Report of the Strategic Planning Conferences
Renal Research Priorities
December 5-6, 1998 & February 4-5, 1999

Progress and Priorities

Renal Disease Research Plan

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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National Institute of Diabetes and Digestive and Kidney Diseases
and the Council of American Kidney Societies

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Sponsored by
National Institute of Diabetes and Digestive and Kidney Diseases
Council of American Kidney Societies

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Contents

Contents

Executive Summary

Introduction

Renal disease is a major and growing health problem that demands the serious and immediate attention of physicians, researchers, and public health advocates. According to the Third National Health and Nutrition Examination Survey, an estimated 10.9[1] million Americans have reduced kidney function. In 1997, 361,000 patients required dialysis or a kidney transplant to stay alive, more than double the number requiring such treatment 10 years before. The direct economic cost of health care for kidney failure, borne largely by the Federal Government, is more than $15 billion a year.

Diabetes is the leading cause of kidney failure, followed by hypertension, glomerulonephritis, and cystic kidney and urologic diseases. The elderly and minorities are disproportionately affected. For example, African Americans represented 29.8 percent of people treated for kidney failure but only 12.6 percent of the total U.S. population in 1996.

There is no cure for kidney disease but, for many, progression to kidney failure may be slowed if the disease is diagnosed and managed early. Yet, relatively few strategies exist to prevent and treat kidney disease.

The Renal Research Retreat

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Council of American Kidney Societies recognized the need to identify research priorities and the potential synergistic benefits of collaborating on a strategic plan.

[1] Jones, C.A., et al., Serum creatinine levels in the US population: third national health and nutrition examination survey. American Journal of Kidney Diseases, vol. 32, no. 6, pp. 992-999, December 1998.

Led by the American Society of Nephrology (ASN), the Council and NIDDK sponsored Strategic Planning Conferences on Renal Research Priorities on December 5 and 6, 1998, and February 4 and 5, 1999. More than 100 researchers and patients gathered in Washington, D.C., to discuss the state-of-the-art and to identify research priorities and impediments to our search for better ways to prevent and treat renal disease. Participants worked in "focus" groups:

- Cell Physiology and Transport
- Growth, Development, Angiogenesis, and Neoplasia
- Progressive Renal Disease
- Diabetic Nephropathy
- Hypertension in Kidney Disease
- Immunologic Renal Disease
- Hereditary Renal Diseases
- Acute Renal Failure
- Dialysis
- Transplantation

In discussing priorities for renal research, participants were guided by key questions:

- How will priorities be implemented?
- How will priorities affect patient care?
- What obstacles block paths leading to goals?

Future Directions in Renal Research: Setting Priorities and Identifying Tools

Participants in each working group identified priorities and mapped implementation strategies. They identified important scientific resources that would be needed to reach research goals. By creating a specific list of required tools, participants were able to offer a tangible "wish list" that will, hopefully, guide funding. From these many specific priorities came global ones, including:

- Conducting More Epidemiological Studies;
- Creating Centers and Cooperatives;
- Creating New Ways to Study Renal Injury;
- Focusing More on Genetic Susceptibility;
- Developing a Renal Genomics Project;
- Increasing Research on Treatments; and
- Improving Grant Review at the National Institutes of Health.

Workforce Issues: Vanishing M.D. Scientists

All groups identified workforce and training as paramount in determining the success or failure of proposed research initiatives. One factor at work in reducing the number of physician-scientists has been the marked restriction in funding for investigator-initiated research grants at the National Institutes of Health over the past decade. Changes in patient-care funding and associated pressures on academic medical centers have exacerbated these trends, leading to the loss of an entire generation of physician-scientists committed to basic and clinical research on kidney disease. The consequences of these events include not only a dearth of young, well-trained individuals beginning promising careers in research but also a shortage of well-trained mentors to the next generation.

To meet the challenges of the 21st century, we cannot simply rely on a few select leaders in the field to develop cutting-edge technologies and state-of-the-art equipment. The future of renal research rests on our ability to invest in the most important aspect in any field of medicine--people. Presently, the pool of expert M.D. scientists is dwindling at a rate that cannot be ignored. Therefore, critical steps must be taken to reverse recent trends that seriously threaten gains in research and patient care realized over the past few years.

Renal Disease Awareness and Education

Despite the complexity of renal disease and the many remaining research and treatment challenges, there is evidence that the public and many medical professionals are unaware of important management tools now available that may prevent the progression of kidney disease. Meeting participants agreed that patient and physician education is vital to bridge the gap between what we know and what we practice. An excellent evidence-based model being considered for kidney disease is the National High Blood Pressure Education Program led by the National Heart, Lung, and Blood Institute at the National Institutes of Health.

Introduction

Kidney disease is a serious and costly public health problem on the increase in the United States. There is no cure. For now, our best hope is to postpone progression to kidney failure, one of the most feared consequences of the disease.

If our society is to gain control over the escalating fiscal and human cost of kidney disease, researchers and public health agencies urgently need to collaborate on a research agenda to identify ways to prevent the disease, its progression, and its complications.

How Many People Have Kidney Disease?

Kidney failure, or kidney death, is experienced by more than 360,000 people who depend on dialysis or a kidney transplant to survive. The number of people with kidney failure has actually doubled over the past 10 years, and the pool of candidates is large. Conservatively estimated,[2] 10.9 million Americans have kidney disease and face the possibility of a future on dialysis or with a kidney transplant. Even with these remarkable treatments, nearly 58,000 people with kidney failure died in 1997.[3]

Who Are They?

People from all walks of life, all races, and all ages develop kidney failure, which researchers also call end-stage renal disease (ESRD).

[2] Jones, C.A., et al., Serum creatinine levels in the US population: third national health and nutrition examination survey. American Journal of Kidney Diseases, vol. 32, no. 6, pp. 992-999, December 1998.

[3] USRDS 1999 Annual Data Report, National Institutes of Health, NIDDK, Bethesda MD, April 1999, Table ES-1, p. xvii.

No one is safe from it, and yet, certain populations are at increased risk for kidney failure:

- **The Elderly.** The average age of people with kidney failure is 56, but most are between ages 65 and 69.
- **African Americans.** They account for 32 percent of ESRD patients but only 12.6 percent of the U.S. population.
- **Native Americans.** They account for 1.5 percent of patients and only 0.8 percent of the U.S. population.
- **Men.** They make up 54 percent of ESRD patients and less than 49 percent of the U.S. population.
- **Hispanics and Pacific Islanders.** They also appear more vulnerable to kidney failure, but data are incomplete.

What are the Costs?

The human cost of kidney disease is staggering. Dialysis and transplantation are modern wonders that sustain life, and yet, patients are plagued by fatigue, anemia, bone disease, dietary restrictions, medication side effects, organ rejection, and an increased risk for coronary artery disease and stroke. Children face the added devastation of impaired growth and development.

Although no price can compensate for human suffering or loss of life, the escalating cost of treating kidney failure magnifies the need to improve diagnosis and treatment. The National Institutes of Health's U.S. Renal Data System reports that estimated medical costs for ESRD totaled $15.64 billion in 1997. Federal funds paid roughly 75 percent of the bill—$11.76 billion—primarily through steadily rising Medicare claims.

Year	Medicare Cost
1992	$6.25 billion
1993	$7.10 billion
1994	$7.93 billion
1995	$8.94 billion
1996	$11.0 billion

What Causes Kidney Failure?

The main causes of kidney failure in the United States are diabetes, hypertension, glomerulonephritis, cystic kidney diseases, and urologic diseases, in decreasing order of magnitude.

- **Diabetes** accounts for 34 percent of all kidney failure cases and nearly 42 percent of new cases. About 36 percent of kidney failure cases among older Americans are from diabetes. The disease is also the alarming cause of 65 percent of kidney failure among Native Americans.

- **Hypertension**, or high blood pressure, is the second leading cause of kidney failure, claiming nearly 25 percent of all patients and 35 percent of new cases of kidney failure in people ages 64 and older. African Americans have higher rates of kidney failure from this disease compared to other racial and ethnic groups.

- **Glomerulonephritis** is an inflammatory disease of the kidney that causes 11 percent of cases. It is the most common cause of kidney failure in people under age 20 years, accounting for nearly 32 percent of ESRD patients in that age group. This disease disproportionately affects Asian and Pacific Islanders and is the cause of kidney failure for nearly 18 percent of this population.

- **Cystic, hereditary, and congenital diseases** as a group is the second leading cause of kidney failure among people under age 20 (26.2 percent).[4]

Despite recent progress, scientists have not had a focused, coordinated plan to address major unanswered research questions in kidney disease. Researchers agree that while basic science advances are being translated into clinical realities, significant clinical research advances are also urgently needed to improve care for patients.

[4] USRDS 1999 Annual Data Report, National Institutes of Health, NIDDK, Bethesda MD, April 1999.

The Renal Research Retreats

On December 5 and 6, 1998, and February 4 and 5, 1999, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Council of American Kidney Societies (CAKS) gathered more than 100 researchers from top academic centers and patient advocates to discuss renal research needs, opportunities, and barriers. Ten working groups were asked to develop coherent, thoughtful and bold research plans for the next 5 to 10 years. The groups identified priorities, obstacles, and tools needed to reach goals.

Working Group Topics

1. Acute Renal Failure
2. Cell Physiology and Transport
3. Diabetes
4. Dialysis
5. Hypertension
6. Immunologic Disease
7. Progressive Renal Disease
8. Renal Growth, Development, Angiogenesis, and Neoplasia
9. Hereditary Renal Diseases
10. Transplantation

Key Questions

1. How will priorities be implemented?
2. How will priorities affect patient care?
3. What obstacles block paths leading to goals?

Participants drew on extensive experience and expertise in renal disease to provide historical perspectives and strategies for overcoming obstacles. During deliberations, working group members considered the three key questions in the box to the left to help guide them through the process.

Renal Research: Status, Needs, and Priorities

Participants in the 10 working groups identified at the end of this report reviewed the current status of research and drew on varying and extensive backgrounds to broadly and thoroughly assess recent progress and remaining challenges before formulating recommendations.

Cell Physiology and Transport

Researchers are striving to learn more about the functions of individual cells that make up the body's complex parts. This fascinating field is called "cell physiology." Our understanding of cell physiology and transport of substances into and out of cells has improved in the last few years. Chief among recent advances is the cloning of several major transport proteins from renal epithelial cells and the development of antibody and cDNA probes for these proteins. The rapid progress in cloning allows researchers to measure the abundance and distribution of the proteins, but we still know little about transport protein structure, function, interaction with regulatory pathways, and expression during development.

Each year, billions of dollars are spent treating volume, electrolyte, and blood pressure disorders related to abnormalities in kidney cell physiology and transport. The long-term objective in cell physiology and transport research is to identify and characterize proteins and physiologic processes involved in renal growth and differentiation and maintenance of normal homeostasis, and to understand the pathophysiological processes resulting from abnormal transport.

Growth, Development, Angiogenesis, and Neoplasia

Altered kidney development is a major cause of morbidity and mortality in children. In the mature, adult kidney, epithelial cells are normally relatively inactive but can grow rapidly. In situations such as acute injury to the kidney, cells multiply to repair the damage. This essential growth appears to be tightly regulated. In contrast, unregulated and ultimately destructive growth results in renal cancer, polycystic kidney disease, compensatory hypertrophy following damage to a portion of the kidney, diabetes mellitus, and most other forms of glomerular injury. Better treatments for these diseases will be possible once researchers better understand the molecular mechanisms controlling normal and abnormal kidney development and growth.

Growth. Growth studies focus on "repair" after renal injury, renal growth associated with polycystic kidney disease, loss of renal mass, diabetes mellitus, etc. This work has identified genes, signaling mechanisms, and processes responsible for transition from the inactive state, entrance into a new growth period, sometimes initiation of destructive processes, and then either a return to the inactive state or continuation of unregulated growth.

Development. Studies on kidney development are beginning to illuminate the genes, proteins, and processes that direct and oversee the design and differentiation of the kidneys' nephrons (filtering units), as well as maintenance of the mature kidney.

Angiogenesis. Studies on angiogenesis have introduced an entirely new approach to regulating renal tissue growth. The field has given new promise to areas in which the complexity of the growth process has confounded approaches to control unregulated growth.

Neoplasia. Neoplasia studies focus on continued and unregulated growth apparently not initiated by injury and not intended to repair damage. This field has benefited from advances in cancer research and sheds light on the genes and processes responsible for renal cell cancer and the repair of injured renal tissue.

Progressive Renal Disease

Several therapies effectively slow the progression of renal disease in some patients:

- strict blood pressure control in most renal diseases;
- angiotensin converting enzyme inhibitors;
- strict glycemic control in people with diabetes, especially type 1; and
- possibly dietary protein restriction.

While not all patients respond to these treatments, not all patients who could benefit have the opportunity. There is a gap between what we know and what we practice, according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

Research has also improved the management of many symptoms and complications of advanced renal disease, including anemia and bone disease. In contrast, cardiovascular disease, malnutrition, and infection continue unabated. The care of people with chronic renal insufficiency, those not yet needing dialysis, is fragmented, poorly organized, and results in lost opportunities to retard disease progression to kidney failure. Some recent evidence suggests that early care by a nephrologist may delay progression of kidney disease and reduce morbidity and mortality after dialysis has begun.

Research priorities include preventing:

- Development and progression of renal disease;
- Development and progression of cardiovascular disease;
- Uremic complications;
- Late recognition and, therefore, late treatment of chronic renal disease by primary care providers; and
- The need for emergency initiation of dialysis or transplantation.

Diabetic Nephropathy

Kidney disease of diabetes is the leading cause of kidney failure in the United States and the fastest growing group of ESRD patients. In 1997, 34 percent (124,000)[5] of all people treated for ESRD had

[5] USRDS 1999 Annual Data Report, National Institutes of Health, NIDDK, Bethesda MD, April 1999, Table B.3 (124,348DM/361,031Total).

diabetes and 42 percent (33,000)[6] of people starting ESRD treatments that year had diabetes. From 1992 to 1996, the annual increase in the number of people with diabetic ESRD was 9 percent, compared to a 5 percent increase in kidney failure from all causes.[7]

Moreover, only 18 percent of people with diabetes survive 5 years after beginning treatment for kidney failure. Many cancer patients have better survival. Estimated annual costs for treating kidney failure from diabetes exceed $6 billion. A greater research investment in this problem is justified based on the huge financial burden and human suffering caused by this disease.

Current research reveals challenges to reversing these trends. For example, researchers have found familial clustering of kidney disease in both type 1 and type 2 diabetes. This pattern is not explained by known risk factors and strongly suggests an important role for genetic factors in the development of kidney disease. More studies are needed to further analyze preliminary data suggesting a connection between gene defects and susceptibility to diabetic nephropathy.

Hypertension in Kidney Disease

Hypertension is a key factor in vascular disease leading to stroke, heart attack, as well as kidney failure. Hypertension also accelerates the loss of kidney function in people with all types of kidney disease. Interventions have been successful at reducing the risk of hypertensive stroke and myocardial infarction, but renal failure from hypertension has not declined. The reasons for this are not fully understood, but may relate to susceptible subgroups in the hypertensive population and lack of timely initiation of established treatment algorithms in susceptible and underserved populations such as African Americans.

About 25 percent[8] of people treated for kidney failure in the United States have lost kidney function because of hypertension, a disease on the rise. Moreover, hypertensive renal disease causes significant morbidity even before kidney failure. Large clinical

[6] USRDS 1999 Annual Data Report, National Institutes of Health, NIDDK, Bethesda MD, April 1999, Table II-2, p. 27.
[7] Ibid.
[8] Ibid., Table B.3 (89,406HTN/361,031Total).

trials such as the Modification of Diet in Renal Disease Study and the Effect of Angiotensin Converting Enzyme Inhibition in Diabetes (type 1) have contributed to our knowledge about the role of hypertension in renal disease. When completed, the African American Study of Kidney Disease and Hypertension Trial will expand on that base of clinical information.

However, these studies have not identified either underlying cellular and molecular events actually causing hypertension or genetic or environmental factors associated with increased susceptibility to kidney disease. Studies have neither pinpointed the early natural history of hypertension nor identified markers to predict people at high risk for developing hypertensive renal disease at a stage when treatment might more successfully prevent or postpone renal and vascular damage.

Immunologic Renal Disease

The quantity and quality of basic research on immunologically mediated glomerular and interstitial diseases have increased dramatically over the past decade. From a discipline largely focused on morphology and immunopathology in the 1970s and 1980s, the area has moved headlong into cellular and molecular biology with major advances in understanding mediation of immune renal injury. Of particular note have been definitions of the role of complement and complement regulatory proteins, oxidants, and proteases, a variety of cytokines, chemokines and growth factors, and adhesion molecules and matrix components.

