 1999, the Consortium was established to identify genetic pathways that may be critical for the development of diabetic kidney disease as well as to identify candidate genes and/or pathways that may be amenable to therapeutic strategies to prevent the onset or progression of kidney disease. Though originally conceived as an effort to identify genes associated with diabetes-related kidney disease, FIND investigators discovered an important clue regarding non-diabetic kidney disease. The two studies were published in the journal* Nature Genetics *in October 2008; the citations are* Nat Genet *40: 1175-1184, 2008 and* Nat Genet *40: 1185-1192, 2008.*

## STORY OF DISCOVERY


[1] *Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, and Levey AS: Prevalence of chronic kidney disease in the United States. JAMA 298: 2038-2047, 2007.*

[2] *U.S. Renal Data System, USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2008.*

[3] *Kundhal K and Lok CE: Clinical epidemiology of cardiovascular disease in chronic kidney disease. Nephron Clin Pract 101:c47-c52, 2005.*

[4] *Kiberd BA and Clase CM: Cumulative risk for developing end-stage renal disease in the US population. J Am Soc Nephrol 13: 1635–1644, 2002.*

[5] *Kitiyakara C, Kopp JB, and Eggers P: Trends in the epidemiology of focal segmental glomerulosclerosis. Semin Nephrol 23: 172–182, 2003.*

[6] *Kopp JB and Winkler C: HIV-associated nephropathy in African Americans. Kidney Int Suppl 63: S43–S49, 2003.*

[7] *Eggers PW and Kimmel PL: Is there an epidemic of HIV infection in the US ESRD program? J Am Soc Nephrol 15: 2477–2485, 2004.*

# More Intensive Dialysis Does Not Improve Outcomes among Patients with Acute Kidney Injury

*Dr. Paul M. Palevsky*

*Dr. Paul M. Palevsky is a Professor of Medicine in the Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, and is Section Chief of the Renal Section at the VA Pittsburgh Healthcare System. His research interests focus on the prevention and treatment of acute kidney injury and the management of kidney replacement therapy in acute and chronic kidney disease. In May of 2008, Dr. Palevsky described the findings of the Veterans Affairs/ National Institutes of Health Acute Renal Failure Trial Network Study in a featured presentation at the annual American Thoracic Society International Conference in Toronto, Canada. The following summary is based on that presentation. The results of the study were subsequently published in the July 3, 2008, issue of the* New England Journal of Medicine.

Acute kidney injury (also called "acute renal failure") is a serious medical condition characterized by a relatively rapid loss of kidney function, usually over a period of several hours or days. The resulting inability to excrete nitrogenous waste products and maintain fluid and electrolyte balance poses urgent health problems for patients and their physicians. Acute kidney injury may arise from a number of causes, most commonly sepsis (a serious, whole-body inflammatory reaction caused by infection), decreased blood pressure, or kidney damage from drugs or other toxins. It is a relatively common complication among hospitalized patients; it affects between 2 and 7 percent of all hospitalized patients.[1] Even though a significant fraction of patients with acute kidney injury will regain kidney function, many do not, and this medical condition is associated with high in-hospital mortality rates ranging from 50 to 80 percent among the critically ill.[1]

There is no effective drug therapy to reverse acute kidney injury. The goal of treatment is to prevent fluid and waste from building up in the body while waiting for the kidneys to resume functioning. Treatment involves hemodialysis and other forms of life-sustaining therapy to replace lost kidney function. Dialysis removes waste products from the blood, and it also helps control blood pressure and keeps the proper electrolyte balance.

Although dialysis has been used to treat acute kidney injury for over 60 years, it is still not clear when it is best to initiate therapy, which method of dialysis is best to use, and what dose of dialysis to deliver. Several recent, small studies had suggested that increased frequency or intensity of dialysis might improve survival in patients with acute kidney injury. However, the results of these studies have not been definitive. This uncertainty raises the possibility that some patients may be receiving a sub-optimal dose or frequency of dialysis, or that other patients may be receiving excessive dialysis that may carry no clinical benefit and may, in fact, expose them to unnecessary risk. In order to investigate this issue, the NIDDK partnered with the U.S. Department of Veterans Affairs to launch a clinical trial comparing "standard" with "intensive" dialysis in patients with acute kidney injury.

**Design of the ATN Study**

The VA/NIH Acute Renal Failure Trial Network (ATN) Study was designed to determine whether higher-dose (intensive) dialysis would reduce the death rate, shorten the duration of the illness, and decrease the number of complications in other organs among patients with acute kidney injury, as compared to standard-dose dialysis. It enrolled over 1,100 critically

ill patients—defined as patients with acute kidney injury as well as either sepsis or the failure of at least one other organ. Notably, the trial did not enroll patients with chronic kidney disease. These patients were not studied in this trial because the causes and progression of their acute kidney injury are different from that seen in people without underlying chronic kidney disease.

