# American Society of Nephrology Renal Research Report

**In the spring of 2004, the Board of Advisors and the Council of the American Society of Nephrology believed it necessary to conduct a series of research retreats to steer priorities appropriately in an era of limited resources. In this regard, retreats were conducted by five working groups in areas that were identified to require distinct attention: acute renal failure, diabetic nephropathy, hypertension, transplantation, and uremic cardiovascular toxicity. The goal of each retreat was to join experts, both within and outside the renal community, to identify areas of basic science and clinical research that should receive highest priority in the next five years. The five retreat summaries with their individual listings of research priorities allow for the distillation of three overriding recommendations that strongly emanate from them:**

1. **Continued support and expansion of investigator initiated research projects.** In each of the five subjects on which this report is focused, there are areas of investigation that require the support of investigator-initiated projects if ultimately progress is to be made in the understanding of the basic mechanisms that underlie the diseases processes on which we want to have an impact in the next decade. It is recommended that there be an expansion of support for research in the areas highlighted in this report that lend themselves to this mechanism of funding by encouraging applications with appropriate program announcements and requests for proposals. In addition to vigorous support for RO1 grants, continued funding of Concept Development and R21/R33 grants is essential to support development of investigator-initiated clinical studies in these areas of high priority.
2. **Support for the development of a collaborative research infrastructure.** The reader of this article cannot but be impressed by the common theme that independently emerged from each report regarding the urgent need to develop an infrastructure for kidney research. This infrastructure requires the development of core facilities for the centralized processing of biologic materials (genomics, proteomics, and metabolomics), *in vivo* imaging, development and distribution of antibodies and other molecular reagents, development and distribution and phenotyping of mouse models, and perhaps others. These need to be complemented with core bioinformatics centers that collect and analyze data and finally with a network of clinical study coordinating centers. Expansion of kidney research infrastructure can be achieved by vigorous funding of a program of kidney research core centers. Specifically, we propose that the number of kidney centers be increased with the goal of providing core facilities to support collaborative research on a local, regional, and national level. It should be emphasized that such a program of competitively reviewed kidney core centers would facilitate investigator-initiated research in both laboratory and patient-oriented investigation. This approach is also very much in line with the collaborative research enterprise conceived in the National Institutes of Health's Road Map.
3. **Support programs that have an impact on the understanding of the relationship between renal and cardiovascular disease (CVD).** It is now widely recognized that chronic kidney dysfunction is an important risk factor for the development of CVD. It therefore is not surprising that essentially every one of the retreat reports emphasizes the urgency to examine this relationship. It is recommended that the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute (NHLBI) work cooperatively to support both basic and clinical science projects that will shed light on the pathogenesis of this relationship and to support the exploration of interventions that can decrease cardiovascular events in patients with chronic kidney disease. Thus, we specifically propose that the NHLBI support investigator-initiated research (RO1, Concept Development, and R21/R33) grants in areas of kidney research with a direct relationship to CVD. Similarly, the NHLBI should work collaboratively with the National Institute of Diabetes and Digestive and Kidney Diseases to support the proposed program of kidney core research centers. This subject provides an excellent opportunity to foment a collaboration between two institutes, along the lines of the present-day overall philosophy of the National Institutes of Health.

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In December 1998 and February 1999, the American Society of Nephrology (ASN), in collaboration with the Council of the American Kidney Societies, conducted two strategic planning meetings that brought together experts in various disciplines of nephrology to provide a summary of the status, needs, and priorities for renal research in the ensuing years. The timing of the report reflected the now fulfilled expectation that the National Institutes of Health budget was to grow generously, in fact double, over the subsequent five years. Several initiatives outlined in these reports were taken under advisement by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) leadership and served as guides for requests for application (RFA); the launch of various new programs, such as the National Kidney Disease Education Pro-

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gram; the initiation of consortia to undertake clinical trials; and the development of centers to study diabetic complications in animal models.

Now in a dramatically altered fiscal environment, in the spring of 2004, the Board of Advisors and the Council of the ASN believed it appropriate to conduct another series of research retreats to similarly steer priorities in an era of more limited resources. In this regard, retreats were conducted by only five (as opposed to 10 in the previous occasion) working groups in areas identified to require distinct attention: acute renal failure (ARF), diabetic nephropathy, hypertension, transplantation, and uremic cardiovascular toxicity. The goal of each retreat was to join experts, both within and outside the renal community, to identify areas of basic science and clinical research that should receive highest priority in the next five years. Primary regard was given to priorities that are likely to translate into discoveries that improve the understanding of the pathogenesis of renal disorders and that improve the outlook of patients who are afflicted with kidney diseases.

Society leaders selected the five areas of interest as we believe that these carry the burden and that their solution provides the best hope in making a dent in reducing kidney disease, which is growing at an alarming rate and is a disabling and costly public health problem. The number of patients in the ESRD program continues to grow, and, in parallel, the cost of such programs has escalated in the past decade. Concurrently, we have recognized, with better measures of renal dysfunction, that there is a significant number of people with various degrees of renal insufficiency, individuals who are at risk for further swelling the ranks of the ESRD population in the coming decade. At this point, diabetes, hypertension, and failed graft function are the three most common causes of initiation of dialysis treatments. Furthermore, it is evident from a number of large clinical trials, as well as from population-based observations, that the presence of even mild renal insufficiency conveys a significant added risk for cardiovascular diseases (CVD) in these patients.

The ASN, along with others who participated in this effort—the National Kidney Foundation, the American Society of Pediatric Nephrology, the American Society of Transplantation, the American Society of Hypertension, and the Kidney Council of the American Heart Association—as well as the entire renal research community hope that this article, drawing from the wisdom and expertise of numerous participants (see Appendix) will provide a helpful guide to the leaders of the NIDDK and the National Heart, Lung, and Blood Institute (NHLBI), to whom we respectfully submit this report, as they plan the allocation of resources in the coming years.

## Acute Renal Failure

*Introduction*

ARF remains a vexing and significant clinical problem. Hospitalizations for ARF have dramatically increased in the past two decades. ARF may also be a precursor to ESRD as approximately 13% of patients with ARF proceed to ESRD over a 3-yr period. ARF during hospitalization represents an independent high risk for mortality, particularly for patients who require renal replacement therapies. In the past two decades, understanding of the pathophysiology and mechanisms of renal dysfunction has been greatly enhanced by focused investigations related to the pathobiology of this disorder. This knowledge has led to the limited development of preventive and therapeutic advances. However, barring a few successes, most clinical trials of new modalities or interventions have been unsuccessful. Despite the progress made in the fundamental biology of this disease, characterization of human ARF has been lacking. In most instances, an abrupt decline in kidney function is secondary to an injury that leads to a functional or structural change in the kidney. Therefore, in the absence of an accepted definition for ARF, we use the term acute kidney injury (AKI) to reflect the entire spectrum of this disease. AKI is a complex disorder that comprises multiple causative factors and occurs in a variety of settings with varied clinical manifestations ranging from a minimal elevation in serum creatinine to anuric renal failure.

The goals of the ARF retreat were to:

- Summarize the current state of knowledge;
- Explore and arrive at potential solutions to barriers that preclude effective translational studies;
- Develop specific recommendations—what to implement and how;
- Explore the potential for new discoveries and program development.

To accomplish these goals, retreat participants were divided into several working groups. The deliberations and recommendations of these working groups follow.

*Recommendations*

**Classification and Stratification Group.** This group acknowledged difficulties with the term "acute renal failure," considered multiple alternatives, and reached a consensus for the term "acute kidney injury." However, they recognized that other societies and organizations have a vested interest in this field and that others should be consulted to reach a consensus for terminology that would be accepted worldwide.

The highest priorities are to:

- Develop common terminology;
- Define ARF (AKI);
- Stratify patients with ARF (AKI).

To this end, the group believed that a consensus conference, with representation from various societies and organizations, should be organized.

Additional priorities are to:

- Emphasize and educate regarding the predictive validity of small changes in serum creatinine;
- Increase epidemiologic research in AKI.

