# AREA OF FOCUS #3

## *End-Stage Renal Disease*

End-stage renal disease (ESRD) is a major public health problem in the United States, and the incidence rate has steadily increased over the past decade, from 155 per million population in 1988 to 296 in 1997. Similarly, the point-prevalence rate has increased from 557 per million population in 1988 to 1,131 in 1997.

There are striking racial and ethnic differences in the incidence and prevalence rates. Racial/ethnic minorities, specifically African-Americans, American Indians and Alaska Natives, Native Hawaiians and other Pacific Islanders, and Hispanic Americans, have disproportionately greater incidence and prevalence rates. For example, in 1997 the incidence rates were 218 per million population in Caucasians, 873 in African-Americans, 344 in Asian-Americans and Native Hawaiians and other Pacific Islanders, and 586 in American Indians and Alaska Natives. Eleven percent of all new ESRD patients were Hispanic Americans.

- The four major causes of ESRD include diabetes mellitus (primarily type 2), hypertension, glomerulonephritis, and cystic renal disease. There is significant variability in the cause of ESRD among the various racial and ethnic groups. For example, whereas diabetic nephropathy is the predominant cause of ESRD in American Indians/Alaska Natives, Asian-Americans and Native Hawaiians and other Pacific Islanders, Hispanic Americans, and Caucasians, hypertensive nephropathy is the most frequently reported cause of ESRD in African-Americans. However, diabetes mellitus is also an important cause of ESRD among African-Americans.

- When compared with Caucasians, African-Americans show a disproportionate increase in the incidence rate of hypertensive ESRD in all age groups, beginning at age 15, with an overall ratio (African-Americans to Caucasians) of 6 to 1. This ratio is nearly 20 to 1 in the 20 to 44 years of age group. Other diseases causing ESRD in which African-Americans and other racial and ethnic minorities show a disproportionate increase over Caucasians include systemic lupus erythematosus; focal and segmental glomerulosclerosis, especially in children; and AIDS, which is an especially important cause of ESRD in African-Americans and Hispanic Americans.

- The reasons for the racial and ethnic disparities in the incidence and prevalence rates of ESRD remain largely unknown. NIDDK devotes considerable fiscal resources in understanding the basic mechanisms underlying the causes and progression of kidney disease to end-stage renal disease. Specific programs have been initiated to address the racial and ethnic disparities in the specific areas identified.

# Current Activities

## Family Investigation of Nephropathy and Diabetes: Increased Minority Recruitment

### Background

Kidney disease has a disproportionate impact on minority populations, especially African-Americans and Native Americans. In 1996 the point-prevalence rates of ESRD per million population (adjusted for age and sex) were 3,404 in African-Americans and 2,761 in American Indians/Alaska Natives compared with 754 in Caucasians, differences of 4.5- and 3.7-fold, respectively. African-Americans develop end-stage renal failure at an earlier age than Caucasians; their mean age at ESRD incidence was 55.8 years compared with 62.2 in Caucasians. African-Americans constitute almost 30 percent of prevalent ESRD patients yet constitute only 12.6 percent of the U.S. population.

The Family Investigation of Nephropathy and Diabetes (FIND) study was funded as a Cooperative Agreement (U01) from the RFA DK-99-005. The aims of the FIND consortium are to identify genetic loci and, ultimately, genes that influence the susceptibility and severity of diabetic nephropathy in Caucasian, African-American, Hispanic, and Native American populations across the United States. The study consortium consists of eight Participating Investigative Centers and a Genetic Analysis and Data Coordinating Center. The External Advisory Committee for FIND has expressed concern that the susceptibility genes may differ in these subpopulation groups and that the sample size projected for African-Americans may not offer adequate power to address analyses in this group. Given the high susceptibility of African-Americans to kidney disease and the substantial health burden on this population, an increased emphasis on this population was felt to be appropriate.

### Research Goals and Scope

Several of the FIND Participating Investigative Centers are able to expand minority recruitment by developing affiliations with minority institutions or inner-city dialysis clinics. Complementary studies in the African-American Study of Kidney Disease and Hypertension (AASK) clinical trial population are also proposed. This population comprises approximately 1,000 African-American patients with renal insufficiency, mostly subjects with hypertensive nephrosclerosis. In this population, phenotypic parameters, such as rates of progression of nephropathy and response to treatment, are well characterized. Genetic analyses in this population will provide a comparison sample for analyses on diabetic nephropathy in patient populations of different ethnic backgrounds. Both family-based and mapping by admixture linkage disequilibrium approaches are planned.