Immune Renal Diseases

ANCA Nephropathies
Focal Glomerulosclerosis
Goodpasture Syndrome
Henoch-Schonlein Nephritis
IgA Nephropathy
Lupus Nephritis
Membranous Nephropathy
Membranoproliferative Glomerulonephritis
Minimal Change Disease
Postinfectious Nephropathies
Scleroderma
Sjogren's Syndrome

Individual cell types have been employed to establish *in vivo* relevance of the host of new vasoactive and inflammatory mediators. The role of the cellular immune system in mediating glomerular disease, of transforming growth factor-beta in renal fibrosis, of proteinuria in progressive renal disease, and of specific genes and proteins such as the Goodpasture antigen and nephrin in disease processes has been defined. Some of these advances have had important and relatively immediate therapeutic implications.

Hereditary Renal Disease

The importance of primary and secondary genetic abnormalities in the development and progression of kidney diseases, both genetic and acquired, cannot be overstated. Nephrons, the filtering units of the kidney, are comprised of a highly complex array of glomeruli and tubules that generate urine from blood plasma. Genes that are usually transcribed normally encode enzymes, proteins, and other molecules that accomplish this task. However, the functions of these genes may be disturbed by genomic mutations possibly passed from parent to child.

During the past 5 years, researchers have approached inherited renal disorders from two primary avenues:

- The responsible gene may be identified from an informed guess, based on knowing the gene function. This is the "candidate gene" approach.
- The basis of a genetic disorder may be determined by linkage analysis. This is the "positional cloning" approach.

However, studying inherited diseases does not end with the discovery of gene mutations and aberrant proteins. Understanding the disturbed biology consequent to dysregulation and generating specific therapies for the resulting illness are even greater challenges for the future.

Acute Renal Failure

Acute renal failure (ARF) is a sudden, unexpected "shut-down" of the kidneys. This rapid kidney failure is diagnosed in about 115,000 people each year and is associated with high mortality and high hospitalization costs. There are many causes, including operative hemodynamic changes, sepsis, and drug toxicity. Dyes used in radiological imaging cause as many as 13 percent of all cases.

We have made significant progress in preventing ARF and in identifying pathophysiological mechanisms in animal models of ischemia-induced ARF and tissue-culture models of epithelial cell injury. We are at a significant point in the history of ARF research:

- First, lessons learned from principles of renal development are currently melding with paradigms of injury and repair.

- Second, the concepts of signal transduction are being applied to gene regulation, important in proliferation, inflammation, differentiation, and regeneration.
- Third, the availability of transgenic and knock-out animals in which a specific protein is expressed or eliminated allows us to examine whether specific molecular mechanisms contribute to the pathophysiology of ARF.
- Finally, the biotechnology industry has become involved, presenting tremendous opportunities to move research from the laboratory to the patient's bedside. There are now promising experimental therapies in animals that are nearly ready for testing in humans.

Dialysis

Dialysis is a life sustaining treatment for which there has been an explosion of epidemiological research using computer-based registry data. Technology or "hardware" to monitor solutes such as sodium, urea, and hydrogen ions is now available, allowing quick correction of incipient problems. Better methods are being developed to monitor blood flow through vascular access, the Achilles heel of hemodialysis. Researchers have identified a number of "middle" molecules, thought to be harmful to the body but difficult to remove during hemodialysis. Cardiovascular disease is well established as the leading killer of dialysis patients, far exceeding rates in the general population. Finally, infections of the blood and of vascular and peritoneal dialysis accesses are the second leading cause of death in ESRD patients.

More research is needed to:

- Understand the causes of the enormous rates of cardiovascular disease in the renal failure population;
- Identify the best time to start chronic dialysis, a widely debated and still controversial topic;
- Improve techniques for creating permanent vascular access and define criteria for placement and intervention for infections and other complications, and improve the design, biocompatibility, blood flow and infection rates of temporary catheters needed for emergency hemodialysis in acute and end-stage renal failure; and
- Refine operational definitions of middle molecules and determine the biochemical character and role of these molecules in clinical outcomes.

Transplantation

Renal transplantation is the treatment of choice for most people who experience kidney failure. Two themes govern research in transplantation:

- Studies directed at increasing the availability and function of transplanted organs; and
- Studies directed at the interaction between patient and transplanted organ.

There is a shortage of organs for transplantation. Strategies to expand the donor pool and increase organ and patient survival are critical. Studies seeking to increase the supply of organs require an understanding of the consent process; the normal aging process of the kidney (senescence); the nature and potential reversal of retrieval injury; and the science and ethics of xenotransplantation, in which animal organs are transplanted into humans.

Improved patient and graft survival is the fruit of transplant research. However, these successes have also generated new challenges for researchers:

- Increasingly powerful immunosuppressive drugs have greatly improved both graft and patient survival. However, almost half of working renal grafts is lost when patients die. A challenge is to understand the interplay between transplantation and comorbid conditions such as cardiovascular disease, hypertension, and infection.
- Animals may fill the need for more organs. Strategies to surmount immunologic barriers across species using molecular genetic tools have begun.

Expanding transplantation research may bring to fruition the dream of successful replacement of failed organs for the natural lifetimes of patients.

Renal Research: Overarching Priorities

Establishing priorities for renal research is an important and difficult process that was made the goal of the Renal Research Retreat. Working group members reviewed the current state of research in the 10 areas identified in the previous section, evaluated key progress and deficiencies, and identified research priorities and frontiers. From these specific priorities came the following global, overarching recommendations for research to be done in the next 5 to 10 years.

Epidemiology

Ongoing longitudinal studies of patients with chronic renal disease are urgently needed. These studies should collect and analyze data on:

- Chronic renal disease incidence and prevalence, and on risk factors, including genetic and biochemical differences and exposure to toxins and medications; and
- Cardiovascular disease incidence, prevalence, and genetic, biochemical, and other risk factors.

These studies would also be a resource to help identify susceptibility and progression genes and should, therefore, emphasize collection and storage of human blood, urine, renal tissue, and other specimens for future studies.

More studies are needed on treatment patterns, especially among the elderly, neonates, and children.

Epidemiological research on factors affecting survival of dialysis patients is needed. Studies should compare patient (racial and ethnic groups, genetic dispositions, and genders) and treatment variables (hemodialysis versus peritoneal dialysis and hemodialysis membrane biocompatibility and flux) that are associated with

better outcomes, including evaluation of cause-specific mortality. Understanding these factors would help target areas needing special attention, the use of specific dialysis techniques, and perhaps identify circumstances under which treatment would be futile.

Centers and Cooperatives

Clinical studies of human kidney disease are greatly hampered by the lack of collaborative networks to conduct clinical trials and to analyze tissue, serum, and DNA from patients with well-defined clinical and histological diseases. A network of registries and repositories for patient samples should be established to facilitate such studies.

Therefore, more should be done to establish a permanent, cooperative multi-center human kidney studies consortium to study acute renal failure and chronic renal disease. This network would help define disease epidemiology and criteria for introducing potential therapeutic agents into patients' treatment strategies. Basic science should be well represented in these consortia so that bench-to-bedside and bedside-to-bench throughput can be facilitated. Steps should also be taken to:

- Evaluate and validate markers;
- Identify pathology;
- Develop severity of illness scores;
- Increase communication with FDA, industry, and others; and
- Design and implement clinical trials.

Models of Renal Injury

Disease models and methods of studying injury to the kidney and its effects need to be improved. This research falls into two main areas:

Animal Models

- Animal models reflecting complexity of human illness;
- Animal models of catabolism;
- Transgenic animals that permit exploration of candidate mechanisms leading to development, injury, and/or tolerance to injury;

- Less complex models to take advantage of evolutionarily conserved mechanisms involving responses to anoxia and induction of tolerance; and
- Animal models of inflammation/endothelial dysfunction/sepsis.

Cellular Models

- Approximating fully differentiated cells;
- Reflecting endothelial/tubular and tubular/tubular cell interactions;
- Reflecting cell/matrix interactions; and
- Reflecting "*in vivo*" injury and repair.

Genetic Susceptibility

A major goal is to make progress in studying genetic susceptibility to renal injury. Two specific areas to focus on include (1) pharmacogenetics and nephrotoxins and (2) susceptibility to ischemia/sepsis. Related is the need to identify causal, susceptibility, and response genes in immunological renal diseases.

A patient's genetic background is likely a major factor in the development of immunological renal disease. This seems to determine the response to initiating events, particularly the severity of tissue injury that occurs, as well as the outcome of the disease, including recovery, response to treatment, or progression to renal failure. Although some information on genetic susceptibility is available for some immunologic renal diseases, there are large knowledge gaps, and very little is known about several diseases. Understanding the genetic basis of these diseases will greatly facilitate efforts at prevention, prognosis, and rational therapy.

Renal Genomics

When the human genome project has been completed, researchers should use the information to define the genetic programming of renal growth, development, angiogenesis, and neoplasia. Knowing the human genome will open the door to efficiently establish linkages between patterns of gene expression in the kidney and renal function. Identification of these linkages will permit the development of new therapeutic targets and clinical profiles that will allow identification of patients at risk for genetic-associated

renal diseases. The field of renal genomics is relatively new, but it is one area holding great promise for transferring basic science advances from the laboratory bench to the patient's bedside.

Improving Treatments

Additional research should focus on:

Malnutrition and Catabolism

New basic and clinical investigation should explore the relationship between nutritional parameters, inflammatory mediators, and outcomes in kidney failure patients. One hypothesis to examine in detail is the relationship between nutrition, chronic inflammation, and clinical outcome. Interventional strategies for malnutrition should be developed.

Vascular Access

Focused research is needed to define the optimal construction and maintenance of vascular access for hemodialysis to minimize complications (neointimal hyperplasia, thrombosis, and infection) and maximize delivery of the dialysis prescription. Areas ripe for investigation include the development of appropriate cell cultures and animal models, testing of different biomaterials, and pharmacological and genetic modulation of hyperplasia. Of particular interest in hemodialysis are venous (instead of arterial) stenosis and the effects of mechanical trauma from repeated needle punctures and high blood-flow rate. Methodologies for assessing access function and optimizing the timing and type of interventions also should be improved.

Uremic Toxins

Studies should be aimed at identification and kinetics of uremic toxins, for example, small proteins such as beta-2 microglobulin, granulocyte inhibitory proteins and other substances isolated from uremic plasma. Dialytic (high flux dialysis and hemofiltration) and non-dialytic (adsorbents) methods to remove uremic toxins are needed. The biological effects and clinical outcomes of uremic toxin removal are essential.

Optimal Dialysis

“Optimal” and “adequate” dialysis need to be further defined for both chronic and acute renal failure. Parameters including small solutes such as urea, middle molecules, salt, and water should be studied.

Atherosclerosis
It is now clear that both the prevalence and case-fatality rate from cardiovascular disease in people with chronic renal disease far exceeds that observed in the general population without chronic renal disease. The excess risk of cardiovascular disease probably reflects the high frequency of "traditional" risk factors for cardiovascular disease, as well as putative "uremia-related risk factors." Understanding the nature of uremia-related risk factors and developing optimal strategies for managing traditional risk factors requires basic and clinical research.

Enabling Technologies: Tools of the Trade

Participants in the Renal Research Retreat identified important scientific tools needed to help reach goals. By creating a specific list, participants were able to offer a tangible "wish list" that will, hopefully, become standard research resources in the near future.

Develop Specific Diagnostic Tests for Stratifying Clinical Phenotypes of Disorders of Renal Cell Physiology and Transport.

Provide Technologies for a Renal Genomics Project
- Develop a database of (human and murine) kidney-derived, developmental stage-inclusive expressed sequence tags (EST);
- Develop chip and high throughput technology for nucleic acid analysis;
- Bioinformatics, new technology for data analysis;
- Develop methods such as laser micro dissection to acquire tissue for microanalysis (high throughput technology);
- Develop methodologies to acquire genetic material from archival samples;
- Develop new archival resources; and
- Develop new genetic models for renal diseases, for example conditional and tissue-specific gene knock-in and knock-out.

Develop Advanced Informatics
- Database of kidney cell-specific and segment-specific genes and proteins;
- Database of mouse mutations with defined renal phenotypes;
- Database of polymorphisms for genes related to renal cell physiology and transport processes; and
- A Web-based resource site relating to phenotypes. This site would offer patient education, information about available antibodies and other reagents related to kidney cell physiology

and transport, and information and protocols for investigators wanting to use new technologies to study cell physiology and transport processes.

Develop Animal Models

Develop and implement model systems for studying renal cell physiology and transport, including:

- Non-mammalian systems such as *C. elegans*, Zebrafish, Yeast, and Drosophila;
- Mammalian systems, including generation and distribution of well-differentiated human and mouse cell lines, generation of mutant mouse models, knock-out mice, inducible and nephron segment-specific targeting of expression, and implementation of new knock-out technologies; and
- Development and implementation of better technologies for studying small animal physiology.

Develop Repositories

- Develop a repository and core development for clones, libraries, cell lines, promoter constructs, ESTs, antibodies, vectors, mouse embryos and gametes, and yeast 2-hybrid libraries;
- Develop a repository for human kidney tissue.

Develop Array Methods

Create a "Center for Development" of kidney-specific and segment-specific DNA arrays for investigations of renal gene expression, disease, and development.

Identify Surrogate Markers

Identify surrogate markers of progression such as cytokines and enzymes and correlate them with solid end-points from clinical trials and treatment effects, including:

- Standardization of assay methods for large sample number;
- The use as well of stored specimens and databases from existing completed clinical trials could be used; and
- For future trials, develop methods to standardize assays, collection methods, and storage.

Also needed are additional markers for:

- Predisposition to ARF;
- Initial stages of renal injury;
- Severity of renal injury;
- Severity of catabolism;
- Recovery and repair; and
- Response to therapy.

Novel Diagnostics Imaging
Develop new noninvasive technologies to assess renal function and structure *in vivo* and on the cellular level. Multifaceted approaches are needed, including:

- Positron Emission Tomography scan to assess metabolism in regional zones of the kidney;
- Magnetic Resonance Imaging for blood flow and structural abnormalities;
- Optical techniques in research protocols;
- Gene and protein detection methods to detect and monitor renal damage; and
- Radiopharmaceutical markers of kidney function.

Banks and Registries
A registry of patients with histologically well-defined diseases and a mechanism to collect, store, and distribute material from such patients would greatly facilitate goals listed above.

Grant Review

The National Institutes of Health's peer review process is inherently inhospitable to certain types of projects necessary to reach renal research goals:

- Organ-specific projects heavily weighted toward basic science. Basic study sections that review these applications are especially critical of projects led by physician-scientists;
- Innovative, high-risk research;
- Clinical trials, epidemiology, and outcomes research; and
- Projects proposing the development of scientific tools.

The dissolution of the Physiology Study Section has had a negative impact on review of renal research by General Medicine B Study Section (GMB). One possible solution would be for the National

Institutes of Health's Center for Scientific Review to create an advisory panel of investigators with broader perspective of the renal field. Alternatively, the Center might create a kidney-directed study section.

Finally, we strongly urge the Center for Scientific Review to form a Special Emphasis Panel for Clinical Nephrology, analogous to panels for Clinical Oncology and Clinical Cardiovascular Sciences. Such a panel could review applications across the spectrum of clinical research in nephrology, including patient-oriented, epidemiologic, behavioral, outcomes, and health service projects. This would also include traditional General Clinical Research Center-like studies on pathophysiology in humans as well as larger epidemiologic, clinical trials, and outcomes research studies. Currently, proposals for such research are typically reviewed by GMB, Pathology A (Path A), or Epidemiology and Disease Control (EDC) study sections. GMB and Path A review few clinical grants and rosters include nephrologists but few clinical researchers. The EDC roster includes clinical researchers but no nephrologists, and it reviews few nephrology applications.

Workforce Issues: Vanishing M.D. Scientists

Each working group at the Renal Research Retreat identified workforce and training issues as paramount in determining the success or failure of research initiatives described in this report.

One factor responsible for the decreasing number of physician-scientists has been the marked restriction in funding for investigator-initiated research grants from the National Institutes of Health over the past decade. Changes in patient care funding and associated pressures on academic medical centers have exacerbated these trends. This has led to the loss of an entire generation of physician-scientists studying basic aspects of kidney disease.

Another major factor has been the failure to develop a cadre of investigators skilled in new methods of clinical research such as longitudinal studies, clinical trials, and outcome research. The implications of these events include not only a dearth of young well-trained individuals beginning research careers, but also a shortage of well-trained mentors to train the next generation of investigators. We face not only a lack of people to train, but also a relatively old (by scientific standards) pool of trainers.

While basic scientists will likely continue to make discoveries and identify new molecules and genes at an accelerated pace, the ability to apply these discoveries to understand and treat human diseases will be greatly impaired by the disappearance of the M.D. scientist from the basic and clinical research pool. There is no question that efforts must include a substantial increase in funding directed at repairing the situation. Obviously, this problem is not unique to renal disease but, in fact, affects the entire United States medical research enterprise.

While the recent increase in funding for investigator-initiated research grants following the improved budget climate at the NIH is needed and welcome, there is clearly a need to devote some of the increase to workforce development. An important priority is to recognize the important role of clinical investigators. Translating basic research into clinical practice is complicated. Researchers who take cutting-edge

discoveries from the laboratory to the patient warrant and require significant support. Constructive approaches to these alarming problems include:

- Increasing salary stipends for M.D. research fellows so that a research fellowship is financially attractive, not punitive;
- Developing a mechanism to ensure a period of secure grant support for promising investigators successfully completing accredited research training programs;
- Removing salary restrictions for senior investigators;
- Developing new support mechanisms to facilitate interactions between M.D. and basic scientists.