**Biomarkers Group.** The Food and Drug Administration (FDA) representative in this group expressed great interest in biomarkers and surrogates as a way of expediting the drug development process. He cited the Critical Path Initiative, issued by the FDA in the spring of 2004, which stated, "Addi-

tional biomarkers (quantitative measures of biologic effects that provide informative links between mechanism of action and clinical effectiveness) and additional surrogate markers (quantitative measures that can predict effectiveness) are needed to guide product development." This was accompanied by a provocative statement that, "In some cases, datamining and analysis, with possibly a single additional clinical trial, may be all that is necessary to confirm the surrogacy of a particular marker." He also cited Dr. Robert Temple, a senior clinical regulator at the FDA, who defined a surrogate end point as a laboratory measure or a physical sign used as a substitute for a clinically meaningful end point.

This group recommended that the highest priority is to standardize and/or discover biomarkers to:

- Diagnose AKI before the rise in serum creatinine;
- Stratify patients with respect to severity of injury;
- Provide prognostic indicators.

To accomplish this task, the group strongly suggested that a biomarker core facility be established to facilitate validation and standardization of putative biomarkers that are currently under investigation and that form the nexus for discovery of new biomarkers. The aims of such a project would include:

- Evaluate multiple potential biomarkers, since no single marker will provide sensitivity and specificity across a spectrum of acute kidney injury;
- Developing a network among laboratories within the biomarker field;
- Linking with clinical investigators who perform prevention and treatment studies;
- Collecting samples for biomarkers that already exist, for discovery of new biomarkers and for storage for future identification of genetic and other markers.

**Preventive and Therapeutic Intervention Studies Group.** This group considered input from industry and the FDA as being critical to advancing preventive and therapeutic strategies for ARF. An industry representative believed that it was critical that the community agree on a definition that will provide a commercially viable indication. In other words, physicians in practice would view intervention as providing tangible benefit. The treatment paradigm for AKI should be aligned with critical illnesses such as stroke and myocardial infarction, for which the treatment window is defined in hours rather than days. The major difficulty of arriving at an end point is that the currently used end point of mortality is often influenced by nonrenal factors.

The group considered all of the potential difficulties and barriers in designing a clinical trial. The major difficulty with a therapeutic trial *after* renal failure is established is that the intervention may be too late to make a difference. The major difficulty with a preventive trial is that the event rate is generally low, requiring huge patient populations per study. Therefore, designing a preventive trial, limited to a patient group at high risk for developing ARF, seems to be an appropriate starting point. An additional advantage of this strategy is that most animal studies have been targeted at studying mechanisms and therefore have been preventive in nature. The group identified high-risk patients who undergo cardiothoracic vascular surgery as the most appropriate subjects for an initial observational or therapeutic trial. The primary objective of such a trial would be to establish a network of centers with a broad spectrum of experience and diverse populations of patients with AKI. Thus, the highest priority for this group was the establishment of a clinical trial network to:

- Work cohesively and effectively to collect data and biologic samples for assessment of biomarkers;
- Assess the feasibility of each participating center to enroll patients and adhere to a common protocol;
- Provide preliminary data to inform the development of clinical trials for the prevention or treatment of AKI.

***In Vitro* and *In Vivo* Systems Group.** Unfortunately, most animal models do not seem to be applicable to the treatment of human ARF. However, it is noted that in human studies, treatments are used *after* the establishment of ARF, whereas in most of the animal studies, mechanisms were examined and treatments were initiated *before* induction of ARF. Nonetheless, the consensus was that one model is unlikely to fit all exigencies.

In view of these facts, the group believed that the highest priority should be given to the development of complex models of ARF that better reflect the human setting. Investigators who are developing such models should be further encouraged to pursue this course.

**Collaborative Network Group.** This group, similar to the Preventative Therapeutic Intervention Studies Group, believed that a permanent, collaborative network would facilitate productive research, including cross-sectional and longitudinal observational studies, single and multicenter interventional studies, and health services–related research. The following barriers were identified:

- The network would be expensive to establish and maintain. It would be difficult to justify this expense until several early clinical studies have been completed and potentially important therapeutic agents have been identified;
- The network would require buy-in from the pharmaceutical industry.

Because of these difficulties and because there are several very important gaps in our knowledge in the natural history and epidemiology of acute renal injury, this group believed that the highest priority at this time is to develop a registry/data repository to address the following critically important gaps in knowledge about clinical AKI:

- The incidence and prevalence of diseases are unknown;
- The natural history and spectrum of ARF are unknown;
- The knowledge on risk factors for ARF is limited;
- The causes are not defined;
- The variations in process of care are unknown;
- There are no data on long-term outcomes, particularly progression to chronic kidney disease (CKD);
- Information is required to inform the design and conduct of multicenter interventional studies;

- It is essential to establish benchmarks for diseases patterns and their management.

*Proposal*

The steering committee of the ARF retreat has proposed and the Acute Renal Failure Advisory Group has endorsed the establishment of an Acute Kidney Injury Clinical Initiative (AKI-CI) that would address many of the priorities identified in the retreat. The goal of this proposal is to establish a collaborative network of investigators and centers that are dedicated to advancing knowledge and developing refined approaches for the recognition, prevention, and treatment of AKI that will ultimately improve the care and outcomes of patients who are afflicted with this disorder. The network would consist of collaborating investigators from approximately 10 participating centers initially on the basis of (but not exclusively) existing networks (PICARD, VA dialysis study, etc.). The participating centers will use a common definition, staging system, and protocol to identify patients who are at high risk for AKI and established criteria to recognize when AKI has occurred. All centers would contribute a set of common data elements to a pooled database, obtain timed biologic samples that are stored in a repository and are available for assessment, and participate in studies designed either to reduce the vulnerability of patients to AKI or to intervene to improve outcomes. The network will be flexible to accommodate the spectrum of clinical and translational research as well as to capitalize on the expertise of specific participating centers. The network will be scalable to meet the needs of different projects and will be financially responsible, with the ultimate goal of becoming self-supportive. The infrastructure for the network will require three interdependent core functions.

**Core A: Biomarker Core.** A Biomarker Core will evaluate, develop, and explore biomarkers using modern techniques. This core will feature expertise with established techniques and develop an interactive core biomarker facility. Core A would focus on standardizing the best techniques for:

- Collection of biologic samples;
- Assaying these samples;
- Developing new biomarkers and defining biomarkers that could be used for diagnosis, assessment of severity of injury, and prognosis of the disease.

The data from Core A would be interpreted in the context of clinical data that had been collected and analyzed independently by Core B. This core will include a biostatistics capability that will facilitate validation of the predictive diagnostic characteristics of individual and panels of biomarkers, as well as explore innovative technologies to monitor candidate biomarkers. Core A will provide new knowledge of biomarkers in AKI that will ultimately lead to a clinically relevant definition of this disorder on the basis of pathobiologic alterations and will evolve as a resource for future validation and discovery. This core will be supported by a biologic sample repository that will receive samples from the collaborating centers.

**Core B: Registry Core.** A Registry Core will develop a registry of patients with AKI. Patient data for both cross-sectional and longitudinal studies of AKI will be obtained. In conjunction with Core C, this core will identify participating centers with specific expertise for particular subsets of patients (*e.g.*, cardiovascular surgery, community and academic hospital) that will facilitate broad enrollment of patients. It will also select centers to participate with Core C in specific cohort or interventional studies in the future.

Core B will be designed to assess the practicality of obtaining data, ascertaining the most relevant data elements and the frequency of collection, to allow valid and accurate assessment of patient characteristics and process factors to determine the course of the disease.

Core B will provide four key functions:

- Collect systematic, comprehensive, and practical data to provide critical baseline data;
- Provide consistent clinical data and biologic samples for evaluation of standardized biomarkers of AKI;
- Characterize the unique patient populations at each participating site;
- Define current standards of care and outcomes for subgroups of patients with AKI.

This core will be supported by a registry coordination center equipped to facilitate data acquisition and provide statistical support for rapid ongoing analysis. Reporting of results will be widely disseminated to provide new knowledge to direct the design and implementation of clinical trials and ultimately identify best practices for development of evidence based practice guidelines.

**Core C: Clinical Studies Core.** The Clinical Studies Core has two objectives:

- Develop and test the best strategies for the design and conduct of preventive and therapeutic studies for AKI;
- Provide the infrastructure for subsequent large multicenter trials.