Patients were randomly assigned to receive intensive- or standard-dose dialysis. Patients who did not require medications to maintain their blood pressure were treated with conventional dialysis, either three times per week in the standard arm of the study or six times per week in the intensive arm. Patients with very low blood pressure who required medications to increase their blood pressure were treated with more gentle forms of dialysis, either a slower form of hemodialysis, three or six times per week, or a continuous form of dialysis, at a lower or higher dose, as randomly assigned. One important element in the design of the study was that patients were able to switch between forms of therapy as their clinical condition changed, while remaining within the lower or higher intensity treatment arms of the study. This approach reflects typical clinical practice in that it allowed physicians to adjust the method of dialysis as the patient's condition changed, and was chosen so that the results of the trial would be more relevant to actual patient care.

**Results of the ATN Study: Is More Better?**

The primary question the trial was designed to answer was whether more intensive dialysis provided a clinical benefit. The first, and perhaps most important, clinical endpoint was patient survival. After 60 days, no significant difference in rates of death by any cause was found between the two groups of patients. Over this period, 289 of 561 patients (51.5 percent) in the standard-dose treatment group died, compared to 302 of 563 patients (53.6 percent) in the intensive treatment group. Mortality rates were similar in men and women and across racial and ethnic subgroups.

When the researchers assessed kidney function and other medical conditions, similar patterns were seen. A total of 102 patients (18.4 percent) in the standard-dose group had complete recovery of kidney function after 28 days, and 50 patients (9.0 percent) had partial recovery. By comparison, 85 patients (15.4 percent) in the intensive-treatment group had complete recovery of kidney function over the same time period, and 49 patients (8.9 percent) had partial recovery. A total of 92 patients (16.4 percent) undergoing less-intensive therapy were able to return home without requiring continued dialysis after 60 days, compared to 88 patients (15.7 percent) who underwent intensive therapy. None of these differences between groups was statistically significant. Rates of treatment-related complications across all groups were also similar.

In summary, the ATN Study found no significant differences between the two groups in recovery of kidney function, the rate of failure of organs other than kidneys, or the number of patients able to return home after recovery. In patients enrolled in this trial, there was no benefit to intensive dialysis.

**Implications of the ATN Study**

Although a few studies have suggested that increased frequency or intensity of hemodialysis might improve survival in patients with acute kidney injury, they have been small and conducted at single sites. In contrast, the ATN study enrolled over 1,100 patients from 17 Veterans Affairs medical centers and 10 university-affiliated medical centers across the U.S. The results of the larger ATN Study show that when it comes to dialysis in acute kidney injury, more is not better.

The results of the ATN study, however, should be interpreted carefully. One limitation of the ATN study concerns the exclusion from the trial of patients with advanced chronic kidney disease. Such patients make up a substantial proportion of people who develop acute kidney injury. Therefore, it may be inappropriate to extrapolate the ATN results to persons in whom acute kidney injury develops in

the context of pre-existing chronic kidney disease. Further study will be necessary to resolve this longstanding question and address the optimal treatment of acute kidney injury in this population.

**Conclusion**

The results of the ATN study indicate that increasing dialysis treatments to five to six times per week does not confer an additional benefit beyond a standard three times per week regimen. However, this does not mean that dose of dialysis does not matter. The dose of dialysis targeted in the standard-treatment group was greater than what is often achieved in a typical clinical setting. The results also do not mean that higher doses of continuous therapies are never beneficial, only that routine use of higher-dose dialysis is unnecessary. Nevertheless, the findings of this study may spare patients from unnecessarily-intensive medical interventions. They also underscore the importance of continued research into other approaches to treating acute kidney injury. Future research efforts may include studies to identify biomarkers of kidney injury prior to renal failure, which could enable physicians to predict who is likely to develop acute kidney injury, to lessen its severity through earlier intervention, or to preempt this life-threatening condition altogether.

*The NIDDK has begun a new initiative entitled "Identification and Evaluation of Biomarkers and Risk Assessment Tools for Chronic Kidney Disease and Acute Kidney Injury." The goal of this initiative is to identify and validate biomarkers and risk assessment tools for kidney function, injury, and progression. Both existing and new biomarkers and risk assessment tools will be rigorously evaluated for clinical utility under this initiative. In addition to seeking new molecular markers in chronic kidney disease and acute kidney injury, the initiative will also examine whether these two conditions share common biomarkers.*

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[1] *Palevsky PM, et al: Intensity of renal support in critically ill patients with acute kidney injury. NEJM 359:7-20, 2008.*

## PATIENT PROFILE

# James Willingham

## *Vascular Access—A Major Component To Treating Kidney Failure with Hemodialysis*

**James Willingham**

To listen to the lilt and laughter in James Willingham's voice one would be hard-pressed to believe that this 66-year-old was diagnosed with kidney failure, referred to as end-stage renal disease (ESRD), 5 years ago while in the hospital for congestive heart failure and cardiac asthma, and that he has been undergoing hemodialysis treatments three times a week ever since.