Specific efforts are needed to improve training and to support mentors. One idea is to support clinical and laboratory training programs of at least 1 year for medical students to engage in research beside a mentor. Dual mentors, one from nephrology and one from another discipline, would enhance this program. Financial support should cover tuition and a stipend. Such a program would:

- Introduce and attract students to a career in kidney research at an impressionable age;
- Increase the number of research-motivated applicants joining fellowships in nephrology;
- Reduce the overall debt of students and enhance the possibilities of a research career; and
- Enhance interactions between senior investigators in nephrology and investigators in other disciplines through co-mentoring.

Other activities that could help solve the workforce shortage are:

- Support Ph.D.s and M.D.-Ph.D.s at the post-doctoral and junior faculty stage;
- Expose interested medical residents and clinical fellows to research skills;
- Develop effective mechanisms for concurrent clinical and basic research training;
- Train nephrologists in clinical epidemiology and outcomes research; and
- Through training programs with dual mentors, create interactions with other fields, including:
  --Cell and development biology;
  --Protein biochemistry and metabolism;
  --Sepsis/inflammation/trauma;
  --Endothelial cell biology;

--Clinical epidemiology/outcome research;
--Critical care medicine;
--Cancer biology;
--Atherosclerosis; and
--Stroke and cardiac injury from ischemia.

Special emphasis must be placed on overcoming the shortage of clinical researchers:

- Increase the number and proportion of grants for basic and clinical research and research training from the National Institutes of Health, American Society of Nephrology, National Kidney Foundation, Polycystic Kidney Research Foundation, and others;
- Establish small grants, possibly using R03 or R21 mechanisms, to encourage collaborative clinical studies, including clinical trials and observational studies; and
- Increase the number of large-scale clinical trials and observational studies funded through cooperative RO1 and UO1 mechanisms.

Workforce issues must be addressed if the strategies and goals outlined above are to be implemented and met. To meet the challenges of the 21st century, we cannot simply rely on a few select leaders in the field to develop cutting-edge technologies and state-of-the-art equipment. The future of renal research rests on our ability to invest in the most important aspect in any field of medicine--people. Presently, the pool of expert M.D. scientists is dwindling at a rate that cannot be ignored. Therefore, these important steps need to be adopted and implemented in order to reverse recent trends that seriously threaten the gains in research and patient care that have been realized over the past few years.

Renal Disease: Awareness and Education

Despite remaining challenges and new opportunities in kidney disease research, scientists and physicians agree that more can be done to educate the public about the treatment of kidney disease.

Outstanding models for designing and directing a kidney disease education program are campaigns on hypertension and cholesterol, both coordinated by the National Heart, Lung, and Blood Institute at the National Institutes of Health, and the National Diabetes Education Program sponsored by NIDDK and the Centers for Disease Control and Prevention. These programs have increased public awareness about the dangers of high blood pressure and high cholesterol and the need for better glycemic control in diabetes. A strong scientific base for messages was key to the success of these two campaigns.

A similar education program for the treatment of kidney disease seems logical, despite the complexity of the problem. Members of the renal community have begun discussing possible messages, audiences, and the potential for public and private partnerships to plan and implement an evidence-based program.

Working Group Reports

Participants in the Renal Research Retreat met in small "focus" groups. We have tried to provide uniform formats where possible. However, each report has its own unique character and is primarily the product of the working group.

Cell Physiology and Transport

Introduction

Research on cell physiology and transport remains central to the discipline of nephrology. Each year, billions of health care dollars are spent treating volume, electrolyte, and blood pressure disorders related to abnormalities in kidney cell physiology and transport. The long-term objectives of research in cell physiology and transport are to identify and characterize proteins and physiologic processes involved in renal growth and differentiation and homeostasis; to understand pathophysiological processes resulting from transport dysregulation; and to develop new diagnostic and therapeutic strategies, agents, and initiatives based on basic transport.

Genetic diseases involving specific transport pathways have provided important opportunities to define and characterize epithelial transport processes and to sharpen the focus on underlying pathophysiology. Hypertension is one example, where many factors affect renal salt balance and ultimately result in the clinical manifestation of high blood pressure.

Our understanding of cell physiology and transport has advanced significantly in the last few years, chiefly from the cloning of several major renal epithelial cell transport proteins and the development of antibody and cDNA probes for these proteins, which allows their abundance and distribution to be measured. New and emerging technologies now provide the opportunity to learn more about the structure of proteins, function, interactions with regulatory pathways, and expression during development.

New Frontiers and Priorities for Research

1. Unravel the structural biology of proteins related to renal cell physiology and transport;
2. Define the functions and functional interactions of proteins related to renal cell physiology and transport;
3. Determine the genetic bases for disorders of renal cell physiology and transport;
4. Define the physiologic bases for the phenotypic manifestations of genetic disorders of renal cell physiology and transport;
5. Develop specific diagnostic tests for stratifying clinical phenotypes of disorders of renal cell physiology and transport; and
6. Develop rationale-based therapeutics and pharmacogenetics, including new pharmaceutical agents, rational drug design, and gene therapy.

Tools, Methodologies, and Resources Needed

1. Informatics
   - Database of kidney cell-specific and segment-specific genes and proteins;
   - Database of mouse mutations with defined renal phenotypes;
   - Database of polymorphisms for genes related to renal cell physiology and transport processes; and
   - WWW resource site relating phenotypes and genotypes, for patient education, for information about available antibodies and other reagents related to kidney cell physiology and transport, and for information and protocols for investi-

gators wanting to employ new technologies for the study of cell physiology and transport processes.

2. Development and implementation of model systems for studying renal cell physiology and transport.

Non-Mammalian Systems

- *C. elegans*
- Zebrafish
- Yeast
- *Drosophila*

Mammalian Systems

- Generation and distribution of differentiated, well-characterized human and mouse cell lines to be used as consensus models for investigation;
- Generation and distribution of mutant mouse models
  - Knock-out mice,
  - Inducible and segment-specific targeting of expression, and
  - Implementation of new knock-out technologies;
- Develop and implement better technologies for studying small animal physiology.

3. Centers for technology expertise and Resources
   - Structural biology of membrane proteins
     - Cryo EM,
     - NMR, and
     - X-ray crystallography;
   - Develop and store clones, kidney cell-specific and segment-specific libraries, cell lines, promoter constructs, ESTs, antibodies, vectors, mouse embryos and gametes, yeast 2-hybrid libraries;
   - Store human kidney tissue;
   - Establish a center to develop kidney-specific and segment-specific DNA and protein chips for investigating renal gene expression, disease, and development;
   - Central facility for diagnostics
     - Sequencing of disease-specific genes related to cell physiology and transport, and
     - Analyze urine and other biological samples using new and emerging technologies such as protein chips.
   - Apply bioengineering to the development of new microtechnology.

Challenges and Barriers to Implementing Priorities

1. Too few investigators adequately trained in cell physiology and transport research
   - Length and requirements for clinical nephrology training, and
   - Inadequate time to teach physiology and pathways on wards (M.D.s) and in the basic science curricula (M.D./Ph.D.).
2. Limited access to experts and technology
   Sponsor workshops to foster interactions and introduce new expertise to study cell and transport physiology, meetings to examine interim progress, and recognize the need to attract and fund non-nephrology experts.
3. Potential legal and ethical issues
   - Patient diagnostic information and its clinical implications,
   - Commercialization rights.
4. Problems distributing and sharing resources.
5. Costs and logistical challenges of breeding mutant mice.
6. Funding
   - Need to improve the grant review process,
   - Need to increase funding for cell physiology and transport research, and
   - Need for incentives for innovation.
7. Solutions
   - Debt repayment,
   - Provide incentives for Ph.D. fellows choosing nephrology research,
   - Provide incentives for Ph.D.s training in cell physiology,
   - Provide mechanisms to fund training for non-U.S. permanent residents, and
   - Provide incentives to accept into medical school those students interested in science training.

Overarching Issues and Concerns

1. Traditional academic-based research needs to be revitalized.
   - Attract a greater share of the NIH budget for research in cell physiology and transport commensurate with the health care burden of hypertension, cardiovascular disease, end-stage renal disease, and bone disease.
2. Cuts in length and amount of support for grants impair scientists' abilities to conduct research.
3. Translational research needs to be strengthened.
   - Lack of support for the development of diagnostic and therapeutic approaches to orphan diseases related to cell physiology and transport.
4. The Study Section review process needs improvement.
   - Membership selection
   - Length of service
5. The impact on General Medicine B Study Section of the dissolution of the Physiology Study Section should be recognized. The General Medicine B Study Section should focus exclusively on kidney-related cell physiology, transport, development, and cell biology.
6. Solutions
   - Administratively extend R01 grants (with level funds) for Study Section members whose competitive renewals are due.
   - Exclude bone biology applications from the General Medicine B Study Section.

Growth, Development, Angiogenesis, and Neoplasia

Introduction

Altered kidney development secondary to abnormal growth and differentiation is a major cause of morbidity and mortality in children. In the mature, adult kidney, renal epithelial cells are normally relatively quiescent, but can exhibit rapid increases in growth rates. In some situations, such as following acute injury to the kidney, cell growth is essential to repair the damaged tissue and appears to be tightly regulated. In contrast, unregulated, and ultimately destructive, renal cell growth occurs in renal cancer, polycystic kidney disease, the remnant kidney, diabetes mellitus, and most forms of glomerular injury. Better treatment approaches to developmental abnormalities and diseases will only be possible from an improved understanding of the molecular mechanisms that mediate renal development and altered renal growth rates.

Each of the four topics represents a different approach to understanding the regulation of renal growth. Development research has shed light on the genes, proteins, and processes that direct and oversee the design and differentiation of the nephron and maintain its quiescent state in the mature kidney. Growth research includes studies on repair following renal injury and renal growth associated with polycystic kidney disease, loss of renal mass, diabetes mellitus, etc. Growth studies have identified the genes, signaling mechanisms, and processes responsible for exit from the quiescent state, entrance into a new growth period, sometimes initiation of destructive processes, and then either return to the quiescent state or continuation of unregulated growth. The renal neoplasia field really represents a subfield of renal growth, specifically the one in which hyperplasia is initiated in the apparent absence of renal injury, and then continues in an unregulated manner. This field has benefited from advances in the cancer field in general, and sheds light on the genes and processes that might be responsible for renal cell cancer, as well as those that direct the repair of damaged renal tissue. The angiogenesis field has introduced a whole new approach to regulating renal tissue growth. The field has given new promise to areas in which the complexity of the growth process has confounded approaches to control unregulated growth.

New Research Frontiers and Priorities

#1 Renal Genomics

Description

Use the power of the human genome project to define the genetic programming of renal growth, development, angiogenesis, and neoplasia. Link patterns of gene expression in the kidney to critical functional parameters (renal genomics), and use the data regarding genetic programming to develop new therapeutic targets and to characterize patients at risk.

Technologies

1. Genomic technology
    - Develop a kidney-derived, developmental, stage-inclusive expressed sequence tags (EST) database (human and murine).
    - Develop chip and high throughput technology for nucleic acid analysis.

- Develop new technologies for data analysis of items bulleted above (Bioinformatics).

2. Tissue acquisition for microanalysis
   - Develop methods to acquire tissue, e.g., laser micro dissection) for microanalysis (high throughput technology).
   - Develop methodologies for acquisition of genetic material from archival samples.
   - Develop new archival resources.
3. Develop new genetic models for renal diseases, e.g., conditional and tissue specific gene knock-in and knock-out.

Patient Benefit
Develop more effective and specific therapies by targeting newly defined genes and their products.

#2 Renal Stem Cell Identification

Description
Identify, clone and maintain renal progenitor cells to be used to elucidate the genetic program, mechanisms and signals mediating differentiation into the various cell types of the nephron. Attempt to develop stem cells from non-renal tissues that can potentially be induced into renal progenitor cells.

Technologies
1. Develop technologies to maintain renal and non-renal stem cell cultures.
2. Develop conditions to permit commitment of stem cells into renal progenitors.
3. Develop cell-specific markers and antibodies to facilitate lineage analysis.
4. Genomic technology
   - Develop a kidney-derived, developmental stage-inclusive EST database (human and murine).
   - Develop chip and high throughput technology for nucleic acid analysis.
   - Develop new technologies for data analysis of items bulleted above (Bioinformatics).
5. Tissue acquisition for microanalysis
   - Develop methods to acquire tissue, e.g., laser microdissection for microanalysis (high throughput technology).
   - Develop methodologies to acquire genetic material from archival samples.
   - Develop new archival resources.
6. Develop new genetic models of renal diseases such as conditional, tissue-specific knock-in and knock-out.

Patient Benefit
Develop therapeutic approaches to repairing renal function with new kidney tissue.

#3 Epidemiology of Congenital Renal Diseases and Cancers

Description
Identify causal genes, the role of modifiers in individual gene susceptibility, and the impact of environmental agents on these target genes (gene-environment interactions). Assign functionality to polymorphisms of genes involved in renal disease. Apply pharmacogenetic principles to develop new therapies.

Technologies
1. Establish patient and sample registries to enhance genotype/phenotype correlation (pedigrees, tissue and/or blood samples).
2. Develop genomic technology.

Patient Benefit
This research may improve the development of targeted, individualized therapy, particularly preventive (preemptive) therapy for patients at risk for renal disease.

#4 Architectonics: How the Nephron Grows in Space and Time

Description
Define the inductive mechanisms, in space and time, which result in the appropriate three-dimensional structure of the nephron, its blood vessels, and surrounding stroma. Determine the cell-cell and cell-matrix interactions that result in the assembly, appropriate location and differentiation of renal blood vessels and capillaries, as well as the cell-cell and cell-matrix interactions that determine the structure, location, and differentiated functions of various cells of the nephron.

Technologies
1. Develop new organotypic *in vitro* culture models.
2. Develop new reporter molecules for advanced 3-D imaging technology; develop new computerized imaging technologies for 3-D modeling of kidney structure during development.
3. Develop genomic technology.

Patient Benefit
Develop new therapeutic approaches to the treatment of congenital, as well as acute and chronic renal injury.

#5 Acquisition and Maintenance of Differentiated Renal Function

Description
Define the mechanisms regulating the sequential acquisition of function by differentiated renal cells. Identify the conditions in which cells maintain function during the continuum of development and differentiation. Develop new methods to study embryonic kidney function and integrate classical physiological renal techniques with new molecular genetic approaches.

Technologies
1. Develop new organotypic in vitro culture models.
2. Develop conditions to permit commitment of stem cells into renal progenitors, and then the maintenance of these differentiated cell lines.

Patient Benefit
Development of new treatment approaches for acquired renal diseases.

#6 Growth Control

Description
Identify the molecular mechanisms that maintain quiescence in the mature kidney. Identify the mechanism of induction and mediators of hyperplastic and hypertrophic growth induced during normal development, repair and carcinogenesis. Elucidate the mechanism of the process of cell death and senescence during development and aging, and under conditions of abnormal growth and stress. Determine the role of angiogenesis in the initiation and control of normal and abnormal growth.

Technologies
1. Genomic technology
   - Develop a kidney-derived, developmental stage-inclusive EST (expressed sequence tags) database (human and murine).
   - Develop chip and high throughput technology for nucleic acid analysis.
   - Develop new technologies for data analysis of bulleted items above (Bioinformatics).
2. Develop cell specific markers and antibodies to facilitate lineage analysis.

Patient Benefit
Develop new therapeutic approaches to treat the detrimental sequela of abnormal renal growth.

#7 Targeting Therapies to the Kidney

Description
Develop methods for expressing exogenous gene products to replace a missing function, to modify an existing function, or to introduce a new function in the kidney (renal gene therapy). Develop methods for targeting pharmacological therapies to specific cell types in the kidney. Develop unique systems for delivering exogenous factors, compounds, proteins, and genes to the kidney.

Technologies
1. Genomic technology
   - Develop a kidney-derived, developmental stage-inclusive EST (expressed sequence tags) database (human and murine).
   - Develop chip and high throughput technology for nucleic acid analysis.
   - Develop new technologies for data analysis of bulleted items above (Bioinformatics).
2. Develop cell specific markers and antibodies to facilitate lineage analysis.
3. Develop therapeutic delivery systems, biological or mechanical.

Patient Benefit
Identify new targets for the development of therapeutic approaches to the treatment of renal disease.

Impediments

Global and affect all 7 areas noted above.

Money

1. Genomic and high throughput technologies need to be subsidized and made available to all investigators. This may best be accomplished by developing public and private-sector relationships.
2. Tissue banks and registries need to be established and available to all investigators.
3. Re-institute BRSG-like mechanism for purchasing new equipment that is necessary for investigators to advance their research approaches.
4. Eliminate administrative impediments to inter-institutional research collaboration, e.g., indirect cost accounting.