### Performance Measure

The performance measure will be the total number of African-Americans recruited into the FIND study.

### Outcome Measure

The outcome measure will be successful recruitment of African-Americans into the FIND study.

## Prospective Cohort Study of Chronic Renal Insufficiency

### Background

End-stage renal disease is an important medical and public health problem in the United States that disproportionately affects racial and ethnic minority groups. The increase in the number of ESRD patients is due mainly to an increase in the number of patients with renal disease caused by diabetes. In patients with ESRD, CVD is the leading cause of death, and a better understanding of the risk factors

for this disease burden is required before interventions can be evaluated and implemented. Although numerous epidemiological studies have been conducted in patients with ESRD, leading to improved care and better quality of life, few studies have been performed in patients with chronic renal disease prior to reaching ESRD during a period of chronic renal insufficiency. Of the small number of studies conducted, all of them have significant methodological shortcomings. Thus, our knowledge about the factors that influence the decline in renal function and the development of CVD in patients with chronic renal insufficiency is rudimentary.

Prospective cohort studies have played an important role in defining risk factors for a wide range of diseases, and it is envisioned that data and patient specimens obtained from this cohort study will serve as a national resource for investigations of chronic renal disease and CVD.

### Research Goals and Scope

The objective of this RFA is to establish a prospective, multiethnic, and racial cohort study of approximately 3,000 patients with chronic renal insufficiency to determine the risk factors for the rapid decline in renal function and the development of CVD. Establishing a cohort of patients with chronic renal insufficiency, with the cause of renal disease being similar to that observed in the U.S. ESRD patient population, and following them prospectively will also provide an opportunity to examine genetic, environmental, behavioral, nutritional, quality-of-life, and health resource utilization factors in this patient population.

### Performance Measures

The performance measures will include the total number of grants awarded, the quality of centers funded, the number of patients successfully recruited, and the funding level.

### Outcome Measure

The outcome measure will be the extent to which the results from the study alter clinical practice, including the diagnosis, prevention, and treatment of renal diseases.

## African-American Study of Kidney Disease and Hypertension

### Background

African-Americans are disproportionately afflicted with end-stage renal disease. They constitute approximately 12 percent of the U.S. population but constitute 32 percent of the prevalent ESRD population. Diabetes mellitus is the predominant cause of ESRD in the U.S. population. In African-Americans especially, hypertension is a major cause of ESRD. In 1990 the NIDDK launched an initiative to investigate the underlying cause of hypertensive kidney disease and to study mechanisms that could slow its progression in African-Americans. The clinical trial, African-American Study of Kidney Disease and Hypertension, was initiated to investigate whether a specific class of antihypertensive agents (beta-adrenergic blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors) and/or the level of blood pressure (mean arterial pressure [MAP] of 102-107 mm Hg or MAP of 92 mm Hg) would influence the progression of hypertensive kidney disease in African-Americans.

After a brief pilot study (1992-1994), 20 clinical centers and a data-coordinating center were funded to carry out the full-scale clinical trial in 1994. The 21st clinical center was added in June 1996. As in the pilot clinical trial, all four historically black medical schools were funded to participate in the full-scale trial. The centers required 9 months to revise the protocol for the full-scale trial, and participant

recruitment and randomization began in April 1995. The intervention component ended in March 2002, and the primary analysis of the study results concluded in June 2002. The cohort study commenced at the conclusion of the intervention study. The investigators at the clinical and data-coordinating centers and the program staff at the NIDDK have been meeting and discussing the ongoing After-AASK Cohort Study. The team has completed the design of the study.

### Research Goals and Scope

The AASK cohort will continue to be followed at the clinical centers; however, some patients at centers with a small number of participants will be followed at a nearby larger participating center. In some instances, some of the smaller centers may be asked to recruit additional African-Americans with hypertensive kidney disease to augment the patient population at the center. The patients will be provided with the usual clinical care given to all such patients at the respective centers. Baseline demographic information, selected laboratory tests, and other studies will be obtained at the initiation of the cohort study. Patients will be seen quarterly at the centers, and some selected studies will be done at these visits. Samples will be obtained and stored for later study and analysis. The AASK Cohort Study is similar to the design of the new Chronic Renal Insufficiency Cohort (CRIC) study, which was initiated in late 2002 to permit ultimate integration and comparison of the two data sets.

### Performance Measures

The performance measures will include the total number of patients successfully recruited into the cohort study, a successful cohort protocol, and the funding level.