To achieve these objectives, Core C has five functions:

- Define criteria for patient selection, characterization and evaluation of specific cohorts of patients known to be at risk for AKI (*i.e.* a predefined subset of patients);
- Delineate critical clinical time points for collection of biologic samples (for Core A) and then use these data to better design targeted preventive and therapeutic interventions;
- Standardize data, sample collection, and monitoring tools (in conjunction with Cores A and B) to be used by all centers;
- Develop protocols and procedures for recruiting, training, maintaining, and evaluating participating centers to maximize patient enrollment and optimize completion of studies in an effective and efficient manner;
- Test the feasibility of various preventive and therapeutic approaches in small numbers of patients to inform the development and implementation of definitive protocols designed to explore prevention of injury or interactions to modulate recovery from renal insults.

This core would be supported by a clinical trials coordinating center responsible for organization, education, facilitation, and

evaluation of participating sites to maximize acquisition of patients, maintain data flow, and minimize intercenter variability in protocol implementation and data collection. This core extends and amplifies the database of Core B and provides biologic samples for Core A that are specifically timed to coincide with potential therapeutic interventions.

As shown in Figure 1, a well-coordinated and integrated AKI-CI built on the foundation of these three cores will build a network of centers that are responsible for developing:

- A repository of biologic samples for future investigation as well as establishing the validity of putative biomarkers;
- A databank of patients with AKI that will be the foundation for classification and stratification and provide a rich source of reliable data on which future studies can be based;
- A cohesive and efficient mechanism to define, develop, and implement new strategies for prevention or modulation of AKI and therapeutic interventions to definitively improve patient outcomes. An AKI-CI that functions in a coordinated and interactive manner, as described, will undoubtedly result in improved outcomes for patients, enable translation of biopathologic discoveries to patient care, and allow clinical studies in this domain to be conducted with an enhanced probability of success.

*Implementation*

For establishing and building the AKI-CI, a prospective longitudinal cohort study is proposed as an initial project. Patients who have AKI and are carefully characterized for their clinical course with collection of timed blood and urine samples and, if possible, renal biopsy tissue will be enrolled. This study will focus on two groups of patients: Those whoa re at high risk for developing AKI and those who present with AKI in the hospital. These two categories of patients, which represent the clinical spectrum of AKI, have been identified because the time course of disease will vary in each of these groups. High-risk patients can be identified before they develop AKI and thus offer an opportunity to characterize the course of the disease in response to an injurious event. Identification and monitoring of these patients will offer the opportunity to evaluate the impact of underlying disease on development of AKI and to evaluate early response to injury. In contrast, patients who present with AKI have already had an inciting injury and hence will provide information concerning severity of injury and the "recovery" phase of the disease.

A group of collaborating centers will be identified to enroll patients and to conduct three specific projects concurrently. Core B will collect and analyze cross-sectional and longitudinal data across the entire spectrum of AKI in hospitalized patients (intensive care unit and non–intensive care unit). Core C will initially focus on a subset of high-risk patients (*e.g.*, cardiac surgery) to delineate critical risk factors or events that may lead to AKI and to obtain samples before and after the potential AKI inducing event for biomarkers to help define appropriate points for diagnosis and initiation of preventive or therapeutic interventions. Samples from all patients who are entered into this cohort study will be provided to Core A for analysis of existing biomarkers and potential discovery of new indicators of injury or recovery. In the first phase of this endeavor, each

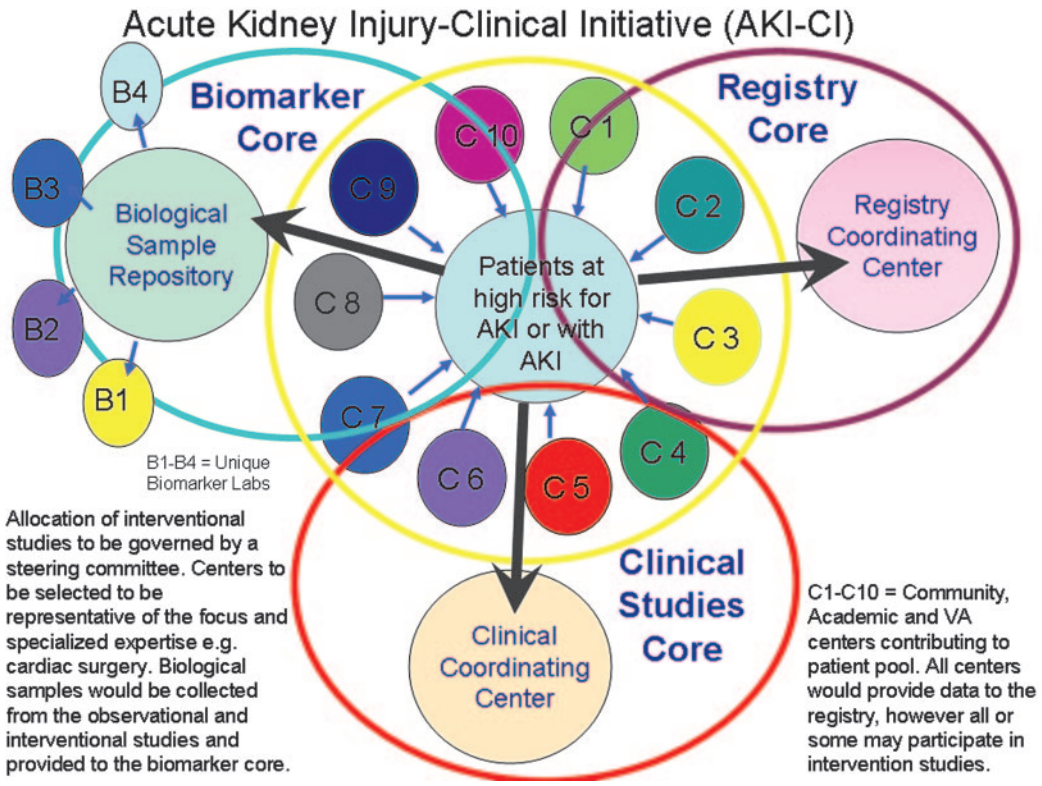


*Figure 1.* Acute Kidney Injury Clinical Initiative.

core will focus on establishing essential infrastructure, adding coordination with participating centers to obtain data that will be used to inform and design studies to be carried out in subsequent years. An ongoing AKI-CI will benefit patients, both at risk and with established AKI, and will provide new insights into this complex, multifaceted disease.

*Significance*

It is evident that we have a limited knowledge of the natural history of AKI. Although several new molecular, genomic, and proteomic techniques are available and have been used successfully to characterize the spectrum of disease, from CKD through transplantation, these techniques have yet to be applied to ARF. There are several unanswered questions regarding the role of various factors in the pathogenesis and continuation of injury in human ARF. Recent advances in the availability of new biomarkers specific for tubular injury and new techniques to probe and characterize renal tissue samples provide an opportunity to characterize the human disease and validate the concepts established in animal models of ARF. The establishment of an AKI-CI on the basis of three integrated cores, each of which contributes new knowledge, will catalyze clinical studies and inevitably lead to improvements in patient care, outcomes, and our understanding of the clinical aspects of this intriguing but difficult disorder.

## Diabetic Nephropathy

*Introduction*

Diabetic nephropathy (DN) remains the leading course of progressive renal disease. The care of patients with this disease represents a significant financial burden to the health care system. The recent epidemic of obesity and diabetes in children suggests that DN may become a problem in the coming decades.

The DN retreat was convened to focus on the following two areas:

- Epidemiology of diabetes and biomarker discovery;
- Pathogenesis-cellular and animal studies.

Each of these groups:

- Reviewed what is known;
- Considered what needs to be known;
- Emerged with specific priorities for future investigations.

*Epidemiology of DN and Biomarker Discovery*

**What We Know; What We Need to Know.** The natural history of DN remains largely unknown, particularly in ethnic minority populations. The role of metabolic syndrome in either initiating nephropathy or modifying the course of DN is also unclear. Renal function in the individual with diabetes should be considered as part of a spectrum of microvascular and macrovascular complications (cardiovascular, cerebrovascular, and ocular). For generating optimal data on the natural history of DN and the effects of the metabolic syndrome on disease risk and for facilitating the search for nephropathy susceptibility genes and biomarkers, large sample sizes are required. If possible, future studies of DN should take advantage of existing cohorts to leverage the available phenotypes for study of natural history and risk factors for DN. Large, ongoing, observational studies provide a unique opportunity to augment diabetes or obesity studies with novel renal, cardiovascular, or cerebrovascular end points; similarly, cardiovascular observational studies afford the opportunity to add renal components. Established and emergent technologies for phenotyping and biomarker discovery could be used in these cohorts with limited additional cost. Cohorts that are assembled by other institutes should be reviewed as valuable resources for these studies.