Manpower

1. Establish a program to repay medical school debts by completing research training in nephrology.
2. Develop a mechanism to foster M.D./Ph.D. collaborations within clinical departments.
3. Develop a mechanism to target M.D./Ph.D. students for careers in academic nephrology.

Time

1. Increase the NIH salary cap to better represent and appropriately support percent effort.
2. Fund administrative staff and other academic infrastructure support.

Knowledge

1. Fund short-term training programs for nephrologists to train in new technologies.
2. Develop incentive programs to encourage scientists trained in other disciplines to focus on renal diseases.

Technologies

1. Correction of all of the above impediments will facilitate the development of the new technologies described in the seven areas presented.
2. The lack of collaboration between the public and private sectors significantly slows the development and incorporation of needed technologies into the academic research setting.

Progressive Renal Disease

Introduction

About 360,000 people are treated for end-stage renal disease (ESRD) in the United States, and the prevalence is rising. Cardiovascular disease mortality is still the leading cause of death. Other serious complications include malnutrition, metabolic abnormalities, infection, bone disease, and anemia. Additional problems in children include growth and developmental delays. The high economic cost and poor outcomes of ESRD are extraordinary burdens on patients and society.

The earlier stages of chronic renal disease can be recognized from a decline in renal function or detection of urinary abnormalities, including proteinuria. We will refer to this earlier stage as "chronic renal insufficiency." The overall objective of the research priorities outlined below is to prevent ESRD and its complications.

Investigations of the mechanisms of progression of chronic renal disease and therapies to retard progression have been highly successful. We now have a number of therapies, which have been tested in experimental animals and proven in clinical trials to be effective in slowing the progression of renal disease. These include strict blood pressure control, ACE inhibition, strict glycemic control in diabetics, and possibly dietary protein restriction. Yet, not all types of renal diseases benefit from these therapies and, in practice, therapies are not applied uniformly to patients who might benefit.

Great progress has also been made in the investigation and treatment of a small number of uremic complications. In particular, provision of 1,25 dihydroxy-vitamin D and human recombinant erythropoietin have substantially ameliorated uremic bone disease and anemia, respectively. These therapies can now be offered to patients during the stage of chronic renal insufficiency, but most evidence shows that few patients receive this treatment. In contrast, investigation of cardiovascular disease, malnutrition and infection during the stage of chronic renal insufficiency is in its infancy, and these complications continue unabated.

The cost of care for ESRD is financed through the U.S. Medicare ESRD Program. However, the Medicare ESRD Program does not pay for the care of patients with chronic renal insufficiency. Thus, the care of patients with chronic renal insufficiency is fragmented and poorly organized, with consequent lost opportunities for the prevention of ESRD and its complications. This is especially evident in the lack of preparation of patients for initiation of treatment with dialysis or renal transplantation.

Thus, research priorities for progressive renal disease include the discovery and implementation of measures to prevent the following: development and progression of renal disease, development of cardiovascular disease, uremic complications, failure to recognize and treat chronic renal disease by primary care providers and delayed initiation of dialysis and transplantation.

Basic (Laboratory) Research

Much of the current research focuses on a relatively small number of strategies to affect blood pressure, lipids, or proteinuria. Development of additional therapeutic approaches based on experimental insight in models of progressive renal disease will be of value. Knowledge of mechanisms of fibrogenesis and tissue regeneration, gained through cell

and molecular studies, are expected to yield therapeutic potential. Potential surrogate markers that will reflect more subtle functional and structural changes that are associated with progressive renal injury are clearly needed. Early disease intervention in humans appears to provide the maximal benefit for preventive therapies, and thus, techniques or tests for early identification of progression may provide the best approach to achieve successful outcomes. An increased understanding of the genetic factors that may influence the progression of kidney injury will be critical. These will require both the development of basic techniques and insights, as well as their application to human diseases. A more directed molecular and cellular understanding of the pathogenesis of cardiovascular disease (endothelial cell and vascular smooth muscle cell) as it applies to patients with progressive renal disease will allow for the development of more focused interventions to reduce cardiovascular death.

As with any basic science endeavor, the insights that are developed from cellular, molecular and genetic investigations will require an effort to better define their relevance in human diseases. Nonetheless, it is clear that this model has served us well, for it has provided the direction for clinical trials. As discussed below, more efficient mechanisms for translational research in humans are much-needed goals for the future.

Clinical Research

In general, the "crisis" in clinical research in general applies especially to progressive renal diseases in nephrology. The historical background in salt and water physiology led to a rapid embrace of cell and molecular biology techniques to address transport, but delayed the emergence of clinical investigation of progressive renal disease. With the exception of investigations of mechanisms of human disease, few investigators have received rigorous training, and grant support through NIH is less than in other institutes. The following definitions are taken from the December 1997 report of the National Institutes of Health Director's Panel on Clinical Research. Excluded from the definition of clinical research are in vitro studies that utilize human tissues but do not deal directly with patients. In other words, clinical or patient-oriented research is research in which it is necessary to know the identity of the patients from whom the cells or tissues under study are derived.

1. **Patient-Oriented Research.** This area of research is defined as research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects
   - Mechanisms of human disease. Studies of renal injury and repair, atherogenesis, and other uremic complications are proceeding due to advances in human cell biology and genetics. In vivo studies of progression are limited due to requirement for renal biopsy, and difficulty in interpreting studies of peripheral blood and urine.
   - Therapeutic interventions. Major advances have occurred in anemia and bone disease. Insensitive and non-specific markers of disease progression, atherogenesis and malnutrition limit advances in other areas.
   - Clinical trials. Clinical trial methods have been successfully applied to progression studies, and have yielded relevant results, but at high cost. Additional studies are necessary to evaluate other treatments, as well as to address cardiovascular disease and malnutrition. The major limitation of these studies is the lack of valid surrogate endpoints, requiring use of "hard endpoints" (renal function decline, onset of ESRD, clinical CVD) and therefore large sample sizes. Costs and low prevalence of renal disease (compared to heart disease) remain major barriers. Greater commitment by government and industry is necessary, as is improved infrastructure to conduct multicenter trials.
   - Development of new technologies. Use of growth factors, cytokines, etc is promising, but at present are "blunt instruments" which are difficult to apply and evaluate.

2. **Epidemiological and Behavioral Studies.** These studies are in their infancy. There are virtually no data on the prevalence and risk factors for chronic renal disease (other than ESRD). Similarly, there are virtually no data on cardiovascular disease, nutritional status, etc in chronic renal disease (other than ESRD). Observational studies are necessary for a foundation of clinical trials and improvement in patient care. The nephrology community should learn lessons from NHLBI-sponsored observational studies on CVD, with subsequent clinical trials and patient and provider education (National High Blood Pressure Coordinating Council, National Cholesterol Education Program Coordinating Council). Similarly, observational studies conducted by the USRDS have led to ongoing clinical trials and development of current clinical practice guidelines.
3. **Outcomes and Health Services Research.** These studies are also in their infancy. Usefulness of this type of research in ESRD suggests that it will be useful in progressive renal diseases, too. However, studies are much harder to do, since administrative databases are much less complete than Medicare ESRD. The most immediate applications are to develop recommendations and clinical practice guidelines for patients with chronic renal insufficiency, including earlier referral to the nephrologist and timely initiation of dialysis and transplantation.

Research Priorities

#1 Conduct Epidemiological Studies of Patients Who Have Chronic Renal Disease or Those at Risk. Special Emphasis Should Be Placed on Elderly, Neonatal, and Pediatric Patients.

Studies should investigate:
1. Incidence, prevalence, and risk factors for chronic renal disease, e.g., genetic, biochemical, toxins, medications;
2. Incidence, prevalence, and risk factors for cardiovascular disease, e.g., genetic and biochemical;
3. Incidence, prevalence, and risk factors for protein-energy malnutrition;
4. Outcomes, including for cardiovascular disease; and
5. Treatment patterns.

Special emphasis should be placed on:
1. Screening populations for susceptibility and progression genes; and
2. Obtaining and storing human specimens such as blood, urine, and renal tissue for future studies.

#2 Conduct Intervention Trials in High Risk Groups of Patients With Progressive Renal Disease, Including Children, Elderly, and At-Risk Ethnic Groups

1. Diabetes mellitus;
2. Hypertension;
3. Proteinuria; and
4. PKD.

Interventions such as lipid lowering agents, modification of oxidant stress (e.g., vitamin E), life style modification, and AII antagonists in children. Trials should also examine damage to the eye, myocardial/coronary artery disease, and macrovascular disease. Insights into the progression of renal disease can be gained for examination of renal outcomes in trials and other populations.

#3 Identify Surrogate Markers of Progression such as Cytokines and Enzymes and Correlate with Hard End-Points from Clinical Trials and Treatment Effects:

1. Standardize assay methods for large samples;
2. Stored specimens and databases from completed clinical trials could be used; and
3. For future trials, standardize assays, collection, and storage.

#4 Study Mechanisms of Progression of Renal Disease

1. Develop murine models of renal disease that can take advantage of genetic technologies in this animal;
2. Define genes leading to susceptibility to progressive renal disease in animals;
3. Identify mechanisms of injury related to proteinuria;
4. Identify shades of adaptive renal growth and tissue remodeling; and
5. Explore innovative therapies in animal models.

#5 Study Mechanisms of Cardiovascular Disease in Adult and Pediatric Patients With Chronic Renal Insufficiency

1. Role of protein-energy malnutrition;
2. Role of cell proliferation;
3. Role of inflammation;
4. Role of toxins (e.g., AGE, homocystine, oxidants);
5. Role of insulin resistance;
6. Role of lipids;
7. Common mechanisms leading to cardiovascular and renal disease (microalbuminuria); and
8. Unique factors that accelerate vascular disease in renal failure.

#6 Study Mechanisms and Treatment of Uremic Toxicity:

1. Inflammation/infection, altered immunity;
2. Growth and development;
3. Anorexia/protein-energy malnutrition, muscle metabolism and function; and
4. Malaise/fatigue.

#7 Study Basic and Clinical Issues in Elderly Patients With Chronic Renal Disease

1. Mechanism of renal injury; and
2. Nutritional and clinical management of elderly patients with CRI.

#8 Examine How To Optimize Health Services Utilization for Patients With Chronic Renal Disease

Use intervention studies (clinical trials and demonstration projects) to improve process variables such as access to medical care and outcomes such as cost and hospitalizations.

Overarching Issues and Concerns *and* Challenges and Barriers to Implementing Priorities

Progressive Renal Disease

1. Collaborate with laboratory and clinical investigators from other disciplines such as genetics, cardiovascular diseases, endocrinology and metabolism, infectious diseases, and immunology.
2. Emphasize translational research, including mechanisms to bring together laboratory and clinical investigators.
3. Identify large patient populations and methods to enhance recruitment of patients into observational studies and clinical trials. Large sample-size and long duration are necessary for observational studies and clinical trials. The high cost of large clinical studies remains an obstacle and will require new solutions.

Professional and Patient Education About Preventing, Detecting, Evaluating, and Managing Chronic Renal Disease

We recommend that the National Institutes of Health establish a kidney disease education project analogous to the highly successful National High Blood Pressure Education Program and National Cholesterol Education Program funded by the National Heart, Lung, and Blood Institute.

Manpower and Funding

1. **Training Physician Investigators and Funding Clinical Research.** Major obstacles to be overcome include shortage of sources of funding for trainees and mentors, lack of peer review within NIH study section for clinical application directed at clinical topics in progressive renal disease. The recommendations that follow are common to all areas of clinical research in nephrology.
   - Increase the number and proportion of ***clinical research training grants*** funded by the National Institutes of Health, American Society of Nephrology, National Kidney Foundation, and other groups.
   - Increase the number and proportion of ***clinical research grants*** funded by the National Institutes of Health, American Society of Nephrology, National Kidney Foundation, and other groups.
   - Establish a ***new study section*** for clinical research in chronic renal disease (or alternative mechanisms, such as a "special emphasis panel" as currently exists for urology-related grant applications).
   - Develop a ***registry*** of multicenter clinical trials and observational studies.
   - Fund ***small R01 grants*** to facilitate formation of collaborative clinical research, including clinical trials and observational studies.
   - Increase the number of ***large-scale clinical trials*** and observational studies (cooperative RO1, UO1 and NO1 mechanisms).
2. **Mechanisms to support and encourage pursuit of careers in investigative nephrology.** Continued emphasis must be placed on recruiting and retaining basic investigators.
3. **Collaboration with other agencies and organizations to increase research funding.**
   - Collaboration among National Institutes of Health components such as the National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute on Aging; National Institute of Child Health and Human Development; Office of Research on Women's Health; and the Office of Research on Minority Health.
   - Collaboration between the National Institutes of Health and agencies such as the Agency for Health Care Policy and Research, Health Care Financing Administration, Health Resources and Services Administration, and Centers for Disease Control and Prevention.
   - New models of collaboration between Government and industry (pharmaceutical companies, biotech companies, dialysis providers, insurance companies, and managed care organizations).

Diabetic Nephropathy

Introduction

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States and causes 42 percent of all new cases. People with kidney failure and diabetes have a 5-year survival of only 18 percent, worse overall survival than people with cancer. The cost of treating ESRD exceeded $15 billion in 1997, including $11.76 billion from Medicare. More than 40 percent of these costs are related to diabetic kidney failure. In 1998, NIDDK support for diabetic nephropathy research was $10.2 million—equal to 7.3 percent of the Institute's entire kidney disease research budget and less than two-tenths of 1 percent of the cost of treating diabetic ESRD.

Ultimately, we want to eliminate diabetes as a cause of end-stage renal disease. We can realize this goal by advancing knowledge of critical mechanisms contributing to the initiation and progression of diabetic nephropathy and by rapidly translating advances into clinical practice. This will require the collaboration of a multidisciplinary set of investigators, an energized and educated patient population, and administrative commitment to a stable investigative infrastructure. Also required are additional resources to substantially redress the current imbalances in research funding, whereby diabetic renal complications receive disproportionately small allocations, thus seriously threatening progress in this area.

New Frontiers and Priorities for Research

#1 Identify the Natural History of Diabetic Nephropathy

Description

Although diabetic nephropathy is the major cause of ESRD in the United States, the natural history of diabetic nephropathy, particularly in people with type 2 diabetes, is not well known. There is an urgent need for comprehensive, well-designed epidemiological studies to examine the roles of known, postulated, and yet-to-be-postulated risk factors in the ***genesis*** of diabetic nephropathy and its ***progression*** to ESRD. Among risk factors to be studied are genetic susceptibilities, behavior, diabetes-related metabolic abnormalities, developmental differences such as glomerular number, and environmental exposures. Studies should also seek to validate known and new markers or techniques to diagnose nephropathy early and predict progression to ESRD. Also needed are studies to identify factors contributing to increased morbidity and mortality in people with diabetic ESRD.

Epidemiological studies comparing ethnic groups are needed since the development and progression of diabetic nephropathy most likely varies between groups. Most importantly, separate studies are required to determine the epidemiology of nephropathy in type 1 and type 2 diabetes.

Patient Benefits

Data from comprehensive epidemiological studies will provide a foundation for developing accurate hypotheses about the ***genesis*** of diabetic nephropathy in humans and about factors associated with ***progression*** to ESRD. The same data will also form the basis for developing cost-effective preventive and therapeutic protocols on early diabetic nephropathy. Epidemiology also provides a foundation for improving the treatment of people with diabetic kidney disease and failure.

Tools and Methodologies

A variety of epidemiological study designs can be employed, including cross-sectional surveys, case-base studies, and longitudinal observations similar to the Framingham Heart Study. At a minimum, these studies need to incorporate measurements of genetic susceptibilities, new measures of glycemic exposure, novel methods of detecting disease onset and monitoring progression, and defining adequacy of ESRD therapies.

Important differences between the epidemiology and natural history of nephropathy in type 1 and type 2 diabetes have been sufficiently documented to mandate separate studies in these two important populations. Moreover, the risk of diabetic nephropathy is much higher in black compared to white patients with type 2 diabetes, arguing for separate studies among certain racial groups.

Resources

To conduct these studies, investigators must have access to a large number of people with diabetes and its complications. This can be accomplished by organizing studies within large diabetes treatment centers or health maintenance organizations, or by forming consortia of smaller providers. It is important to attract epidemiologists and biostatisticians to this field. Given the slow natural history of diabetic nephropathy, long-term studies are a necessity. Resources would be most efficiently utilized by combining epidemiologic studies with genetic studies and with efforts to develop biomarkers of nephropathy risk and surrogate endpoints for early renal injury.

#2 Identify Genes Responsible for Susceptibility to Diabetic Nephropathy

Description

Evidence of the importance of genetic factors in the development of diabetic nephropathy is compelling. It now appears most likely that susceptibility to diabetic nephropathy is due to a major gene effect or the effect of a few oligogenes. Whether these genes determine the genesis of early renal lesions or the progression to ESRD is unclear. Recent developments in molecular genetics, together with knowledge coming from the Human Genome Project, create an unprecedented opportunity to discover genes, proteins encoded by them, and hence pathways involved in the development of diabetic nephropathy.