"I was in the hospital being treated for my heart and asthma conditions when they checked my kidneys and found that they were functioning at only 10 to 15 percent of normal. They immediately put me on dialysis," says James. Dialysis is a treatment for kidney failure; the dialysis machine cleanses the blood—a vital process that would normally be done by working kidneys. Patients with ESRD need either dialysis or a kidney transplant to live.

A couple of months after his ESRD diagnosis, James was asked if he would like to take part in one of the clinical studies being conducted by the Dialysis Access Consortium, or DAC, sponsored by the NIDDK. The DAC Study was testing the impact of anti-clotting reagents in preventing early failure in "vascular access," which is required for dialysis. A vascular access is the site on the body where blood is removed and returned during dialysis treatments.

James responded in the affirmative. "I figured that even if I couldn't help myself, maybe I could help someone else" as a result of participating in the study.

*"I have my good days and bad," says James, "but if I exercise a bit, and don't go overboard with what I eat and drink, I can live a pretty good life on dialysis."*

**Family History**

According to James, there's been a long history of high blood pressure and type 2 diabetes in his family. Yet, none of his four siblings has ESRD. However, three of his first cousins, the children of his mother's sister, are on dialysis as well.

James has known that he's had high blood pressure since his high school days. He's not sure exactly when, but later in life he was also diagnosed with type 2 diabetes. "When I was young I never took it seriously, never treated it," he says. But by around age 50, it caught up with him, eventually resulting in his kidney failure. He began taking steps to improve his health.

## PATIENT PROFILE

He no longer needs to take insulin for his diabetes. "I control it mostly by diet," he says. He also walks 2 to 3 miles a week.

"I have my good days and bad," says James, "but if I exercise a bit, and don't go overboard with what I eat and drink, I can live a pretty good life on dialysis."

**Dialysis and the Importance of Good Vascular Access**

When renal failure occurs, the kidneys lose their capacity to remove bodily waste from the blood. Hemodialysis is a method for removing waste products such as urea and creatinine, as well as extra water from the blood when the kidneys are no longer functioning properly.

An important first step before starting regular hemodialysis sessions is preparing a vascular access on the body that will be used at each dialysis session for inserting a needle and tubing, through which blood is circulated out of the body, to the dialysis machine for cleansing, and then back into the body. The vascular access site is usually placed in the forearm or the upper arm. To maximize the amount of blood cleansed during hemodialysis treatments, the vascular access should allow continuous high volumes of blood flow. For easier and more efficient removal and replacement of blood with fewer complications, the access should be prepared weeks or months before dialysis is required.

Because James' kidney disease was diagnosed at such a late stage, he needed dialysis immediately. Consequently, physicians temporarily outfitted him with a traditional catheter in his chest. Catheters are not ideal for permanent vascular access because they can clog, become infected, and cause narrowing of the veins in which they are placed. But if hemodialysis needs to start quickly, as it did in James' case, a catheter will work for several weeks or even months while a more permanent, surgically created access has time to develop. In this situation the catheter was left in James' chest for an entire year, as no infections or any other complications developed.

**Types of Vascular Access**

In addition to traditional catheters, which are recommended only for temporary use, the two other types of vascular access are arteriovenous fistulas (AV fistulas) and arteriovenous grafts (AV grafts).

A properly functioning AV fistula is considered the best long-term vascular access for hemodialysis because it provides adequate blood flow, lasts a long time, and has a lower complication rate than other types of access. A fistula is an opening or connection between any two parts of the body that are usually separate—for example, a hole in the tissue that normally separates the bladder from the bowel. While most kinds of fistulas are a problem, an AV fistula is useful for hemodialysis patients because it causes the vein to grow larger and stronger for easy access to the blood system.

A surgeon creates an AV fistula by connecting an artery directly to a vein. Usually placed in the forearm, the vein of a new AV fistula will grow thicker after 3-6 months so that it can take repeated needle insertions and allow blood to flow quickly to the dialyzer. Once AV fistulas are working well for dialysis treatments, they tend to last longer than other types of dialysis access like catheters and AV grafts. A good fistula can function up to 10 years or longer.