Currently available biomarkers are not adequate. Thus, albuminuria, a strong predictor of DN risk and a strong indicator of therapeutic response in clinical trials, is, nonetheless, of insufficient precision to serve adequately as the sole indicator of risk of a protection from DN or as the single entry criterion and/or end point for clinical DN trials. Biomarker research should focus primarily on the early stages of disease to develop risk predictors and, at the same time, gain insight into mechanisms of the genesis of early diabetic renal injury. Biomarkers at later stages that predict the rate of renal functional decline from overt DN to ESRD are of indisputable importance but may not be totally specific to diabetes and may be under separate pathogenic and genetic regulatory control compared with the earlier stages and would be complicated by the influences of therapeutic interventions. Accurate description of these early phenotypes is key. A risk or protection algorithm will need to be derived from albumin excretion rate, family history, and demographic and clinical variables (*e.g.*, $HbA_{1c}$, BP, ambulatory BP, GFR, retinopathy data, lipids, BMI) in combination with proteomic and genomic data sets. Inclusion of information obtained from cross-sectional or longitudinal renal biopsies in these data sets should be considered carefully. The explosion in the incidence of obesity-related type 2 diabetes among the young (adolescent to young adult), particularly among minority population groups that are known to be highly susceptible to DN complications (black, Hispanic, Native American), has enormous public health consequences as complications develop in these patients. With this looming disaster comes the opportunity and the necessity to use this rapidly growing cohort of patients with type 2 diabetes to develop natural history information and to identify biomarkers. This is critical to select individuals who are at especially high risk for the intensive therapies that are known to influence outcomes. Efforts to do so on a global scale (*i.e.*, treat all patients intensively) would require greater resources.

**Research Priorities.** The epidemiology and biomarker groups identified the following priorities:

*Priority 1.* To build on existing observational cohorts to:

1. Address the natural history of kidney structure and function in youths with diabetes (available cohorts include Search for Diabetes in Youth Study [SEARCH] and Treatment Options for Type 2 Diabetes in Adolescents and Youth [TODAY]) to understand renal, cardiovascular, and cerebrovascular disease risk in multiethnic populations through the following:

- Collecting baseline samples and data;
- Using longitudinal follow-up data and samples;
- Performing targeted kidney biopsies for analysis using tissue for standard and experimental approaches;
- Assessing existing and emergent biomarkers of disease state and performing genetic and functional studies to associate morphologic (structural) change with functional genetic, demographic, and biochemical data sets;
- Analyzing efficacy of imaging methods for detection of diabetic renal, cardiovascular, and cerebrovascular disease.
- The majority of participants will be youths with type 2 diabetes and obesity, although there will be individuals with type 1 diabetes or diabetes that will be difficult to classify. If adequate information cannot be obtained from existing studies, then establish an inception cohort for study of natural history in young patients with new-onset type 2 diabetes of broad ethnic/racial diversity and for collection of the requisite clinical and laboratory data and materials (see priority 2).

2. Determine whether metabolic syndrome initiates or modifies renal disease progression using existing studies of renal disease (*e.g.*, Chronic Renal Insufficiency Cohort [CRIC]) or CVD (*e.g.*, Coronary Artery Risk Development in Young Adults [CARDIA], Atherosclerosis Risk in Communities Study [ARIC], Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis [MESA], and Honolulu Heart Program) to:

- Assess cardiovascular end points in renal (CRIC) studies;
- Assess renal end points in cardiovascular (CARDIA, ARIC, etc.) studies;
- Use available data, collected samples, and DNA to determine mechanisms by which metabolic syndrome modifies phenotype;
- Integrate data from multiple organ systems to determine risk profiles that can account for the observed heterogeneity and ethnic differences in risk.

*Priority 2.* An integral component of the epidemiologic studies suggested in Priority 1 would be development of a DN biomarker consortium, in some ways parallel to the animal models consortium. This group should develop efficient study designs; tighten phenotype description; consider analytic strategies; formulate recruitment strategies; establish protocols for uniform biologic materials acquisition and processing, including renal biopsy; and ensure broad availability of valuable repositories of clinical and biologic resources to qualified investigators. Biomarker search strategies should include both supervised (targeted candidate) and unsupervised candidate-generating (*e.g.*, microarray, proteomics, metabolomics) approaches. Candidate pathways include podocyte injury markers and oxidative stress pathways. The goals of Priorities 1 and 2 are development of biomarkers and predictive algorithms to identify patients at risk for renal and cardiovascular complications in early-onset obesity, metabolic syndrome, and type 2 diabetes.

*Priority 3.* Recognizing that renal, cardiovascular, and cerebrovascular disease risk is determined by overlapping genetic and environmental risk factors and that the full delineation of risk is determined by multiple effects on multiple organ systems, it is recommended that an "Integrative Systems Biology Workshop on Diabetic Nephropathy" be conducted to bring investigators from multiple disciplines together to discuss novel and complementary approaches to research. The initial focus, for example, could be the use of populations, individuals, cells, and DNA in humans and animal models to explore the potential of glycemic memory on diabetic renal disease.

### *DN Pathogenesis: Cellular and Animal Models*

**What We Know; What We Need to Know.** Despite increased knowledge of physiologic and biochemical pathways, the mechanisms that mediate diabetic renal dysfunction continue to be a pressing research need. The basic biology of DN has seen considerable advances in the past 5 yr. A critical question remains to be answered: "What are the distinguishing features (*i.e.*, predictors) of individuals who are susceptible to DN *versus* those who are resistant?"

In Vivo *Models of DN:* Several animal models for both type 1 and type 2 diabetes are available. Initial work has focused on rat models of diabetes, either chemically induced with streptozotocin to model type 1 diabetes or diet-induced in genetically susceptible strains with insulin resistance and obesity to model type 2 diabetes. Because of the multiple advantages that the mouse provides for dissecting out cellular, molecular, and genetic mechanisms, there is now a clear preference among investigators to develop murine models of DN. Mice that receive multiple low doses of streptozotocin develop stable, long-lasting diabetes, and the Akita mouse with an *ins2* mutation also mimics type 1 diabetes. The *db/db* mouse, with a mutated leptin receptor, has insulin resistance and therefore models type 2 diabetes. The main drawback of all available murine models is absence of progressive renal failure. In addition, mouse strain–modifying genes influence diabetogenesis, as is the case with the kk mouse, and renal disease susceptibility. Backgrounds such as *dba* or *rop* render mice that are diabetic more susceptible to progressive renal disease. The establishment of the Animal Models of Diabetes Complications Consortium (AMDCC) has been an important step. The major goal during the present funding period has been to develop an animal model that more truly mirrors human DN, a task that remains in progress. Significant differences in susceptibility to DN exist between different strains of mice. Several noteworthy contributions have been made, including the use of HPLC for a more accurate assessment of mouse blood creatinine and insulin-based measurements of GFR in conscious mice. New transgenic models with gene deletions of decorin, endothelial nitric oxide synthase, or bradykinin receptor type 2 deficiency render diabetic mice more susceptible to progression.

In addition to these rodent models, porcine, canine, and primate models have been developed. All of these models are imperfect, however. Most do not have well-defined genetic backgrounds, and in most, the relationship between diabetes and DN and the type of renal disease that is observed differ from those in humans. Nonetheless, although studies in these

species lack the genetic uniformity of inbred mouse strains, their disease may more closely mirror that observed in humans. Progress in dissecting these models *in vivo* has been suboptimal. Success has been hampered by problems in assessing the impact of hypertension and glycemic control, the lack of standardized measures of urinary albumin excretion and renal function, and the variability in analyzing morphologic parameters. The roles of important clinical variables such as lipid abnormalities, inflammation, and gender effects remain unclear.