Patient Benefits

Identification of genes that confer susceptibility to diabetic nephropathy will dramatically accelerate the development of new protocols to prevent and treat this complication. For example, once susceptible individuals can be identified, current therapies such as improved glycemic control and treatment with appropriate drugs can be directed more effectively. Simultaneously, discovering new proteins and pathways will provide targets for developing new and more effective drugs, as well as tools for their delivery.

Tools and Methodologies

In human and animal models, the spectrum of methods of molecular genetics and molecular biology can be employed, including:

1. Gene identification through positional cloning to identify susceptibility loci for genesis and progression of diabetic nephropathy;
2. Gene expression profiles in kidneys specific for different stages of diabetic nephropathy;
3. Protein profiles specific for different stages of diabetic nephropathy; and
4. Pharmacogenetics of different stages of diabetic nephropathy.

Resources

A specific infrastructure must be developed to facilitate utilization of the technologies listed above for:

1. Gene identification: DNA from several panels of appropriate families, derived from different racial groups, must be established and made available to researchers. These panels should include:
   - Multiplex families, with at least two diabetic siblings concordant (CSP) or discordant (DSP) for diabetic nephropathy;
   - Simplex families, with individuals with diabetic nephropathy and their parents (TDT families).

   In addition, assurance is needed that the Genomic Centers will sequence chromosomal regions containing diabetic nephropathy loci once they have been identified.
2. Since gene expression and protein coding profiles will require new, high-throughput technologies (cDNA microarrays, two-dimensional electrophoresis, and mass spectrometry) and major bioinformatics support, specialized centers or consortia should be established. These centers should be able to process tissue specimens provided by researchers. Moreover, databases of gene expression and protein-coding profiles specific for various stages of diabetic nephropathy should be established and available to researchers, as are DNA sequencing data.
3. Pharmacogenetics: Large, ongoing NIH- and industry-sponsored clinical trials provide a unique opportunity to identify people susceptible or resistant to specific interventions. DNA samples from individuals in such trials should be acquired and made available for collaborative research.

#3 Develop and Characterize Animal Models of Diabetic Nephropathy

Description

No existing animal model accurately reproduces all major features of human diabetic nephropathy. Basic and clinical research requires animal models, especially mice, to gain technological advances in genetic manipulations. Such models will also enhance understanding of the molecular and genetic pathophysiology of diabetic kidney lesions. Separate models of susceptibility to diabetic nephropathy may be needed for type 1 and type 2 diabetes.

Patient Benefits

Three areas will be advanced:

1. Human genetic studies will raise questions about pathogenetic mechanisms underlying genetic susceptibility to diabetic nephropathy which are best answered in animal models;
2. Identifying genetic susceptibility to diabetic nephropathy in animals may help identify susceptibility factors in humans;
3. An animal model will be immediately useful for developing drugs to prevent or treat diabetic nephropathy.

Tools and Methodologies

Genetic and other pathophysiological methodologies can be used to identify susceptibility loci for diabetic nephropathy and to learn how these loci promote disease. To facilitate this work:

1. Establish a consortium of centers and investigators for large breeding and linkage studies to identify loci of genetic susceptibility to diabetic nephropathy in mouse models of type 1 and type 2 diabetes (e.g., NOD mice, ob/ob, db/db, k/k), an effort requiring bioinformatics support;
2. Standardize definitions of diabetic nephropathy in the mouse and other models such as rat, rabbit, dog, and pig and develop appropriate techniques to study pathobiology relevant to diabetic nephropathy and its treatment;
3. Investigate gene expression profiles in the animal diabetic kidney specific for different stages of disease;
4. Develop knock-in and knock-out models to help test the roles of specific genes in the development of diabetic nephropathy. Develop cross-breeding experiments to explore the interactions of specific genes with various genetic backgrounds.

Resources

Since gene expression and protein coding profiles will require new, high-throughput technologies such as differential display-PCR, cDNA microarray, suppression subtraction

hybridization and major bioinformatics support, specialized centers or consortia should be established. These centers should have access to or be able to process tissue specimens from researchers.

Databases of gene expression and protein-coding profiles for specific stages of diabetic nephropathy in murine or other animal models should be created and available to researchers as are DNA sequencing data. Well-characterized animal models should be available for testing new pathophysiological hypotheses, developing new disease markers or surrogate outcome measures, and exploring new treatment strategies.

#4 Better Understand Renal Cell Biology and Biochemistry in Diabetic Nephropathy

Description

Despite major recent advances in this area, mechanistic steps responsible for susceptibility, initiation and progression of diabetic nephropathy are incompletely understood. Understanding the basic fields of renal cell biology and biochemistry should fill this gap and build a solid foundation for treating and preventing the disease. Efforts should aim to:

1. Define enzymatic and non-enzymatic pathways potentially responsible for initiation and progression of diabetic renal injury, using whole animal as well as tissue culture systems that encompass all relevant target cell types (glomerular, vascular, tubular, and interstitial).
    - Characterize the regulation of the different glucose transporters in target cells that may be relevant to diabetic renal complications.
    - Identify key regulatory steps in the enzymatic pathways for glucose metabolism that may be affected by diabetes. This may include such pathways as polyol, hexosamine, hexose monophosphate shunt, myo-inositol metabolism, fatty acid and lipid metabolism (diacylglycerol synthesis and arachidonate metabolism, etc.), and reactions involved in oxidative injury.
    - Define the cytoplasmic signaling steps and the nuclear transcriptional machinery that couple glucose metabolism to gene expression and regulation.
    - Analyze the chemical structure of naturally-occurring products of the early, intermediate and advanced non-enzymatic glycation and glycoxidation reactions, their putative receptors and signaling pathways, and define their biological actions and disposition.
    - Examine methods to study systems of cell-cell cross-talk and interactions that may have relevance for the different renal compartments.
2. Identify naturally occurring mediators, agonists, and antagonists that may operate downstream from glucose metabolism. In addition, characterize steps in production, activation and inactivation, and intracellular signaling pathways in renal cells, including vasoactive agents such as endothelins and angiotensin II; hormones such as insulin and related agents; and cytokines, chemokines, and growth factors such as transforming growth factor-beta (TGFβ).
3. Analyze cellular and molecular biochemical interactions that result from the injury of hemodynamic stress, and how this is linked to hypertrophy, cell proliferation and survival, and fibrosis.
4. Study individual constituents of extracellular matrix molecules, their synthesis, metabolism, degradation, assembly, supramolecular structure, and related aspects of integrin regulation, cell-matrix, and matrix-matrix interactions.

Patient Benefits

Advancements in basic knowledge of pathogenetic mechanisms related to metabolic derangement will greatly accelerate the development of interventions to prevent initiation and halt progression of diabetic nephropathy.

Tools and Methodologies

To establish a repository or bank of human and animal cell lines encompassing a host of different renal cell types (glomerular, vascular, tubular, and interstitial) for cell culture, phenotypic characterization, and expression studies. Other focus areas in this report have stated the need for appropriate animal models to examine diabetic nephropathy.

Resources

In addition to other needed resources identified in this report, the renal community should invest work to attract basic scientists from other areas to apply their expertise more directly in diabetic nephropathy.

#5 Define the Pathophysiology of Diabetic Microvascular Disease

Description

While the importance of mesangial sclerosis (mesangial matrix expansion) is a well-established component of diabetic nephropathy, a related and possibly central component of this process is injury from mesangiolysis (the fraying and focal dissolution of the mesangial matrix) and glomerular capillary microaneurysm formation. The pathogenic determinants of these processes are not currently understood. Diabetic nephropathy is also a disease of the vasculature. Large-vessel disease of extra-renal arteries manifests as an accelerated and severe atherosclerosis, which is a major contributor to the early mortality and severe morbidity of diabetes mellitus. Factors determining accelerated atherosclerosis in diabetes, otherwise indistinguishable from advanced atherosclerosis in non-diabetic patients, remain unknown. Small renal arteries and arterioles, and particularly glomerular arterioles, exhibit a characteristic thickening of the vessel walls and diffuse accumulation of poorly defined hyaline material (local accumulation of plasma proteins) in the vessel walls in diabetic nephropathy. With massive hyalinosis, the vascular lumina can narrow or occlude, with downstream effects on the renal tissues resulting from compromised or interrupted blood flow. This microvascular injury of diabetes may additionally result in hypertensive injury (a consequence of damage to the arteriolar resistance vessels), which is then superimposed upon primary hyperglycemic injury to the kidney. The unique features of diabetic microvascular disease remain poorly understood. There are no currently available model systems to study pathologic features of mesangiolysis, scarring and repair, and diabetic microvascular disease.

Patient Benefits

Characterization of the sequence of events and molecules that regulate processes of mesangiolysis, repair, sclerosis, and progressive occlusive vascular disease are essential to developing new targets for therapeutic interventions to retard or prevent progressive and end-stage renal disease. Such interventions are likely to be independent of interventions to improve metabolic control of the hyperglycemic state and may take the form of maneuvers to prevent or retard the accumulation of matrix proteins that result in mesangial sclerosis and interstitial fibrosis.

Tools and Methodologies

Traditional pathological, physiological, and molecular genetics methodologies can be employed to dissect the sequence of mesangial and microvascular injury mediators in human tissues, animal models, and tools described in sections two and three. Such approaches will include:

1. Developing and analyzing new murine models that manifest mesangiolytic and microvascular injury resembling diseases in humans. These models will help define events in vasculopathy and help identify growth factors (e.g., platelet-derived, transforming growth factor-β, and insulin-like), matrix regulatory molecules (e.g., proteoglycans and integrins) and key metabolic pathway regulatory molecules (identified in section four) that control and promote vasculopathy.
2. Utilizing genetic analyses to complement and provide loci for investigating human susceptibilities, outlined in section two. Studies would include characterizing genetically defined murine strains susceptible to diabetic injury; regulating tissue-specific manipulations of gene expression, including the use of knock-out and knock-in technology in animal models and cell lines; analyzing diseased human and animal model tissues using genomic hybridization and microarray analyses to identify constellations of gene expression that determine specific disease manifestations.
3. Exploiting novel experimental systems currently used in other areas of vascular biology. An example would be gene delivery systems using viral or liposome

vectors, which have been used to deliver specific growth factors into arterial vasculature. These approaches can test the role of specific growth factors or their antagonists in promoting or ameliorating vascular disease. These studies may also provide a basis for gene therapy.

4. Developing appropriate physiologic preparations of intact vessels from experimental animal systems and human tissues to identify physicochemical determinants and test interventions that would abrogate abnormalities of vascular reactivity and tone, permeability, and endothelial and vascular smooth muscle cell dysfunction that occur in diabetes.
5. Identifying the extracellular milieu (e.g., matrix components, cell-matrix adhesion molecules, and resulting phenotypic changes in cellular constituents of vascular structures) that characterizes diabetic vascular injury in humans and in animal models.

Resources

These studies require the development of new and relevant animal systems, which is addressed elsewhere in this report. New and well-characterized renal cell lines that behave like human kidney cell types in the diabetic milieu will be essential for some of these studies and may be derived from these new animal model systems or human tissues. The infrastructure to support tools for tissue microdissection, and for the gene chip analysis envisioned for genetic studies, needs to be developed and made available to investigators.

#6 Develop New Therapeutic Approaches for Diabetic Nephropathy

Description

There have been major recent advances in the treatment of diabetic nephropathy. The Diabetes Control and Complications Trial, funded in part by the National Institutes of Health, demonstrated that tight blood glucose control decreases the likelihood of early clinical expression of diabetic nephropathy, while similar studies have demonstrated that tight control prevents the earliest diabetic renal lesions in type 1 diabetic patients. However, strict control is difficult to achieve and maintain, and serious hypoglycemia is a risk. Pancreas transplantation can reverse established diabetic renal lesions, but organ shortages and the need for major surgery and life-long immunosuppression limit its potential. Antihypertensive therapy slows progression of overt diabetic nephropathy and angiotensin converting enzyme inhibition (ACEi) may particularly benefit patients with moderate renal insufficiency, but most will progress to ESRD despite this treatment. Despite improvements in dialysis and transplantation, morbidity and mortality remain unacceptably high, especially among diabetic patients. Thus, new therapeutic strategies are needed at every stage of diabetic nephropathy. Despite the ongoing explosion of knowledge about novel drugs, drug delivery systems, and gene therapy, application of this knowledge to diabetic nephropathy is sorely lacking. This provides a great opportunity for the National Institutes of Health to facilitate the development of a partnership between the academic community and industry to create and develop new therapeutic tools.

Patient Benefits

1. Development of new drugs, genetic manipulations, or new approaches to achieving normoglycemia could eradicate the risk of diabetic nephropathy by preventing the genesis of the early lesions.
2. Reversing the altered dynamics of extracellular membrane turnover induced by diabetes could heal established lesions.
3. Patients with clinical renal disease will benefit from these specific approaches as well as from improved understanding and manipulation of mechanisms driving the progression of advanced renal injury.
4. There is a real potential for reducing the high cardiovascular morbidity and mortality associated with diabetic nephropathy and uremia.

Tools and Methodologies

1. Identification of gene therapy vectors that target specific renal cells and that have a controlled rate of gene expression;
2. Identification of novel drugs that counteract glucotoxicity to glomerular, vascular, and tubular cells;
3. Treatment of early and advanced stages of diabetic nephropathy with existing drugs having therapeutic potential;

4. Studies in early diabetic renal injury of the blocking of growth factors such as TGFβ1, cell signaling pathways such as PKC, effects of glycosylation of important molecules, or oxidant tissue injury are needed;
5. Clinical consortia and Clinical Research Centers dedicated to evaluating new treatment approaches to diabetic nephropathy;
6. Industry partnerships.

Resources

Proposed studies will require large numbers of patients; multicenter cooperation; and joint research funding from the National Institutes of Health, industry, the American Diabetes Association, and the Juvenile Diabetes Foundation International. Groups must make a commitment collaborate on the long-term development and assessment of new therapeutic agents in clinical trials.

Other sections of this report address the basic and clinical science advances needed to fully implement the intent of this section. These interdigitating and interdependent priorities emphasize that support of the broad range of research objectives outlined here is the most efficient approach to solve this enormous problem.

#7 Understand the Biology of Reversing Diabetic Nephropathy with Pancreas Transplantation

Description

Pancreas transplantation in people with type 1 diabetes reverses established diabetic kidney structural abnormalities over the long term. This renal healing represents a switch from excessive production of renal extracellular matrix (ECM) relative to its removal, to greater ECM removal than production. Thus, renal cells can remodel themselves under appropriate conditions and signals. Studies are urgently needed to understand mechanisms regulating the balance between renal ECM production and removal. The ultimate goal of studies would be to develop strategies to switch renal signaling by growth factors, cytokines, or integrins toward removal of accumulated ECM.

Patient Benefits

Diabetic nephropathy largely develops as a consequence of renal extracellular matrix accumulation, a potentially reversible process. Novel approaches are needed to prevent or reverse diabetic renal lesions in spite of imperfect glycemic control. The development of tissue-specific delivery of agents that can manipulate the appropriate cell signaling pathways would restrict the potential side effects of this approach. These strategies would also apply to a broad range of important nondiabetic renal diseases.

Tools and Methodologies

Human and animal *in vitro* and *in vivo* models using state-of-the-art molecular and cellular biologic approaches should be employed to:

1. determine the pathways regulating the balance of renal ECM production and removal;
2. determine the influence of the diabetic state and genetic susceptibility to diabetic nephropathy on these pathways;
3. develop the agents to “switch” cellular regulation from ECM accumulation to ECM removal;
4. develop tissue-specific delivery of agents to localize action to affected tissues.

Resources

Appropriate animal and human cell lines are necessary to determine the mechanisms of cell/matrix communication and the resultant intracellular signaling pathways involved in switching cell protein production toward ECM removal. Well-defined animal models of diabetic nephropathy with structural and ECM changes that parallel human disease are needed to confirm the *in vitro* observations and to test the emerging treatment strategies. Human renal biopsy or cellular materials will be necessary to determine the relevance of *in vitro* and animal data to humans. Finally, human clinical trials, most likely using tissue-specific drug delivery, will be necessary to determine the effectiveness of this approach in diabetic patients. Ultimately this strategy would have great utility to a broad variety of nondiabetic renal and nonrenal disorders.

#8 Identify Indices of Diabetes Exposure and Diagnostic Markers of Early Diabetic Nephropathy

Description

To develop programs to prevent diabetic nephropathy, new more accurate markers to monitor diabetic renal injury and its progression should be identified. In addition, new indices of diabetes exposure should be developed to allow interpretation of and integration with markers of genetic susceptibility. Some markers could be used as surrogate endpoints for early intervention clinical trials. These are of great importance since, without surrogate endpoints, studies of treatment strategies aimed at primary prevention would be too long to be practical if they depended on clinical outcomes.

Patient Benefits

Susceptibility markers will allow selection of patients at risk, while markers of disease progression will allow the monitoring of the effectiveness of preventive and therapeutic protocols. Dosimetry of diabetes exposure is important for establishing therapeutic goals for patients and physicians and for unraveling pathogenetic mechanisms such as genetic susceptibility.