### Outcome Measure

The outcome measure will be the extent to which the results from the cohort study strengthen clinical practice in the diagnosis, prevention, and treatment of hypertensive renal disease in African-Americans.

## Minority Organ and Tissue Donation Program

### Background

Racial/ethnic minorities, particularly African-Americans, American Indians, Alaska Natives, and Hispanic Americans, are disproportionately afflicted with end-stage renal disease. Although transplantation is the preferred renal replacement therapy because it improves survival and quality of life for successful transplant recipients, these racial and ethnic minority groups are less often the recipient of a transplant operation. A frequently cited reason is that the organ donation rate for minority groups is much lower than their representation in the ESRD patient population. With an increased number of organs from minority groups in the pool, there would be a better match and, ultimately, better graft survival for minority patients.

Over the past 5 to 8 years, several programs have been initiated to increase organ and tissue donation in minority groups. The National Center on Minority Health and Health Disparities/NIDDK-funded Minority Organ Tissue Transplant Education Program was established, in which intensive educational and information activities have occurred in 15 cities across the United States. During the same period, the U.S. Department of Health and Human Services intensified educational and information programs throughout the United States through the

Organ and Tissue Donation initiative. Perhaps as a result of these combined efforts, organ and tissue donation has increased, especially in the minority communities. However, the rate of organ and tissue donation from minorities is still lower than their representation in the population with organ failure, especially ESRD. Increasing the educational activities in other minority communities will enhance minority organs in the pool and, hence, increase the chances of a better match and improved graft survival.

Several potential grantees have been in contact with NIDDK program directors and have expressed their wishes to participate in the educational process, especially in minority communities.

### Research Goals and Scope

The purpose of this initiative is to create an environment supportive of organ donation by:

- Increasing exposure to donation messages and to opportunities to express donation commitments. This could be accomplished through increasing exposure in national and local media, increasing community interventions (e.g., schools, churches), increasing the promotion of organ donation through health promotion and disease prevention efforts, and disseminating and replicating best practices identified through research and evaluation.
- Evaluating the impact of increased support for living organ donation (e.g., provisions to cover child care, travel, and other expenses for living donors).
- Increasing minority cadaveric and living organ donations.
- Increasing donations from nontraditional donors (e.g., older donors and living donors).

### Performance Measures

The performance measures will include the total number of centers funded, the quality of proposals, and the level of funding.

### Outcome Measure

The outcome measure will be a successful increase in the number of organs and tissues donated by the racial/ethnic minority groups.

## Focal Segmental Glomerulosclerosis in Children and Young Adults Intervention Study

### Background

Focal segmental glomerulosclerosis (FSGS) is a common, irreversible process that results in steroid-resistant nephrotic syndrome. It often appears as a primary condition, with a propensity for an unfavorable outcome—risk of progression to end-stage renal disease. FSGS is one of the most common recurrent diseases posttransplant in children, resulting in allograft injury (20 to 30 percent) or graft loss (40 to 50 percent). The peak incidence is in pre-school-age children, with males more often affected (2:1). The worst prognosis is observed in African-American children. Steroid therapy (e.g., prednisolone or deflazacort) has been used to treat children with FSGS; the response is unpredictable. Limited data suggest that alternative therapy with alkylating agents (e.g., cyclophosphamide or chlorambucil) or with immunosuppressive agents (e.g., levamisole or cyclosporin A) may be beneficial in reducing relapses, reducing proteinuria, and perhaps arresting disease progression.

Nonselective proteinuria, ascribed as contributing to tubulo-interstitial damage and the progression of renal disease, is considered both a marker of glomerular injury and a risk factor for progression. The localization of the gene for the rare inherited type of FSGS to 1q25-q31 has helped define one distinct subset of the disease.

A task force to gather information on the criteria for and nature of interventions for a clinical trial was convened jointly by the NIDDK and the American Society of Pediatric Nephrology in November 2000. This initiative was based on the recommendations of this group.

### Research Goals and Scope

A prospective, randomized, multicenter clinical trial examining the impact of immunomodulatory therapy on proteinuria is proposed. The needed sample size is estimated at approximately 300 patients enrolled over a 3-year period and followed for approximately 24 months. If successful, the results of the clinical trial will guide physicians in providing the safest and most efficient care for children with FSGS.

### Performance Measures

The performance measures will include the total number of grants awarded, the quality of centers funded, the number of patients successfully recruited, and the funding level.

### Outcome Measure

The outcome measure will be clinical practice improvement in the diagnosis, prevention, and treatment of FSGS, especially in minority children and young adults.