In Vitro *Studies Related to DN:* Significant progress has been made in studying DN using *in vitro* approaches. Activation of the intrarenal angiotensin II system and generation of reactive oxygen species (ROS) mediate a variety of pathogenic events. TGF-$\beta$ has been established firmly as the principal mediator of cell hypertrophy and extracellular matrix production in virtually all cell types in the diabetic kidney. Vascular endothelial growth factor has emerged as another potentially important mediator of albuminuria. A significant area of progress has been the definition of a central role for the podocyte in regulating filtration of albumin, in generating a stable interaction with and support of the glomerular capillary wall, and in producing cytokines that affect glomerular cell function. Loss of podocytes by detachment or apoptosis increasingly seems to be a major event in the development of glomerulosclerosis. The kidney tubulointerstitium is now well recognized as a site of critical hypertrophy and fibrogenesis in progressive DN. However, the hypermetabolic effects of the diabetic milieu on tubular cell growth and function and the role of tubular (or interstitial) cell epithelial-to-mesenchymal transition are not well understood. The diabetic microenvironment *in vivo* induces nonenzymatic glycation of proteins and matrices; causes glomerular hyperfiltration, hypertension, or capillary dilation; and dysregulates cell metabolism. The impact of these events on cell–cell and cell–matrix interactions merits consideration. Cells that have been exposed to a diabetic microenvironment *in vitro* retain their diabetes-associated phenotype in long-term culture even after exposure to nondiabetic conditions. Long-term follow-up of the Diabetes Control and Complications Trial [DCCT]/Epidemiology of Diabetes Interventions and Complications Study [EDIC] cohort has documented analogous hyperglycemic "memory" in humans. The cellular basis for hyperglycemic memory is unknown. Thus, the diabetic metabolic state may cause epigenetic effects that produce persisting changes in cellular phenotype and organ function.

**Research Priorities.**

*Animal Models*

Priority 1. The Animal Models of Diabetes Complications Consortium should receive continued support to continue characterization of established models and development of new models of progressive DN that better mimic human DN. As animal models of DN are developed, a common "clean" repository, obviating quarantine, should be established for distribution of animals to the investigative community. Specific goals include:

1. Identification of specific genes that predispose to development of DN;
2. Identification of biomarkers with altered expression levels of specific protein lipids and mRNA that correlate with development of DN;
3. Characterization of the pathophysiology of DN:

- Diurnal variations in BP and role of tubular transport in regulation of GFR;
- Studies of the cellular basis for altered metabolic function;
- Response to the diabetic milieu that may predispose the kidney to unique forms of injury (*e.g.*, increased oxygen utilization [nonenzymatic glycation]);
- Determinants of renal cell hypertrophy and extracellular matrix metabolism and regulation of serum protein handling across GBM and by podocytes and tubular cells;
- Contributions of the vasculature and endothelium.

4. Refined studies of nephropathy in animals to mimic more closely the human condition and to facilitate comparisons among different experimental models:

- Insulin delivery to lower glucose levels;
- Effect of marked fluctuations in glucose or insulin levels on outcomes;
- Improved method for monitoring BP, renal function, and albuminuria;
- Microarray, proteomic, and metabolomic studies of established or promising new models of DN;
- Use of promising animal models to test novel and emerging experimental therapeutics.

Priority 2. Comparative genomics using data from the Animal Models of Diabetes Complications Consortium and human studies (*e.g.*, Family Investigation of Nephropathy of Diabetes Consortium [FIND], EDIC, Genetics of Kidneys in Diabetes [GoKIND]) should be promoted to identify environmental and genetic modifiers, including but not limited to inflammation, hypertension, lipid abnormalities, oxidative stress, single-gene mutations, gender, and strain differences, including quantitative trait loci and differences in global gene expression.

In Vitro *Models*

Priority 3. To complement the animal studies, we also recommend further study of the basic cell biology of DN *in vitro*:

1. Studies of cell type–specific behavior in the diabetic milieu, including:

- Analysis of maintenance of cell phenotype, including differentiation, de-differentiation, and cell memory of diabetic conditions;
- Cell turnover studies, including regulation of the cell cycle, hypertrophy, and apoptosis;
- Cell–extracellular matrix interactions, particularly with reference to podocyte loss;
- Modulating effects of diabetic metabolic abnormalities (insulin, byproducts of glucose metabolic pathways, and nonenzymatically derived adducts) on signal transduction pathways;

- Cell–cell communication;
- Cell stretch/tension.

2. Studies of oxidative metabolism: Refining methods to assess antioxidant *versus* pro-oxidant repertoires, identification of pathways for the generation of ROS by mitochondria and other organelles, studies of ROS effects on different renal cell types, and effects of the diabetic milieu on signal transduction;
3. Open-ended studies to generate new hypotheses: genomic/proteomic/metabolomic studies of tissue and individual cells.

## Hypertension

*Introduction*

Hypertension remains one of the leading causes of renal failure and is clearly a contributor to accelerated loss of renal function in the setting of other forms of renal disease. Likewise, the kidney itself is central to the pathogenesis of hypertension.

The Hypertension retreat targeted the following major areas:

- The kidney as a cause of hypertension
- The kidney as a target for hypertension
- Hypertension in patients with kidney disease

On the basis of previous work in the field, these areas were identified as most promising for discoveries that would promote understanding of disease pathogenesis and provide potential for identifying new approaches for therapy and cardiovascular prevention strategies. The recommendations of the group are outlined below.

*The Kidney as a Cause of Hypertension*

Many lines of evidence from human genetic studies, physiologic studies, and cross-transplantation experiments highlight the critical role of altered renal excretory function as a final common pathway in the development of chronic hypertension. By extension, subtle abnormalities in kidney function seem to be a common cause of hypertension. However, the precise molecular and cellular pathways that are responsible for these perturbations are not clear, especially in patients with essential hypertension. Accordingly, research that focuses on the kidney as a cause of hypertension is an important area for research emphasis. Results of work in this area should advance strategies for diagnosis, treatment, and prevention of hypertension, a disorder that affects more than 40 million individuals in the United States. Specific areas were believed to be priorities for future investigation.

Priority 1: Studies on renal ion transporters in hypertension:

- Genetics of abnormal ion transport in human hypertension;
- Characterization of routes of transcellular NaCl transport: Genetics and regulation and dysregulation of newly discovered ion transporters and channels;
- Molecular physiology of pressure natriuresis: Sensory pathways, molecular signaling, and effectors (transporters and tight junctions);
- Mouse models to study altered transporter function in hypertension and to identify and test new therapeutic targets.

Priority 2: Developmental biology of the kidney in hypertension: Molecular and genetic mechanisms of perinatal programming of renal development;

Interventions to interrupt and compensate for adverse perinatal programming;

Clinical correlates of perinatal programming in later life.

Priority 3: Renal vascular biology in hypertension:

- Regulation of renal vascular resistance in hypertension and CKD
- Tubuloglomerular signaling in hypertension;
- Renal mechanisms of salt and BP sensing;
- Oxidative stress and other pathogenic mechanisms.

*The Kidney as a Target in Hypertension*

Along with its causative role in hypertension, the kidney is a target for damage from chronic elevation of arterial pressure. Moreover, hypertension is a major risk factor for progression of CKD. Loss of kidney function from hypertension leads to a vicious cycle of worsening hypertension and continuing kidney damage. Although the capacity of high BP to injure the kidney is widely recognized, the molecular pathways that are responsible for pressure-dependent injury are not clear. Various human populations, such as black individuals, seem to be more vulnerable to hypertensive kidney damage, but the nature of this apparent genetic susceptibility is unknown.

Priority 1: Support initiatives to develop and identify more precise methods for assessment and quantification of hypertensive kidney injury:

- Imaging approaches for assessing structure and function of vascular, glomerular, tubular, and interstitial compartments;
- Biomarkers in urine and blood for detecting injury;
- New approaches to collect and evaluate renal biopsies;
- Identification and study of informative patient populations;
- Better animal models of hypertension renal injury;
- Novel approaches for assessment of renal hemodynamics and pressure transmission in vascular and interstitial compartments.

Priority 2: Renal hemodynamic and cellular factors in hypertensive kidney injury:

- Microcirculatory/endothelial factors;
- Ischemia and oxygen balance;
- Autoregulation-regulation of afferent and efferent arteriolar tone;
- Inflammation;
- Glomerular size and number;
- Vascular rarification and angiogenesis;
- Genetic susceptibility to hypertensive nephrosclerosis.