Tools and Methodologies

Clinical and epidemiological studies can assess the value of:

1. Indices of exposures relevant to diabetic nephropathy, e.g., serum and tissue levels of glycosylated molecules, burden of oxidative stress, activation of the PKC pathway, and accumulation of sorbitol pathway products;
2. Markers of genetic susceptibility, e.g., specific DNA sequence differences, and measurements of gene expression or protein levels);
3. Non-invasive techniques and markers to detect early disease processes and their rates of progression:
   - Biomarkers of glomerular and tubular dysfunction, e.g., new measures of glomerular filtration and glomerular permselectivity, plasma prorenin levels, and urine and serum levels of IL-6;
   - Biomarkers of progressive renal damage, e.g., measurement of urinary proteins indicating changes in glomerular, tubular or interstitial ECM or ECM-related molecules such as cytokines or growth factors;
   - New imaging techniques to detect functional and morphological abnormalities, for example, magnetic resonance imaging or position emission tomography.
4. Invasive techniques to detect early disease processes, including the development of safer renal biopsies in order to obtain:
   - Surrogate quantitative structural endpoints (renal morphometry);
   - Renal biologic disease markers and potential surrogate endpoints, e.g., quantitative *in situ* hybridization and polymerase chain reaction and other novel methods of measuring local tissue gene expression and quantitative immunohistochemical markers;
   - Phenotypic or genotypic cellular risk markers, e.g., *in vitro* behavior of renal or other cells such as skin cells grown from biopsy materials obtained from well-characterized, individual patients.

Resources

These studies will require parallel progress in some of the epidemiologic and genetic studies outlined above. Moreover, repositories of appropriately collected serum, tissue, and cellular samples along with careful phenotypic patient descriptions are needed. The development of surrogate markers of diabetic nephropathy risk and progression will require separate, large and long-term studies in both type 1 and type 2 diabetes, and in different ethnic populations. Resources are needed to attract imaging scientists to the field of diabetic renal complications. New approaches to the study of renal biopsy materials require the fostering of collaborative interactions between basic and clinical scientists.

#9 Build the Infrastructure to Develop New Diagnostic and Therapeutic Protocols for Diabetic Nephropathy

Description

Significant progress is being made in understanding the etiology and pathogenesis of diabetic nephropathy. However, translating

this knowledge into new diagnostic and therapeutic protocols has been significantly delayed by the disappearance of physician scientists from clinical research, largely consequent to inadequate review processes and inadequate funding for clinical studies. Filling this gap is critical for substantial progress in the prevention and treatment of diabetic nephropathy. To accelerate this process the following steps should be undertaken:

1. Increase the number of young *nephrologists* trained as clinical investigators specializing in diabetic nephropathy. This can be accomplished by establishing two to three O'Brien-type centers dedicated to research on diabetic nephropathy, particularly clinical research on the development of diagnostic and therapeutic protocols. Also, training grants in nephrology can be encouraged to include a module devoted specifically to the early diagnosis and treatment of diabetic nephropathy;
2. Grant mechanisms should be developed to attract basic scientists and to encourage interaction with clinical scientists in this field. Particular attention should be given to supporting the mentoring of clinically trained individuals in relevant basic science laboratories;
3. NIH grants should foster collaboration between academic centers and health maintenance organizations (HMOs) or large diabetes clinics to make available patients with potential early diabetic renal changes for testing clinical protocols. As well, increased mechanisms for collaborative research support between the National Institutes of Health, industry, and organizations such as the Juvenile Diabetes Foundation International and the American Diabetes Association should be developed;
4. The American Society of Nephrology should collaborate more with organizations such as the American Diabetes Association and Juvenile Diabetes Foundation International in lobbying for both basic and clinical research in diabetic renal disease. Particularly lacking is participation of nephrologists in the clinical research sponsored by American Diabetes Association and Juvenile Diabetes Foundation International.

In addition, support for multicenter clinical trials and for program project grants fostering local and multicenter basic and clinical scientific interactions needs to be greatly expanded.

Patient Benefits

The potential benefit to patients is clear. If new diagnostic and therapeutic protocols for diabetic nephropathy are not tested in humans, there will be no progress in preventing diabetic end-stage renal disease.

Tools, Technologies, and Resources

New study designs tailored to diabetic nephropathy are needed. Given the long natural history of the disease, the length of studies should be determined by the high quality of the study design and not by arbitrary grant cycles. Implementing and analyzing studies will depend on collaboration with biostatisticians.

Also critical is a source of patients with early diabetic nephropathy for clinical studies. This can be influenced by efforts to educate diabetes specialists, nephrologists, and patients about the importance of diagnosis and intervention at the early stages of diabetic nephropathy (similar to the effort made to promote the detection and treatment of hypertension, hypercholesterolemia, and diabetes). Toward this end, the American Society of Nephrology has an opportunity to assume a leadership role.

Challenges and Barriers to Establishing and Implementing Priorities

1. There is no strong advocacy group of patients and professionals to promote research on the development of effective programs to prevent and treat diabetic nephropathy.
2. The Federal and private investment in research on diabetic nephropathy is very small compared with the cost of treating ESRD due to diabetic nephropathy.

3. There are too few established basic and clinical scientists studying diabetic nephropathy.
4. There are no mechanisms for attracting and training young basic and clinical scientists into the field of diabetic nephropathy.

Overarching Issues and Concerns

At a Systemic Level

There are no economic incentives for providers (or patients in their care) to diagnose and treat diabetic nephropathy early in contrast to subsidies for the treatment of ESRD due to diabetic nephropathy.

At a Professional Level

1. Nephrology training inadequately addresses primary and secondary prevention of kidney diseases, particularly diabetic nephropathy.
2. Groups such as the American Society of Nephrology and American Diabetes Association do not cooperate in developing coordinated educational curricula for professionals and joint diabetic nephropathy research initiatives.

Hypertension in Kidney Disease

Introduction

Hypertension has been recognized as a key factor in vascular disease leading to stroke, heart attack, and kidney failure. Interventions directed at reducing the risk of hypertensive stroke and myocardial infarction have proven successful, yet have not had an impact on the occurrence of end stage renal disease secondary to hypertension. The reasons for this are not fully understood, but may relate to the widespread occurrence of hypertension, the multiple causes and clinical settings in which hypertension occurs, and the established risk of hypertensive renal damage in susceptible populations such as African Americans. Moreover, hypertension has long been recognized as a factor accelerating the loss of renal function in patients with underlying renal disease.

The cost of hypertensive renal damage is staggering. At present, approximately 30 percent of patients with ESRD in the United States are diagnosed with hypertensive nephrosclerosis.

In addition, persistent hypertension in the ESRD population not only complicates clinical management but also is a major cause of morbidity and mortality in these patients. Additionally, the number of hypertensive patients susceptible to renal damage is increasing and hypertensive renal disease causes significant morbidity even before ESRD is reached.

The large NIH-funded clinical trials "Modification of Diet in Renal Disease Study" and "Study of ACE Inhibition [captopril] in Type 1 Diabetic Nephropathy" have defined several characteristics of hypertensive renal disease. The current "African American Study of Kidney Disease and Hypertension" will add to currently available clinical information. However, they have not been able to identify underlying cellular and molecular events causally related to the development of hypertension nor identified genetic or environmental factors associated with increased disease susceptibility. Nor have they been successful in pinpointing the early natural history of hypertension or in identifying any markers that could help identify patients at risk for hypertension during the preclinical phase, when interventions may be more successful in avoiding or preventing hypertensive renal and vascular damage.

Recent basic research has been successful in identifying single-gene mutations that result in hypertension such as Liddle syndrome and glucocorticoid-remediable aldosteronism. However, the majority of people with hypertension have essential hypertension, a polygenic disorder with complex environmental interactions. There is much evidence that hypertension is linked in some fundamental way to disordered renal function, but the basis of this relationship has escaped definition. Identification of transport mechanisms, the cell biology of the renal microcirculation, the role of mechanotransduction and cell signaling, and the genetics of hypertension are needed.

Goals for research on the causes and treatments of hypertension are:

1. Facilitate the rapid transfer of insights from basic science research to the clinical arena;
2. Identify factors that influence renal susceptibility to hypertensive damage;
3. Elucidate mechanisms by which the kidney participates in the initiation and perpetuation of hypertension.

The following new frontiers have been singled out as research priorities; underlying them all is the need for (1) a strong interdisciplinary approach, and (2) a cadre of physician and Ph.D. scientists, including clinical investigators, to carry out these goals.

New Frontiers and Priorities for Research

#1 Chronobiology of Hypertension and Its Impact on the Kidney

Late presentation of patients with hypertension limits our understanding of the time course of it development and the genetic and phenotypic susceptibility factors responsible for hypertension and hypertensive renal disease. This problem can be overcome if new advances in genetics and cell biology are used in conjunction with a longitudinal multi racial/cultural cohort study in non-hypertensive children and adolescents and in high risk hypertensive subjects. Such a study will give insight into genetic and phenotypic susceptibility factors that might prestage the development of hypertension and hypertensive renal disease.

Technologies

1. Genetic technologies, including functional genomics.
2. Biochemical profiling.
3. General clinical research centers.
4. Vascular and renal biology and physiology.
5. Computing facilities, including Bioinformatics.
6. Central tissue banks.
7. Non-invasive approaches to renal structure-function aspects of the kidney.

Impediments

1. Non-invasive approaches to structure functional aspects of the kidney.
2. A cadre of well-trained clinical investigators.

Patient Benefit

1. Early understanding of cellular-molecular-biochemical environmental mechanisms influencing susceptibility.
2. Therapeutic interventions to prevent renal dysfunction secondary to hypertension.
3. Potential to develop cost-effective strategies to prevent and/or retard renal dysfunction.

#2 Define Common Factors Responsible for Renal Dysfunction in Syndrome X (Obesity, Carbohydrate Intolerance, and Hypertension)

The concurrence of hypertension, glucose tolerance, dyslipidemia and obesity is very prevalent and appears to be an important risk factor for renal disease. Current knowledge suggests a linkage between hypertension, glucose, and lipid metabolism, but the linkage is poorly understood. While altered insulin sensitivity may affect vascular function and blood pressure, some data indicate the inverse. Critical will be an interdisciplinary approach at the basic level involving lipid and carbohydrate metabolism, and vascular biology and physiology. Clinical studies are needed to identify markers or risk factors for renal disease associated with altered carbohydrate and lipid metabolism. Also needed are innovative clinical studies to define better pathophysiology as well as intervention trials to prevent renal dysfunction.

Technologies

1. Knock-out or overexpression models including interventions that focus on gene therapeutic approaches to treatment.
2. Vascular biology.
3. Renal microcirculation.
4. New *in vitro* models and *in vivo* markers.

5. Transport physiology, both renal tubular and vascular.

Patient Benefit
1. Identification of mechanisms that have therapeutic significance.
2. Defining mechanisms that influence microcirculation.

#3 Hypertension and Diabetic Nephropathy

Diabetic nephropathy and coexistent hypertension are major causes of ESRD in the United States. The objective here is to obtain prospective trial evidence about optimal blood pressure control and antihypertensive agents (ACE inhibitors or ARB versus beta-blockers or calcium channel blockers) to prevent worsening renal function in this population at high risk for ESRD. A secondary goal is to ascertain the predictive value of microalbuminuria as a risk factor versus surrogate marker for ESRD. About 50 percent of the study population should be African American.

Technologies
1. Non-invasive mechanisms to assess renal function and vascular reactivity
2. Mapping susceptibility/modifier genes.

Barriers
Recruitment of African Americans and other under-represented minorities into clinical trials.

Patient Benefit
Obtaining information to design therapeutic interventions to prevent or retard renal diseases associated with hypertension and diabetes.

#4 The Role of the Kidney in the Pathophysiology of High Blood Pressure

The kidney plays a key role in the pathogenesis and maintenance of hypertension. Certainly, hypertension cannot be sustained without the kidneys' participation. A variety of renal mechanisms can raise blood pressure, including:
1. Alterations of ion transport resulting in sodium retention;
2. Renal neurohumoral mechanisms;
3. Alteration of renal endocrine and autacoid functions, including the renin-angiotensin system, kallikrein, nitric oxide, prostanoids, ANP sensitivity;
4. Alterations of the renal microcirculation; and
5. Experimental models of hypertension.

Despite this large body of evidence, no unifying hypothesis is available to determine, in different human and experimental models of hypertension, which of these mechanisms plays a primary role and which plays a secondary role or is a consequence of hypertension.

To this end an interdisciplinary approach is recommended to test the following mechanisms in human subjects and in known or novel experimental models of hypertension.

Kidney/CNS

Technologies
1. State-of-the-art neuroscience (interdisciplinary).
2. Receptors/signaling.
3. Intra-renal modulators.

Renal Endocrine & Autacoid Function on Systemic and Microcirculation (Renal), Epithelial

Technologies
1. Transgenic knock-outs with over-expressing models.
2. *In vitro* cellular models.
3. Micro-dialysis.
4. Development of non-invasive technologies to assess renal physiology.
5. Novel physiological approaches.

Transport (Epithelial, Endothelial, Mesangial, Smooth Muscle, etc.)

Technologies
1. Animal models translatable to human renal disease with hypertension.
2. Cell lines and cellular models.
3. Better *in vitro* models of renal function/physiology.
4. Translation of tissue-methodology to measurement of transport *in vivo*.

Microcirculation

Technologies
1. Apply study of vascular modeling and remodeling to tubular epithelial cells.
2. Physiological approaches such as microperfusion.
3. Develop and apply new techniques.

#5 Basic Mechanisms Underlying the Pathobiology of Salt-Sensitivity, Definitions, and Risk of Decreasing Renal Function

The reasons for the greater susceptibility to renal injury in African Americans remain to be established. This could be partially linked to the greater prevalence of salt-sensitivity and abnormalities in renal hemodynamic adaptation to high dietary NaCl intake. On a high NaCl diet, salt-resistant hypertensive patients manifest an increase in renal blood flow and a decrease in filtration fraction, whereas salt-sensitive hypertensives display an increase in intraglomerular pressure. These renal hemodynamic abnormalities provide a mechanical explanation for the greater propensity of African American patients to develop progressive renal failure. Hypertensive African Americans have worse nephrosclerosis, involving primarily the arcuate renal arteries, and greater reduction of renal blood flow (RBF) than Caucasians. During high NaCl intake, RBF increases and filtration-fraction decreases in salt-resistant patients, whereas RBF in salt-sensitive patients decreases. The sodium-dependent rise in intraglomerular pressure may be in part responsible for the increased propensity of hypertensive African Americans to develop end-stage renal disease.

Research has also shown that salt-sensitive patients with essential hypertension manifest a greater amount of urinary albumin excretion compared to salt-resistant patients. There was a significant correlation between microalbuminuria and changes in glomerular pressure from low to high salt intake. These data suggest that microalbuminuria may be a useful predictor of salt-sensitivity and renal hemodynamic abnormalities in people with essential hypertension. **Thus, an in-depth analysis of the cellular/molecular mechanisms of salt sensitivity and assessment of salt-sensitivity as a risk factor for ESRD is needed.**

#6 Mechanisms and Control of Hypertension in People with End-Stage Renal Disease

The rationale is to minimize the cardiovascular damage that is the leading cause of death in ESRD patients.

Goal
Develop guidelines for the treatment of hypertension in ESRD.

Approaches
1. Choice of drugs (CV and non-CV) and metabolic effects.
2. Better characterize the hypertensive population (BP patterns).
3. Define psychosocial issues that influence compliance.

Barriers
1. Medicare/Medicaid access to anti-hypertensive drugs.
2. Measurements of intra-vascular volume.
3. Education/compliance.

Patient Benefits
1. Better blood pressure control and reduced risk of cardiovascular disease.
2. Obtain Medicare coverage for anti-hypertensive medications.

#7 Hypertension During Pregnancy

Gestation provides a critical research window to understand the early genesis of renal disease in women whose blood pressure increases during pregnancy. Further, a relationship of low birth weight to later hypertensive renal disease is strongly suggested by observational data. Cohorts from previous National Institutes of Health trials such as Calcium for Pre-eclampsia Prevention (CPEP) provide opportunities to longitudinally follow about 4,500 children of mothers whose blood pressure and metabolic status was carefully characterized from gestation week 20.

Approach
1. Clinical trials to gather early predictors of later hypertensive renal disease.
2. Clinical trials to identify predictors of hypertensive disorders during gestation.
3. Clinical trials to predict low birth weight risk early in gestation.
4. State-of-the-art vascular biology studies of placental and umbilical cord tissues.
5. Banking of tissue for genotypic exploration of gestational hypertension and low birth weight.
6. Laboratory models to study vascular biology of arterial pressure control during gestation.

Technologies
1. Clinical trials.
2. Phenotyping and genotyping for susceptibility genes for hypertension and low birth weight.
3. New animal models of gestational hypertension.
4. Bring state-of-the-art vascular biology to the study of placental tissue.

Barriers
1. Clinical trials in pregnant subjects.
2. Blood pressure measurement and tissue sampling in infants and children.
3. No models.