Because James has smaller, weaker veins that wouldn't develop properly into a fistula, he was given an AV graft, a vascular access that connects an artery to a vein using a synthetic tube, or graft, implanted under the skin in his arm. The graft becomes an artificial vein that can be used repeatedly for needle placement and blood access during hemodialysis. A graft doesn't need to develop as a fistula does, so it can be used sooner after placement, often within 2 to 3 weeks.

## PATIENT PROFILE

Compared with properly formed fistulas, however, grafts tend to have more problems with clotting and infection and need replacement sooner. However, a well-cared-for graft can function for several years. Fortunately, that was James' case.

**The Dialysis Access Consortium (DAC) Study**

The NIDDK established the Dialysis Access Consortium, which consists of seven primary clinical centers and a data coordinating center, to undertake interventional clinical trials to improve outcomes in dialysis patients who received either a fistula or a graft.

Two randomized placebo-controlled clinical trials were designed. The first trial evaluated the effects of the antiplatelet agent clopidogrel (Plavix®) on prevention of early AV fistula failure. The AV fistula trial ended in 2007 and revealed that clopidogrel did not improve the likelihood that an AV fistula would develop into a useable fistula for dialysis. The second clinical trial, which James participated in, focused on AV grafts for dialysis access. The AV graft trial studied a drug that combines dipyridamole with aspirin, and had the goal of preventing the narrowing of the vascular access in hemodialysis patients with grafts.

James, who says he is grateful for having been able to take part in the study, took his medication every day, twice a day; once in the morning and once in the evening, and reports having had no complications with his graft.

"The study was a very good experience for me," James says. "I had help monitoring the graft to make sure it was open and that my blood pressure was good. And my outpatient dialysis nurse was terrific. She took very good care of me, talked with me and told me how I was doing every step of the way." He says he did his part by keeping the graft clean and not picking up heavy objects with the grafted arm.

Dialysis is not the most pleasant of processes. "I've been on dialysis every Monday, Wednesday, and Friday morning for 5 years now, and each session lasts about 4 hours. That's a long time to sit in that chair. And it's very painful. It's a 16-gauge needle, about the size of a plastic coffee stirrer that they stick in you. And you don't want the needle to come out or you have a problem." So to be able to maintain a free-flowing, uninfected vascular access without complications is a real plus for patients like James.

The AV graft trial that James was in ended early in 2008, and the results will soon be made public. From James' perspective, he believes in the process. "It is studies like these that help people like me," he says, with that lively, friendly tone in his voice that he employs so well.

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**Hope through Further Research**

To improve the quality of life of patients with end-stage renal disease, the NIDDK currently supports additional clinical and basic science research efforts. For example, the Frequent Hemodialysis Network is conducting two clinical trials: the Daily Trial is comparing conventional hemodialysis (2.5 hours, 3 days per week) to more frequent hemodialysis (1.5 - 2.75 hours, 6 days a week) and the Nocturnal Trial is comparing home conventional hemodialysis delivered 3 days per week to nocturnal home hemodialysis given 6 times per week. Another example of NIDDK-supported efforts for patients with ESRD is a new consortium that will pursue studies to understand the high rate of AV fistula failure seen in many patients that have an AV fistula placed for dialysis access.

## PATIENT PROFILE

The NIDDK is also supporting the Chronic Renal Insufficiency Cohort (CRIC) to better understand how chronic kidney disease progresses to ESRD. Another effort supported by NIDDK is the Animal Models of Diabetic Complications Consortium, which has the goal of improving or creating animal models of human diabetes complications, including diabetic kidney disease. Diabetic kidney disease is currently the leading cause of ESRD in the U.S. The animal models will help scientists to elucidate the causes of kidney disease and develop prevention and treatment approaches. Finally, the NIDDK distributes science-based information on dialysis and other aspects of kidney disease to patients, health care providers, and the general public through its National Kidney and Urologic Diseases Information Clearinghouse (*http://kidney.niddk.nih.gov/*) and its National Kidney Disease Education Program (*http://nkdep.nih.gov*).

The Dialysis Access Consortium Arteriovenous Graft study was carried out at seven NIDDK-funded research sites: Boston University (Dr. Laura Dember); Duke University (Dr. Arthur Greenberg); the University of Iowa (Dr. Bradley Dixon); the University of Maine (Dr. Jonathan Himmelfarb); the University of Texas, Southwestern (Dr. Miguel Vazquez); the University of Alabama (Dr. Michael Allon); and Washington University in St. Louis (Dr. James Delmez). The Data Coordinating Center was located at the Cleveland Clinic (Dr. Gerald Beck). Three satellite sites were supported by NIDDK and five satellite sites were supported by industry.