*Hypertension in Patients with CKD*

More than 20 million people in the United States have CKD, and CKD is a newly recognized risk factor for CVD. This risk is independent of other known risks, including hypertension, hypercholesterolemia, and cigarette smoking. In CKD, there is considerable evidence that inhibitors of the renin-angiotensin-aldosterone system slow progression of CKD. In essential hy-

pertension, BP reduction reduces cardiovascular events. However, there are no studies showing that aggressive control of BP and/or use of renin-angiotensin-aldosterone system antagonists reduces cardiovascular risk in patients with CKD. Although albuminuria also confers significant cardiovascular risk, whether targeted reduction in proteinuria reduces cardiovascular events in CKD is not known. Finally, in the subgroup of CKD patients who develop ESRD, CVD is a major cause of morbidity and mortality. As in CKD, the relationship between hypertension and CVD in patients with ESRD is not clear. For example, studies reveal a J-shaped relationship between BP and mortality in patients with ESRD.

**Research Priority.** To address these critically important questions and the gaps in our knowledge, we suggest that priorities be given to support a clinical trials consortium to study patients at various stages of CKD and patients on dialysis (ESRD):

1. Hypertension in patients with CKD: Clinical trials in CKD should test whether:
   - BP reduction to a target as low as 120/70 mmHg alters renal progression and cardiovascular events in this population;
   - Reduction in proteinuria on the background of BP reduction has renal and/or cardiovascular benefits.
2. Hypertension in ESRD: Clinical trials in ESRD should likewise test whether lowering of systolic BP below 140 to 150 mmHg provides cardiovascular protection in dialysis patients.

### *Resource Centers for Hypertension Research*

The group suggested that development of resource centers focused on areas of common need in this area would be a cost-efficient mechanism for promoting progress in research on the kidney in hypertension. Examples of such resources include:

- Mouse model repository, including database for existing models;
- Mouse and rat model development;
- Physiologic phenotyping resources for mouse models of hypertension;
- Physiologic phenotyping resources for humans with hypertension and kidney disease;
- Repository for antibodies that target hypertension-relevant proteins;
- Proteomics and genomics resources;
- siRNA development and application to hypertension research;
- *In vivo* imaging resources;
- Clinical studies group to coordinate study design and patient recruitment for clinical trials.

## Transplantation

### *Introduction*

Renal transplantation is the treatment of choice for patients with ESRD. In the past two decades, the advent of improved immunosuppressive drugs has resulted in a significant improvement in the prevention of acute rejection. The emphasis on this prevention was predicated on the dominant thinking underlying transplantation and immunosuppressive biology that if acute rejection could be avoided, then the patient would keep the graft for as long as necessary, eventually succumbing to a nonrenal death. Recent epidemiologic studies suggest that this may not be the case. Thus, although current immunosuppressive therapies are very powerful and have dramatically decreased and almost eradicated acute rejection episodes, we have seen no progress in ultimate graft survival. This important new recognition strongly suggests that our previous emphasis focused solely on the prevention of acute rejection with immunosuppression does not, in itself, lead to ultimate long-term graft survival.

There are at least two not mutually exclusive explanations for this observation: Either we are not defining "rejection" properly, or there are additional nonimmune processes that lead to ultimate graft loss. With regard to "acute rejection," our definition has been operational, involving a general clinical state and rise in creatinine. By the time a rise in creatinine is evident because of acute rejection, a significant degree of tissue damage has occurred within the kidney. The use of creatinine as an end point therefore may lead to interventions too late, leaving undiagnosed chronic, lingering damage that contributes to the multifactorial state that has been called "chronic rejection." One classic approach to an earlier diagnosis of rejection involves early or routine biopsy. This approach has limitations, and the definition of "rejection" remains controversial. Another approach involves "molecular" diagnosis. A new "holy grail" among transplant nephrologists is that there may be a molecular "signature" evident in the kidney, blood, or urine indicative of rejection. If this molecular event precedes biopsy evidence that precedes clinical definition of rejection, then perhaps therapy can be provided earlier and the ultimate outcome improved. The second possibility is that more than one pathway is leading to ultimate graft loss. Perhaps an immunosuppressive-resistant process is giving rise to ultimate graft loss. It is certain that some of the most potent immunosuppressive agents (that have helped to nearly eradicate acute rejection) themselves contribute to vascular damage and ultimate graft loss. To prevent drug toxicity, newer protocols have decreased immunosuppression to relieve the significant toxicities of steroids and/or calcineurin inhibitors.

The use of immunosuppressant medications is complicated by their systemic side effects. Infection is a well-recognized complication of immunosuppression. However, these medications may also worsen or cause illnesses such as diabetes, hyperlipidemia, and hypertension, thereby contributing to the CVD burden of the transplant recipient. Thus, the major new paradigm in renal transplantation is that more powerful immunosuppression is not the ultimate answer. The search for strategies for induction and maintenance of immune tolerance in humans continues, but at the same time, new investigation as to the immunologic and nonimmunologic causes of graft loss is required.

The Transplant retreat focused on:

- The problem of ultimate graft loss;
- Posttransplantation CVD.

*Ultimate Graft Loss*

**What We Know; What We Need to Know.** We know:

- It is possible to reduce the rate of acute rejection, but decreasing the rate of acute rejection has not resulted in improving long-term graft survival;
- Acute rejection episodes all are not alike with regard to phenotype, function, molecular expression patterns, or response to therapy;
- Calcineurin inhibitors are nephrotoxic;
- Predictors (correlates) of chronic allograft nephropathy have been elucidated;
- The "quality" of the donor organ affects outcome.

However:

- Surrogate markers of chronic rejection are *not* well described;
- The role of B cells and antibody in chronic rejection is *not* known;
- The role of immunologic tests and biopsies for surveillance is *not* proved (is subclinical rejection a real phenomenon, should it be consistently treated, and does it contribute to poor long-term outcome?);
- The role of parenchymal cells in injury (response to injury) is *not* well characterized.

**Research Priority: To Identify Factors Involved in Chronic Graft Loss.** Progress in this field will clearly require:

1. Development of surrogate markers and valuable biomarkers. In the course of a natural history study, serial patient samples and donor tissue should be archived so that analysis of DNA, RNA, protein, and cells can be analyzed. We do not know which biologic material or which techniques will provide the best markers. It is likely that many different tests performed at the same time will provide more information than any one test. Therefore, we recommend collecting and saving as much material as feasible.
2. Collection of pretransplant or "zero-hour" data. The hope is that this information would be used to augment HLA typing and clinical data that are now used to inform these decisions. The areas of interest are:

- The molecular status of the allograft at the zero hour (and perhaps harvest and implantation);
- The immune status of the recipient at the time of transplantation; although antidonor antibodies are analyzed, there are no routine studies that identify preimmunized, donor-reactive T cells or B cells (cellular and molecular assays needed);
- Genetic polymorphisms (in addition to HLA), for example, pharmacogenomics or immunomodulatory genes.

3. Posttransplantation sequential data collection and analysis:
   - The fundamental nature of the host antidonor immune response (cellular, humoral, and molecular assays are required);
   - The nature of the status of the allograft, including identification of factors that are damaging the organ (pathology, molecular assays, *e.g.*, transcriptional and proteomic analysis).
4. Better understanding of the impact of acute rejection to answer the following questions:

- Does management affect outcome?
- Does complete reversibility of reject affect outcome?
- Are there markers of reversibility of insult?
- Would better measurements of renal function improve outcome?

*Posttransplantation CVD*

**What We Know; What We Need to Know.** We know:

- Death with a functioning graft as a result of CVD is one of the leading causes of graft loss after the first year;
- More than 45% of deaths in renal transplant patients are due to CVD;
- The risk of death from CVD remains twice that of the general population overall and up to 10 times greater in the 25- to 34-yr age group.

However, we do not know whether the increase in cardiovascular events posttransplantation is due:

- Solely to the traditional risk factors, many of which are worsened by immunosuppression;
- To allograft nephropathy causing CKD.

**Research Priorities.**

*Priority 1.* Establish a prospective cohort of renal transplant patients in whom medications, conventional risk factors, cardiovascular outcomes, and graft outcomes are recorded. Patient blood should be banked at defined time points so that nontraditional risk factors and inflammatory mediators may be investigated. This cohort of patients may then be used to ask the following questions:

- Are classical risk factors relevant in renal transplant recipients, and, if, so are they associated with the same degree of risk as in the general population?
- What is the relationship between CVD and CKD in the renal transplant population?
- What is the role of inflammatory mediators in the development of CVD in a population of renal transplant patients who are on immunosuppression and in whom clinical or subclinical immune activation directed toward the graft may also contribute?