#8 Primary Renal Disease and Associated Hypertension

The rationale is to identify genetic and environmental modifiers that can influence susceptibility to develop hypertension.

Technologies
1. Mapping susceptibility/modifier genes.
2. Quantitate environmental modifiers.
3. Central pathology core.

Barriers
1. Interpretation of biopsies.
2. Non-invasive approaches to renal structure function.

Global Barriers

1. Deficient review process for clinical research.
2. Difficulty recruiting patients, especially African Americans.
3. Low visibility of kidney disease as a health problem.
4. Limitations of current technology to facilitate physiological studies in humans.

Overarching Issues and Concerns

1. Need for adequate compensation for clinical trainees.
2. Special NIH study sections for clinical research applications.

Immunologic Renal Disease

Introduction

The quality and quantity of basic research on the immunologically-mediated glomerular and interstitial diseases has increased dramatically over the past decade. From a largely morphologically and immunopathologically focused discipline in the 1970's and 80's, the area has moved into cellular and molecular biology with major advances in understanding the mediation of immune renal injury. Of particular note have been definitions of the role of complement and complement regulatory proteins, oxidants, and proteases, cytokines, chemokines and growth factors as well as adhesion molecules and matrix components. Individual cell types have been and used extensively for in vitro studies, and animal models have been employed to establish in vivo relevance of a host of new vasoactive and inflammatory mediators. The roles of the cellular immune system in mediating glomerular disease, of TGF-β in renal fibrosis, proteinuria in progressive renal disease and of specific genes and proteins such as the Goodpasture antigen and nephrin in disease processes have been defined. Many of these advances have important and relatively immediate therapeutic implications.

Despite substantial recent progress, there remain a variety of areas where progress has been slow or non-existent, and other areas where a meaningful foothold has yet to be established.

New Frontiers and Priorities for Research

#1 Identification of the Causal, Susceptibility, and Response Genes in Immunological Renal Diseases

It is likely that a major contributing factor to immunological renal disease is the patient's genetic background. This determines the response to initiating events, particularly the severity of tissue injury that occurs, as well as the outcome of the disease, including recovery, response to treatment, or progression to renal failure. Although we have certain information on genetic susceptibility for some immunologic renal diseases, there are large gaps in knowledge and very little is known about several diseases. Understanding the genetic basis for these diseases will greatly facilitate efforts at prevention, prognosis, and rational therapy. Diseases in which this approach could prove most fruitful will be minimal change disease, focal sclerosis, and IgA nephropathy.

#2 Methodologies Necessary to Achieve This Goal Involve Standard Molecular Genetic Technologies Applied to Families and Siblings With Well-Characterized Clinical and Histological Diseases

Barriers to achieving this goal include availability of well-defined, homogeneous patient populations and uncertain and overlapping disease phenotypes, potential ethical issues involving study of DNA and genetic material and the current lack of a sufficient number of investigators in nephrology trained in molecular genetics to conduct such studies.

Solutions to these problems require very careful selection of patients for study, attention to ethical issues, generation of adequately trained investigators, and the approaches to workforce discussed elsewhere in this plan. In addition, achievement of this goal would be greatly facilitated by improved liaisons with existing European consortiums, U.S. groups interested in studying polycystic kidney disease, and recruitment of molecular geneticists from outside nephrology.

#3 Researchers Need Murine Models of Immunological Renal Diseases That Closely Simulate Human Glomerular and Interstitial Renal Diseases. Microphysiologic and Histopathologic Techniques and Expertise are also Needed to Study the Models.

Application of currently available technology in cellular and molecular biology to the study of renal disease requires that significant effort be expended in the development of models in mice. These include not only models of discrete diseases but also utilization of transgenic, knock out and knock in technologies to explore the role of specific molecules in disease processes.

The availability of high through-put mutagenesis technology in mice now makes available large number of new phenotypes that may help identify the genes responsible for the development of glomerular and interstitial diseases.

Methods required to capitalize on this technology involve the development of mass screening methods to analyze structure and renal function. Enhanced partnership with industry for the development of microphysiological technology will help further this goal. In addition, greater collaboration with facilities such as Jackson Laboratories to facilitate sharing, housing and distribution of such animals is essential.

Barriers to achieving these goals include the relative paucity of microtechnology for studying mice, the lack of adequate housing for mice in institutions, poor understanding of strain differences as they relate to the development of renal disease, and the lack of qualified pathologists competent to interpret mouse histopathology. Overcoming these hurdles to take advantage of this powerful technology will require the establishment of core centers be to generate, characterize and distribute mice with defined genotype-phenotype for further study by the general community of investigators.

#4 Identification of Exogenous and Endogenous Antigens That Initiate an Autoimmune Response Leading to Immunologic Renal Disease

Researchers believe that most glomerular and interstitial diseases are immunologically mediated by autoimmune mechanisms, but etiological agents that activate immune responses and lead to these diseases in humans are virtually unknown. These agents may be exogenous (e.g., microbial products) or endogenous (e.g., structural renal and non-renal antigens). Technology is now available for antigen identification at the molecular level, and this needs to be applied to the understanding of these diseases. Identification of initiating antigens is critical for approaches to disease prevention, immunologically specific therapy, and re-establishing unresponsiveness to self-antigens. Factors that determine renal specificity of the immune response that leads to kidney disease need to be better understood.

Methods necessary to undertake such studies include microprocessor sequencing technologies for specific antigen identification and the use of humanized mouse models to study the immune response involving relevant human antigens in a well defined immunogenetic background. Obtaining and studying the antigen-specific, renal deposited antibodies and/or immunocompetent cells and screening kidney tissue for genetic footprints of infectious agents will lead to the identification of target antigens.

Barriers to these goals relate primarily to the lack of suitable tissues from well-characterized patients and too few investigators with appropriate training in molecular immunology. An infrastructure that included collaborative networks to identify patients and store tissue would greatly facilitate these goals.

#5 Develop and Validate Non-Invasive Markers of Disease Activity, Severity, and Progression

A major barrier to conducting meaningful clinical studies and selecting appropriate targets for therapy is the absence of reliable non-biopsy markers to accurately quantitate intra-renal events and processes sequentially, and that may be useful for diagnosis, prediction of outcome, and therapy. The application of currently available imaging technologies for non-invasive monitoring of tissue events in the kidney will require considerable development, and the utility of such measures for accurate and specific disease interventions must be validated in experimental models. However, the potential utility of such markers is felt to justify the high risk of investment in this area.

Methodologies to accomplish this goal need to be developed, drawing on extraordinary achievements in high-resolution imaging in such fields as radiology, magnetic resonance, ultrasonography, and nuclear medicine. Also needed are more precise definitions of mediators and components in kidney inflammation and fibrosis and reagents to identify them. Further efforts to delineate mediators at various stages of disease are to be encouraged both as potential non-invasive markers of disease activity and as therapeutic targets.

Barriers to initiating these studies include the need for:

- sensitive and specific markers of disease activity and progression;
- technologies to quantify markers non-invasively in the kidney;
- validated measurements (compare them to conventional histological assessments in experimental models); and
- study sections that are open to innovative, high-risk proposals.

#6 Establish Collaborative Networks to Study and Treat Immunologic Renal Diseases Based on Standardized Diagnostic Criteria

Clinical studies of human immunologic renal disease are greatly hampered by the lack of collaborative networks for the conduct of clinical trials, and analysis of clinical materials including tissue, serum, and DNA from patients with well-defined clinical and histological diseases. Establishing a registry of patients with histologically well-defined diseases and networks for the collection, storage, and distribution of material from such patients would greatly facilitate the goals of A & C above as well as the application of novel therapies.

Diseases such as focal sclerosis, minimal change disease, and IgA nephropathy are most likely fruitful targets for intensive investigation using such material. Such networks would also facilitate the introduction of novel immune modulation therapies such as ablative chemotherapy and stem cell replacement for the treatment of inflammatory glomerular and interstitial renal diseases.

Methods to accomplish this goal include the development of a central facility for organization and operation of networks as well as tissue storage, partnering with biotechnology firms to identify and access new forms of therapy, and marketing strategies to encourage participation of all practicing nephrologists. Coupled to this approach is a need for the development of uniform staging criteria based on histological and functional patient-specific information in order to determine at what point along the spectrum from inflammation to fibrosis, or from normal morphology to sclerosis, various treatments are most likely to be effective.

Barriers to the accomplishment of this goal include access to patients and enrollment, energizing the clinical community, accurate phenotyping of relevant diseases, generation of new treatment protocols, and developing a funding mechanism for such an undertaking.

#7 Better Understanding of the Molecular and Structural Basis of Proteinuria

Recent advances in understanding the molecular basis of congenital nephrotic syndrome lend optimism to the likelihood of defining the molecular and structural alterations in the glomerular capillary wall leading to proteinuria. Not only is this goal important for understanding the basis for glomerular injury, but it is central to clarifying the role of proteinuria in causing interstitial changes that lead to progressive renal failure.

Identification of new or abnormal structural proteins in animal models and human glomeruli will allow the full definition of the glomerular permeability barrier.

Methodologies to achieve these goals will require the development of differentiated cell lines and reliable markers of individual cell types as well as analysis of the normal biology of glomerular cells and their alteration in disease processes.

Available molecular and biochemical methodologies are in hand for analysis of relevant structural proteins. Mutational studies in mice will likely produce additional insights. (See "Development of Murine Models..." above.)

The barriers to achieving these goals are the availability of suitable cell lines, the difficulty of obtaining human tissue for analysis (see "Establishment of Collaborative Networks..." above), and methods for screening of mouse mutants (see "Development of Murine Models..." above).

Overarching Issues and Concerns

Workforce

This working group believes that workforce issues are paramount in determining the success or failure of research. Multiple factors, chief among them the marked restriction in funding for investigator-initiated research grants at the NIH over the past decade, have led to the loss of an entire generation of physician-scientists committed to basic research on kidney disease. The implications of this event include not only the dearth of young well-trained individuals beginning careers in this area, but the scarcity as well of well trained mentors who can take responsibility for training the next generation of investigators. We face not only a lack of people to train but a relatively old and outdated (by scientific standards) pool of trainers. While basic science will likely continue to make discoveries and unravel new molecules and genes at an accelerated pace, the ability to apply these discoveries to understanding and treating human disease mechanisms will be greatly impaired by the disappearance of the M.D. scientist from the research pool. Major efforts to repair the situation must include substantial funding increases.

A second workforce issue is the need to attract a new population of well-trained basic scientists into nephrology to apply their talents to understanding renal related questions.

Budget increases at the National Institutes of Health resulted in needed and welcome funding increases for investigator-initiated research grants. Some of the increase needs to be devoted to the following constructive approaches to alarming workforce problems identified below:

1. Increase salary stipends for M.D. research fellows to make these fellowships financially attractive, not punitive.
2. Develop a mechanism to ensure a period of secure grant support for promising investigators successfully completing accredited research training programs;
3. Increase the length of project periods for individual research grants;
4. Raise salary restrictions for senior investigators; and
5. Develop new support mechanisms to facilitate interactions between M.D. scientists and basic scientists.

Basic Research

Despite encouraging recent increases in NIH funding, there remain many meritorious and approved scientific projects that are not pursued because of insufficient funds.

M.D. and Ph.D. Researcher Interactions

There are too few venues like the O'Brien Research Centers where sustained and productive interactions between physician-scientists and basic scientists can occur.

Research by Physician-Scientists

To provide a full salary, physician-scientists are being asked to spend more time on clinical and administrative work and less time on research. This is a significant barrier to optimal research productivity. Funding and protection of time for physician-scientists who have major research commitments are essential.

Grant Review

The review process at the National Institutes of Health is inherently inhospitable to the type of project necessary to reach research goals. Basic science study sections are biased against physician-scientists and organ-specific research. These are the same groups that often review projects heavily oriented toward basic research but led by physician-scientists. In addition, study sections are often intolerant of the kind of innovative, high-risk proposals necessary to significantly advance knowledge about immunologic renal disease.

Physician-Scientists and Industry Interactions

Improved relationships and interactions between physician-scientists and biotechnology industries are essential to accomplish goals such as the development of microtechnologies for studying mice, development of algorithms to analyze complex patterns of gene expression in renal fibrotic disease, and development of specific gene-targeting modalities applicable to renal diseases.

Hereditary Renal Disease

Introduction

The kidneys are composed of thousands of proteins that are important determinants of the organ's structure and function. Genes that are usually transcribed normally encode each protein. However, the functions of these genes may be disturbed by genomic mutations that give rise to aberrant proteins which in turn cause clinical syndromes that may be transmitted from parent to child as dominant or recessively inherited traits.

The explication of several inherited renal disorders during the past 5 years has proceeded along two primary lines of inquiry. On the one hand a new protein or gene may be identified from a cloning experiment, and a disease identified that upon linkage analysis and selective gene modification studies ties that gene to a particular disease. Examples of diseases examined by this approach include Alport syndrome, Bartter's syndrome, Gitelman syndrome, Liddle syndrome and nephrogenic diabetes insipidus. On the other hand, a genetic disorder with clear-cut single-gene Mendelian features may be examined by linkage analysis and "chromosome-walking," uncovering a candidate gene that is identified and its role in causation certified by the discovery of pathogenetic intra-genic mutations. Examples of diseases studied by this approach include autosomal dominant polycystic kidney disease (ADPKD) and juvenile nephronophthisis.

It is reasonable to suppose that within the next decade, the genes and proteins underlying several other inherited renal disorders (e.g., cystinuria, nephrolithiasis, renal tubular acidosis, Fanconi syndrome, autosomal recessive polycystic kidney disease (ARPKD), tubulointerstitial nephropathy, "renal" hypertension, familial glycosuria) will be identified by one of the above paradigms. But moreover, as candidate structure and function genes are identified in kidney expression libraries, proteins will be discovered that when mutated account for some of the mysterious conditions that currently are not even recognized as clinically unique diseases or disorders.

The study of inherited disease, however, does not end with the discovery of mutated genes and aberrant proteins, for even greater challenges lies ahead in understanding the disturbed biology that is a consequence of their mis-action and the generation of specific therapies to correct or ameliorate the resulting clinical disorders. ADPKD is a case-in-point. This is the most common lethal renal disease, and perhaps the most common overall, inherited as a single-gene defect. Two genes, PKD1 and PKD2, have been identified, and the respective proteins, polycystin-1 and -2, have been described. Yet, the explicit functions of these glycoproteins have eluded a host of researchers. Polycystins are in all organ systems in the body and likely help regulate cell-matrix interactions that control morphogenesis and structure.

ADPKD is also a case in which a specific type of renal disease has led to the discovery of a new family of proteins important for regulating the structure and function of tissues throughout the body. Were it not for polycystic kidney disease, these large, complex proteins might have gone undetected for several more years. This group of diseases serves as an example of how a "renal" disorder may lead to the discovery of new molecules and processes that may be more widely expressed in biological systems. There are many more similar opportunities in the kidneys.

New Frontiers and Priorities for Research

#1 Identify New Renal Disease Genes

Description
Use the new technology of renal genomics to discover genes and encoded proteins possibly linked to known renal disorders. Several diseases have features of monogenic transmission, although in some cases the pattern of inheritance remains to be verified.

1. Monogenic human "glomerular" diseases
   - Thin basement membrane disease, and
   - IgA nephropathy.
2. Monogenic humans "tubular" diseases
   - Fanconi syndrome,
   - Cystinuria, and
   - Familial glycosuria.
3. Monogenic human "tubulointerstitial" diseases
   - Familial hypertension, and
   - Idiopathic tubulointerstitial Nephropathy.
4. Monogenic animal models of glomerular, tubular and tubulointerstitial diseases.
5. Multifactorial traits leading to nephropathy or dysfunction
   - Systemic lupus erythematosus,
   - Amyloidosis,
   - Idiopathic edema, and
   - Calcium nephrolithiasis.

#2 Annotate Gene Function for Identified Disease Genes

Description
Once disease-causing genes and proteins are identified, the explicit steps in pathogenesis must be determined to discover opportunities for therapeutic intervention. This involves methodologies drawn from a broad expanse of biological and chemical science.

1. Biochemistry.
2. Determination of gene and protein chemistry.
3. Cell biology.
4. Understanding the function of native and mutated proteins.
5. Engineered animal models.
6. Evaluating the abnormal gene products in an environment in which redundant mechanisms may modify function.
7. Transcription profiling.
8. 3-D structure of genes and proteins.
9. Determining molecular structure so that interactions with other molecules can be predicted.
10. Human clinical investigation.
11. Testing the knowledge of pathogenesis in the human condition.
12. Designing and testing specific therapeutic agents.

#3 Specific Renal Diseases Ready for Exploration

Description
The genetic basis of several renal diseases that affect significant numbers of patients is understood well enough that rapid progress toward delineating specific pathogenetic mechanisms and translation of this knowledge to practical treatment can be expected within the next decade.