The identification of nontraditional risk factors may be assessed in this population through the use of banked serum. This registry and blood/serum bank overlaps with some of the needs of the surrogate marker group. The establishment of a single large cohort in which both aims are examined and additional specimens, outlined by the biomarker group, are banked would be more fruitful. This would allow for cross-talk, for example, in the area of graft function and inflammatory mediators, given the increasingly recognized role of inflammation in CVD.

*Priority 2.* Determine the effects of intervention on disease progression in the renal transplant population. At present, therapies that are directed at the treatment of cardiovascular risk factors in renal transplant patients are based on the extrapola-

tion of data from the general population. A subset of patients from the initial cohort would be randomized to receive intensive therapy as defined by guidelines such as intense lifestyle modification, BP treated as per JNC VII, target LDL <100, maximization of treatment with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, erythropoietin therapy and $Ca^+/PO_4^-$ management. The outcomes in these patients would be compared with those who receive standard care. The influence of the care provider, nurse, nurse practitioner, or doctor on outcomes would be examined. The two main outcomes investigated would be cardiovascular outcomes and allograft function.

*Priority 3.* Evaluate pretransplant screening process for CVD. Death as a result of CVD early posttransplantation is a significant cause of graft loss very early posttransplantation. There are no current evidence-based guidelines for the evaluation of CVD pretransplantation. Most programs would claim to use protocols that are more aggressive than would be suggested for the evaluation of CVD by the American College of Cardiology. However, we have no data to suggest that this additional effort and expense is warranted. We therefore would propose to evaluate American College of Cardiology guidelines with aggressive pretransplant evaluation to determine the influence on preventing subsequent cardiovascular events. An important resource that will be available is the cohort of patients followed prospectively by the FAVORIT study. The group recommended that RFA associated with these data examining cardiovascular outcomes and/or graft function/survival would maximize the use of this study.

### *Resource Centers for Transplant Research*

**Core A: Clinical Consortium.** The objectives of the clinical consortium are (*1*) to bring together renal transplant programs and therefore patients who will participate in the studies to evaluate the questions outlined in this proposal, evaluation of donor and recipient factors that contribute to graft loss, evaluation of acute rejection as an end point, determination of putative surrogate markers, evaluation of cardiovascular risk, and the benefit of therapeutic intervention in the transplant patient and (2) to provide the infrastructure necessary for subsequent large multicenter trials developed on the basis of initial findings from the studies outlined in this proposal.

**Core B: Biomarker Core.** The purpose of the biomarker core would be to centralize the process for evaluation of putative biomarker. Patients will be enrolled and samples will be collected from those centers involved in the clinical consortium.

1. Development of valuable surrogate markers. In the course of a natural history study, serial patient samples and donor tissue should be archived so that DNA, RNA, protein, and cells can be analyzed. Information gained will lead to the identification of valuable biomarkers. Because we do not know which biologic material or which techniques will provide the best markers, it is likely that many different tests performed at the same time will provide more information than any one test. Therefore, we recommend collecting and saving as much material as feasible.
2. Prospective analysis of potential biomarkers. Posttransplantation sequential analysis will enable optimized and individualized therapy.
   - The fundamental nature of the host antidonor immune response and cellular, humoral, and molecular assays are required;
   - The status of the allograft, including identification of factors that contribute to graft injury, and pathology and molecular assays, *e.g.*, transcriptional and proteomic analysis.

**Core C: Registry Core.** The establishment of a registry of patients with renal transplants for the evaluation of cardiovascular risk factors and the relationship between CKD and CVD as it pertains to the renal transplant population. The registry will be based on the participation of a large number of centers and will facilitate the enrollment of patients into Cores A and B.

## Uremic Cardiovascular Toxicity

### *Introduction*

Despite advances in dialysis, overall mortality among patients with end stage kidney disease remains as high as 23% per year, and cardiac causes account for between 40 and 50% of all deaths. The net result of this burden of CVD is that, when compared with the general population, patients with ESRD have between a 10 and 20 times greater incidence of cardiovascular death. The types of heart disease most commonly seen in ESRD patients are coronary artery disease and left ventricular hypertrophy. The former condition is associated with myocardial infarction and sudden death, and the latter is associated with either diastolic or systolic dysfunction and is also associated with sudden death. There is now also compelling evidence that the incidence and prevalence of heart disease increase as renal function declines. Data accumulating from national epidemiologic studies, regional and community-based epidemiologic studies, and the analysis of randomized clinical trials all suggest that CKD is an important independent risk factor for cardiovascular complications.

There are multiple physiologic derangements that occur in patients with kidney disease and combine to lead to the increased incidence and prevalence of heart disease in this patient group. Among these, hypertension, an abnormal calcium/phosphorus product, vascular calcification, the accumulation of advanced oxidation protein products and advanced glycation end products, the accumulation of inhibitors of nitric oxide such as asymmetric dimethylarginine and phenylacetic acid, the high concentrations of angiotensin II as a factor in cardiac hypertrophy and abnormal remodeling, the accumulation of the amino acid homocysteine, and the problem of inflammation as a pro-atherosclerosis factor are, to name a few, several of the important abnormalities associated with the development of heart disease in this patient population. In addition to these factors, the association of other common abnormalities, which occur in advanced kidney failure such as anemia, can contribute to cardiovascular morbidity and mortality. The aggregate burden of kidney and heart disease exacts an enormous human cost and presents a staggering financial burden as well. The

partial dialysis costs of the growing ESRD population in the United States is estimated to be between $20 and $30 billion per year, and with the growth of the number of dialysis patients to as many of 600,000 Americans by 2010, these costs are likely to rise dramatically. The costs associated with cardiovascular risk in patients with earlier stages of CKD are more difficult to quantify but are also likely staggering, given the high prevalence in the US adult population.

The goals of the Uremic Cardiovascular Toxicity retreat were to:

- Summarize the current state of knowledge in each respective focus area;
- Explore and arrive at potential solutions to barriers that prevent research progress in uremic CVD;
- Develop specific recommendations for advancing knowledge in uremic cardiovascular morbidity and mortality;
- Develop priorities for action and facilitating advances in understanding the pathogenesis of uremic CVD and implementing therapies for uremic CVD.

The broad focus topics for the retreat designed in advance by the planning committee were:

- The epidemiology of cardiovascular morbidity and mortality in patients with CKD;
- The contribution of innate immunity, acute-phase inflammation, and other "nontraditional" cardiovascular risk factors to CVD in this patient population;
- The pathogenesis of and potential therapies for atherosclerosis and endothelial dysfunction in patients with CKD;
- The contribution of left ventricular hypertrophy and other alterations in cardiac geometry to sudden death and other cardiovascular complications in patients with CKD;
- Defining appropriate study populations and study end points for clinical trials in uremic CVD;
- Defining and prioritizing potential interventions to reduce cardiovascular morbidity and mortality in patients with CKD.

## *Epidemiology of CVD in CKD*

**Background.** There are excellent epidemiologic data regarding cardiovascular complications in patients who have ESRD and receive renal replacement therapy:

- The United States Renal Data System, an enormously useful database for examining risk factors for hospitalization, cardiovascular mortality, and all-cause mortality in the dialysis population;
- Dialysis Outcomes Practice Pattern Study, an international observational study of the association of dialysis practice patterns with outcomes;
- The Fresenius Medical Care database and the databases of other provider chains;
- The CHOICE and HEMO studies.

Epidemiologic data available on cardiovascular risk in patients who have CKD and do not receive replacement therapy are comparatively less robust. Emerging data are available from:

- National epidemiologic data (National Health and Nutrition Examination Survey);
- Regional databases (*e.g.*, from Kaiser-Permanente);
- Community-based cohorts (ARIC study and Cardiovascular Health Study);
- CRIC–ongoing.

Data from the first three sources all suggest that the development of CKD may be an independent risk marker for CVD.

**Research Priorities.**

*Priority 1.* Systemically reanalyze previously conducted randomized clinical trials of cardiovascular interventions that have included patients with CKD.

*Priority 2.* Support ancillary studies of CKD cohorts in current National Institutes of Health–funded trials. The analysis of these cohorts' databases should focus on addressing the following unanswered questions:

1. Is there a dose relationship between the extent of kidney dysfunction and development of CVD? Available epidemiologic data suggest a near exponential inverse relationship between estimated GFR and the rate of cardiovascular complications. However, only limited required longitudinal data are available to determine whether change in GFR over time has an important effect on the rate of cardiovascular complications. Furthermore, is the relationship between estimated GFR and cardiovascular risk static, cumulative over time, or accelerated in patients with relatively rapid loss of GFR over time?
2. Is the cardiovascular morbidity and mortality risk in the dialysis population a continuum of CKD-associated risk, or does dialysis therapy carry an independent additive risk? Among the dialysis population, what is the potential role of residual renal function as a cardiovascular risk modifier? Until recently, the high rate of cardiovascular and all-cause mortality in the dialysis population was believed to be substantially higher than in the advanced CKD population. However, recent publications demonstrate a similar strikingly high cardiovascular and all-cause mortality in patients with advanced CKD. Thus, it is currently unclear whether dialysis therapy carries an independent added risk for CVD and mortality. Among both hemo- and peritoneal dialysis patients, there are data to suggest that the maintenance of residual renal function is associated with improved overall outcome and lower mortality. It has been suggested but not demonstrated definitively that residual renal functional clearance of solute may be qualitatively different than solute clearance during hemo- or peritoneal dialysis and may confer survival advantages.

The group recognized two caveats in the interpretation of this epidemiologic data:

- The available randomized clinical trials involve selected populations, which may not be representative of the entire CKD cohort;

- It may be necessary to measure other GFR markers such as cystatin C to better estimate GFR in some patient populations in which currently available formulas such as from the Modification of Diet in Renal Disease study have not been validated.

### *Pathogenesis of Cardiomyopathy and Atherosclerosis in CKD*

**Background.** Considerable epidemiologic data associating CVD with the degree of CKD currently exist. However, associative studies cannot indicate whether the degree of renal disease is in effect a sensor of vascular injury or is a direct contributor to the vascular injury process. Although mechanistic data from animal models and human studies relating, for example, hypertension and anemia to the development of left ventricular hypertrophy and alterations in divalent anion and cation metabolism to vascular calcification exist, there are less well-established mechanisms potentially linking CKD to accelerated atherogenesis.

An improved understanding of whether and how the loss of renal function and concomitant changes in hormonal and metabolic responses that are associated with retention of unexcreted uremic solutes or the dialysis process contribute to the atherogenesis is a high priority in kidney disease research. An improved mechanistic understanding is likely to evolve from a combination of basic science and translational studies.

**Research Priority.** A research priority is to undertake both animal and human studies to define better the mechanisms whereby kidney dysfunction increases CVD. To this end, the retreat suggested the following two approaches:

1. Develop animal models that can be used effectively to understand better how CKD can lead to cardiovascular complications. Several groups have investigated the mouse APO-E null model with 5/6 nephrectomy in which there is accelerated atherogenesis and CVD, as a relatively new model that can be used to study uremic cardiovascular toxicity. Validation of this model and development of other animal models were considered as a high priority in achieving a more mechanistic understanding of uremic CVD.

   In addition to the development of new animal models, consideration should be given to molecular genetic studies of susceptibility to disease progression or protection in animal models. These studies can be applied to both renal progression and CVD progression susceptibility genes. As an example, it is known that there is enormous strain heterogeneity in the development of diabetes progression in mice; these types of studies have to date been underused in studying models of CKD, including both immune and nonimmune disease mechanisms.
2. Define most important kidney disease–specific risk pathways for CVD. In addition to animal models, the pathogenesis of uremic CVD needs to be investigated in carefully planned human translational studies. These studies should focus on relatively small, intensively monitored cohorts of patients who have estimated GFR ≤45 ml/min or are on dialysis. Interventions targeted for potential kidney disease–specific cardiovascular risk pathways can be used as "probes" to detect changes in biomarkers, cardiovascular risk surrogates, and overt measures of CVD.

Several important kidney disease–specific risk pathways were identified as priorities for further translational studies in the context of several potential disease modifiers for the CKD disease process (Table 1).

### *Clinical Research Issues in Uremic CVD*

**Selecting Study Populations.** In defining study populations that should be prioritized for interventional trials, two separate high-risk populations were identified:

1. Patients with advanced stage 3 as well as stage 4 or stage 5 CKD (*e.g.*, estimated GFR < 45 ml/min). This population seems to have accelerated risk for cardiovascular and all-cause mortality and has been underrepresented in many randomized clinical trials conducted to date. Some consideration was given to whether patients who receive dialysis therapy should be included in clinical trials with patients with advanced CKD (as is the case in the ongoing SHARP Trial). The group believed that this should be determined on a trial-by-trial basis depending on the therapeutic agent(s) to be considered. Discussion also ensued as to whether to include patients with stage 2 CKD with adverse prognostic indicators such as the presence of proteinuria without DN. However, the consensus was that these patients have not been systematically excluded from previously conducted or ongoing randomized clinical trials, and thus it is a less pressing priority to study preferentially this patient population at present.
2. Patients with CKD and known cardiomyopathy with congestive heart failure. This patient population, frequently described as having a "cardiorenal syndrome," is at high risk for both progressive heart failure and progressive CKD, and currently accepted therapeutic options do not seem to be entirely satisfactory. Furthermore, whether different regimens designed to prevent and treat congestive heart failure have divergent effects on the progression of CKD (or, alternatively, whether kidney disease "progressors" tend to have more episodes of congestive heart failure) is understudied and of great importance.

**Defining Study End Points.** Clinical trials should rely primarily on clinical end points, including measures of cardiovascular and renal function, cardiovascular event rates, renal disease progression rates, and cardiovascular and all-cause mortality rates. Surrogate biomarker end points have value with respect to validating or refuting proposed mechanisms for uremic CVD.

*Table 1.* Kidney disease–specific risk pathways

| Risk | Disease Modifiers |
|---|---|
| Insulin resistance | GFR level |
| Innate immunity/inflammation | GFR loss (progression) |
| Oxidative stress | Dialysis |
| Endothelial dysfunction | Proteinuria |
| Vascular calcification | |

They would be especially valuable in smaller pilot studies designed to elucidate a more mechanistic understanding of uremic CVD to more rationally choose agents for larger clinical trials.

**Therapies for Atherosclerosis Studies.** There are a number of attractive agents for consideration of atherosclerosis studies in populations with advanced CKD and in patients with CKD and known CVD. Statins are attractive agents, and there are currently at least three large-scale, multicenter, randomized, clinical trials under way comparing statin use with placebo either in the dialysis population or in a combined advanced CKD/dialysis population. A preliminary report from the 4D Trial suggests that there may be limited benefit from statin therapy in dialysis patients, accentuating the pressing need for further research in uremic CVD. Results of these ongoing studies will be extremely valuable to the renal community. There are other potential agents for consideration, including antiplatelet agents, antioxidants, peroxisome proliferator-activated receptor agonists, and possibly anti-inflammatory agents. All-cause mortality is the most appropriate primary end point for these trials, and a higher priority should be placed on larger, relatively well-powered studies that will provide a definitive answer rather than on conducting multiple parallel, less well-powered clinical trials.

**Therapies for Cardiomyopathy and Congestive Heart Failure Studies.** There are a number of potential attractive therapeutic agents for study in patients with CKD and known congestive heart failure or for CKD patients who have GFR $<45$ ml/min at are at high risk for congestive heart failure and cardiomyopathy:

- Eplerenone and other aldosterone antagonists;
- Beta blockers; Inhibitors of the renin-angiotensin system;
- Vasopressin antagonists.

**Genetic Risks for CVD in CKD.** Several gene polymorphisms have now been identified as being associated with adverse outcomes in small studies in the ESRD population. There is a need for a global, more holistic, and large population-based study of the relationship of gene polymorphisms to CVD in CKD/ESRD patients.

**Clinical Trial Networks and Renal Disease Consortia.** Developing renal disease clinical consortia and/or clinical trial networks will facilitate efficient clinical studies of uremic CVD. A prototypical network has been formed through a concept grant from the NIDDK entitled "The Kidney Disease Research Consortium." This and/or other research consortia can provide access to large numbers of CKD and ESRD patients to perform appropriate clinical trials/studies in a speedy, efficient, and cost-effective manner.

## Appendix

*Acute Renal Failure Retreat, June 7 to 9, 2004*

**Planning Committee**

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*Uremic Cardiovascular Toxicity Research Retreat, October 4 to 5, 2004*

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