#3a Renal Cystic Disorders (ADPKD, ARPKD, Nephronophthisis)

1. Define 3-D molecular structure and mechanisms of polycystin function and dysfunction.
2. Define primary and secondary mutagenic mechanisms.
3. Clone ARPKD gene and deduce protein structure.
4. Discover genetic and epigenetic factors that modify expression of PKD.
5. Elucidate the pathogenic pathways leading to renal fibrosis and dysfunction in PKD and develop surrogate markers of progression.
6. Develop and implement strategies for treating progressive renal dysfunction in PKD.

#3b Alport Syndrome

1. Determine 3-D structure and cell-matrix interaction.
2. Elucidate extra cellular matrix processes involved in production and accumulation (remodeling).

3. Examination of other expressed genes in Alport Syndrome using microarray chips and similar methods.
4. Assemble cohorts of patients with genetically defined Alport Syndrome for therapeutic studies.

#3c Congenital Nephrotic Syndrome

1. Explore relation of the newly discovered protein (Nephrin) in other forms of proteinuria.
2. Explore alterations of this protein in experimental animals and relation to specific malfunctions within the glomerular barrier.

Tools, Methodologies, and Resources Needed

1. Databases of renal EST with clusters in radiation hybrid maps. This needs to be multi-centered. Look at each renal monogenic disorder. Can this be a partnership between NIH and industry?
2. Maps and sequences of kidney-expressed genes.
3. Tools to find new genes in current animal models versus continued analysis using knock-out mice.
4. Informatics support for genetic information to be available in the public domain for renal researchers–look to the CGAP program at the NCI as an example.
5. Phenotypically "defined" study populations.
6. Tissue, blood, RNA/DNA, and other banks or registries that are centralized repositories for researchers. Samples could be banked by family trees and by sub-populations.
7. Kidney genome project.
8. Database of nephron promoters.

Challenges and Barriers to Implementing Priorities

1. Identifying and enrolling patients for clinical trials and studies.
2. Genesis of the disease is relatively straightforward, whereas studies of progression are more difficult.
3. The open question of whether animal models will be relevant.
4. People with genetic problems/reasons for ESRD not seen by nephrologist disease too advanced for intervention.
5. Need to get clinical materials identified (tissue banks).
6. Need to identify families with genetic mutations to study for longitudinal periods.
7. Difficulty in identifying patients with specific phenotypes for cohort studies.
8. Need to find ways to remove the "fear factor" and encourage ethnic communities to be involved in clinical research.
9. Threat to insurability because of screening and treatment for a genetic disorder.
10. Issue of access to gene typing and high technology sequencing.

Overarching Issues and Concerns

1. Develop a strategy to teach renal researchers about genetics.
2. Develop a strategy to educate patients about genetics and therapies that will help slow the progression of the disease.
3. Organize patients willing to participate in clinical trials.
4. All renal researchers need access to genetic materials, regardless of institutional affiliation. Bridge information gaps and increase sharing.
5. Educate the public about the disparity between dollars spent on research and the economic impact of disease on society. A knowledgeable public is a strong advocate.
6. Train nephrology fellows in clinical research methodologies. Will there be senior researchers to teach fellows? Facilitate cross-disciplinary training and possibly establish centers to attract researchers to the kidney field. Identify and invite individuals to meetings and workshops.

Acute Renal Failure

Introduction

Acute renal failure (ARF) is common, affecting up to 5 percent of hospitalized patients. Even with a relatively modest rise in serum creatinine of 0.25 milligrams per deciliter (mg/dL) there is about 32 percent mortality among hospitalized patients. Acute renal failure is an independent risk factor for death, and the odds of dying are 5.5 times higher if serum creatinine reaches 2.0 mg/dL. When ARF requires hemodialysis, the mortality rate increases to more than 60 percent! A prospective trial of patients undergoing cardiac catheterization or angioplasty revealed an incidence of ARF of 144 per 1000 patients and 7.7 per 1000 patients required dialysis. Overall hospital mortality of patients who required dialysis was 35.7 percent and 2-year survival was only 18.8 percent. In addition to costs associated with mortality, the medical expenses are estimated at $8 billion a year.

Significant progress has been made in preventing ARF and identifying pathophysiological mechanisms in animal models of ischemia-induced ARF and tissue culture models of epithelial cell injury. However, we have been less successful translating that knowledge from experimental models to humans. In part, this is because there are often multiple contributors to ARF in an individual patient, including ischemia, sepsis and drug toxicity; radiocontrast nephropathy accounts for as much as 13 percent of all cases.

We are at a significant point in the history of ARF research.

- Lessons learned from principles of renal development are melding with paradigms of injury and repair.
- Concepts of signal transduction are being applied to gene regulation, which is important in proliferation, inflammation, differentiation, and regeneration, all features of ARF.
- In transgenic animals, we can examine whether a specific protein is involved in injury and/or repair of the kidney. The biology of inflammation is being applied to the pathophysiology of ARF, especially when sepsis is present.
- The biotechnology industry has become interested in ARF, opening tremendous opportunities to translate basic science into medical practice. Some potentially promising therapies in animals appear ready for human trials.

However, with opportunities come many challenges.

New Frontiers and Priorities for Research

Important advances have been made in understanding ARF in animal models. Translating these advances to patients has suffered from an incomplete understanding of the human disease, which is complicated by its heterogeneity.

A consensus is needed about characteristics of ARF in humans so that more appropriate animal models can be developed. Development of animal models will hasten the development of new therapies for ARF. Testing of these potential therapies will require stratification of patients according to types and severity of renal insufficiency and associated diseases and the identification of appropriate endpoints to validate effectiveness. Representation of the Food and Drug Administra-

tion on consensus panels is critical to allow for design of studies that will satisfy criteria for approval of new therapeutics and will facilitate interactions with industry. It is in the interest of patients for us to facilitate enthusiastic industry participation in clinical drug development for ARF.

Are mechanisms of injury in animals relevant to human ARF? The development of more-appropriate models will lead to new therapeutic targets. There is a need to better understand human ARF and to design more-appropriate clinical trials and related strategies to test putative therapeutic interventions. In humans with ARF, we need to know:

1. What predicts the development of ARF and its outcome?
2. What markers can identify ARF early?
3. What markers predict severity and progression of renal insufficiency?
4. What are predominant mechanisms of ARF in humans?
    - What is the contribution of vascular and endothelial abnormalities?
    - To what extent does tubular injury and obstruction contribute to the pathophysiology?
    - Is the proximal or distal tubule more affected in the initial and maintenance phases of ARF?
    - To what extent does inflammation contribute to clinical disease?
5. To what extent is ARF complicated by catabolism of lean body mass and how does catabolism affect the excessive mortality rate of ARF?

#1 Establish a Permanent, Cooperative Multi-Center Human Studies Consortium in ARF

1. Define characteristics of ARF in man.
2. Establish a standardized database.
3. Evaluate and validate markers of the degree of injury and progression of renal insufficiency.
4. Provide pathology.
5. Develop severity of injury and disease scores.
6. Establish criteria for introducing potential therapeutic agents into patient treatment strategies.
7. Interface with FDA and industry.
8. Design and implement clinical trials.

To develop new therapies, we need animal and cellular models more closely mimicking specific aspects of the human disease. This will be difficult since many factors are associated with the disease in humans. But, better models are necessary to test or screen for markers, therapies, therapeutic targets, and metabolism. Current models are generally unifactorial, for example, ischemic-reperfusion damage to the kidney.

Some questions to be addressed before researchers can develop new strategies:

1. Will mice or other animal models such as pigs provide better insight into human disease?
2. What can we learn from animals or experimental situations exhibiting naturally occurring tolerance to ARF/renal damage?
3. How do we take advantage of “knock-out” and transgenic animals?

In addition, our increasing ability to alter the genetic composition of animals provides the opportunity to target molecules to the proximal or distal tubule or renal vasculature selectively and affect the timing of expression of molecules. We must develop:

#2 Improve Models and Methods of Studying Injury

Animal Models

1. Animal models reflecting the complexity of human ARF.
2. Animal models of catabolism of lean body mass.
3. Transgenic animals that permit exploration of candidate mechanisms that lead to injury and/or tolerance to injury. For example, animals can be engineered to target molecules to specific nephron segments selectively at specific times after injury.
4. Complex animal models that exhibit tolerance to renal injury.

5. Less complex models to take advantage of evolutionarily conserved mechanisms such as responses to anoxia and induction of tolerance to toxic insults.
6. Models incorporating inflammation, endothelial dysfunction, and sepsis.

Cellular Models

1. Approximating events that occur in the kidneys *in vivo* using fully differentiated cells *in vitro*.
2. Reflecting endothelial/tubular and tubular/tubular cell interactions in two- and three-dimensional culture.
3. Reflecting cell/matrix interactions.
4. Allowing insight into *in vivo* injury and repair by designing experiments to maintain differentiated function and metabolism *in vitro*.

Ultimately, information about molecular and cellular pathophysiology will guide the design of therapies to prevent or limit damage in ARF. There is a need to develop and test in experimental animals therapeutic strategies that might then be applied to people with ARF.

#3 Develop New Approaches to Enhance or Accelerate Recovery from Established ARF by Investigating Strategies to:

1. Identify key molecules such as growth factors, cytokines, and adhesion molecules that participate in injury and repair pathways;
2. Modify "target molecule" expression, using antibodies, peptides, and gene therapy;
3. Optimize renal replacement therapy and methods that hasten cellular repair; and
4. Prevent further renal injury resulting from dialysis or other supportive measures;
5. Develop adjuvant therapies to counter adverse effects of dialysis and other supportive measures; and
6. Prevent or ameliorate catabolism of lean body mass and improve nutritional status.

Developing markers is central to implementing strategies to intervene early in ARF, to enable implementation of preventive or therapeutic measures, and to determine effectiveness of therapies in established ARF. We must:

#4 Develop Markers That Establish:

1. Predisposition to ARF.
2. Initial stages of renal injury.
3. Severity of renal injury.
4. Severity of catabolism of lean body mass.
5. Recovery and repair of the kidney.
6. Response to therapy, and allow for
7. Rapid and continuous monitoring of renal function.

Since the cellular damage to the kidney is patchy and poorly defined, and there is glomerular and tubular dysfunction in ARF, we need information about the structure of the kidney in this disease. We should take advantage of the rapid development of techniques that can focus on small areas of intact tissues in humans and can even monitor metabolism in living tissue. The following five technologies need exploration:

#5 Multifaceted Approaches to Noninvasive Assessment of Renal Injury, Function, and Structure

1. PET scan to assess metabolism in regional zones of the kidney.
2. MRI for blood flow and functional/structural abnormalities.
3. Optical techniques in research protocols.
4. Gene and protein detection methods to assess and monitor renal damage and reflect repair processes.
5. Radiopharmaceutical markers of kidney function localizing selectively in normal or injured renal tissue and/or serving as biochemical sensors of local environment.

The variability of clinical outcomes in ARF suggests that genetic factors influence susceptibility to renal damage and/or response to therapy. Concern about the metabolism and excretion of drugs in patients with and without ARF impedes the development of new pharmacologic agents. In addition, nephrotoxicity is a concern, and we have little, if

any, ability to predict which patients are at risk. Consequently, we need to understand more about the:

#6 Genetic Susceptibility to Renal Injury

1. Pharmacogenetics of susceptibility to nephrotoxins.
2. Susceptibility to ischemia/sepsis.
3. Susceptibility to excessive catabolism or detection of abnormalities in metabolism.
4. Genetic contribution to tolerance to injury.

Tools, Methodologies, and Resources Needed

Potential Workshops

1. Laser microdissection.
2. Heavy isotope technology and other methods to assess metabolic state and degree of catabolism.
3. Gene-chip technologies and SAGE to identify genes related to the risk of ARF.
4. Assays of marker protein(s) excreted in the urine.
5. "High throughput" screens for potential therapeutic targets derived from differential screening technologies.
6. Informatics.
7. Clinical trial design.
8. Fluorescence tags for monitoring proteins involved in the injury and repair process.
9. Imaging technologies.
10. Inducible genetic systems in animals and cell cultures and targeted protein expression paradigm.

Challenges and Barriers to Implementing Priorities

1. ARF occurs in a complex clinical setting.
2. There is no ongoing group of investigators providing the infrastructure required to initiate and perform the clinical studies that are critical for the diagnosis and treatment of ARF.
3. There are limited career opportunities and advancement for investigators participating in multi-center clinical trials;
4. Trainees are not prepared to take advantage of the "new biology" that holds so much promise to inform new therapeutic approaches.
5. ARF is often recognized late, nephrologists are not consulted in early stages, and HMO and general medicine physicians refer patients late.
6. There is no patient advocacy group.
7. The 4-year research funding cycle is too short and suppresses innovative research.

Manpower Issues and Concerns

Development of Investigators and Increased Diversity in ARF Research

1. Research opportunities should be encouraged for medical students who will spend at least 1 year with two mentors, including one from nephrology and one from another discipline. Financial support should be adequate to cover tuition and a stipend. This program would provide many advantages. It would:
   - Introduce and attract students to kidney research at an impressionable age;
   - Increase the number of research-motivated applicants in nephrology fellowship programs;
   - Reduce overall debt of students and enhance the possibilities of a research career; and
   - Enhance interaction between nephrology mentors and mentors from other disciplines (since they will be co-mentors).
2. Support Ph.D.s and M.D.-Ph.D.s at junior-faculty and post-doctoral stages.
3. Enhance exposure of medical residents and clinical fellows interested in research to ARF and kidney disease—financial support for intermittent clinical and research training.
4. Train nephrologists in clinical epidemiology and outcomes research.

5. Create interactions with other fields from which ARF research may benefit, including training programs based on two-mentor models. Fields include, but are not limited to:
   - Cellular and developmental biology;
   - Protein biochemistry and metabolism;
   - Sepsis/inflammation/trauma;
   - Endothelial cell biology;
   - Clinical epidemiology and outcomes research;
   - Intensive care physicians;
   - Cancer biology; and
   - Stroke and cardiac injury from ischemia.

Dialysis

Introduction

Renal diseases of various etiologies often culminate in end-stage renal disease (ESRD). The majority of the ESRD patients are treated with dialysis, partly because of the relative inaccessibility of donor organs for renal transplantation. The 1998 U.S. Renal Data System reported approximately 180,000 patients on chronic dialysis, of which 84 percent utilized hemodialysis and the remaining utilized peritoneal dialysis.

Although there have been modest improvements in survival in the U.S. chronic dialysis population in recent years, the statistics remain grim, with a 1-year mortality rate of approximately 20 percent. The causes of death in many of these patients are unclear, although cardiovascular and infectious events have been cited as the common causes. Malnutrition is common among ESRD patients and appears to be a major contributing factor. In addition to the high mortality, the quality of life on chronic dialysis is generally poor.

Issues in dialysis that require much more intense investigation fall into two general areas: the dialysis treatment itself and medical problems of dialysis patients. Improvements and new developments in dialysis technologies are sometimes undertaken by industry and academic researchers are responsible for appropriate application. The medical complications of uremia and of dialysis also fall into the domain of academic researchers.

Federal funding for dialysis research has been modest for the last two decades. One explanation for this low funding level is that resources should be directed at curing kidney diseases, not at ESRD treatments. Another argument has been that industry should fund dialysis research. It is apparent, however, that ESRD, and therefore chronic dialysis, are unlikely to be eliminated in the foreseeable future, with both early detection of chronic renal disease and its definitive treatments being the limiting factors. Currently, new cases of ESRD are increasing by about 9 percent a year. Even with advances in treating renal diseases and in transplantation, the incidence of ESRD is not expected to decline significantly, if at all, in the next 10 years. In addition, acute renal failure remains a major medical problem and dialysis is the most logical modality for renal replacement for this condition. Managing patients with acute and chronic renal failure occupies the majority of clinical nephrologists' time. Further understanding of uremic complications and improvements in dialysis and its outcome are crucial.

New Research Frontiers and Priorities

#1 Malnutrition/Catabolism

Description

Basic and clinical investigations are needed to address the etiologies of malnutrition in ESRD patients. One hypothesis that should be examined in detail is the relationship among nutrition, inflammation and clinical outcome. Sources of occult inflammation in these patients should be identified. Specific signals activating or regulating the degree of catabolism should be identified. Interventional strategies for malnutrition should be developed.

Resources Needed
- Cellular and animal models.
- Clinically practical methods of delivering nutrients.
- Development and proper application of agents that promote appetite, enhance anabolism and inhibit catabolism.

Patient Benefit
Improved nutritional status enhances quality of life, prevents infection and will probably decrease cardiovascular mortality.

#2 Cardiovascular Events

Description
Identify the exact nature of cardiovascular death. Determine the risk factors for cardiovascular events in ESRD patients. One question is whether the conventional Framingham risk factors apply to ESRD patients. If so, what levels are of clinical concern? A corollary is, are there additional risk factors specific for ESRD? Devise strategies to treat these risk factors and end organ damage. Both basic studies and clinical studies are required.

Resources Needed
1. Uremic animal models.
2. Epidemiologic studies.
3. Clinical intervention trials potentially supported in part by industry.

Patient Benefit
Prevention and treatment of cardiovascular disease, the leading cause of death, would improve clinical outcome of the ESRD population.

#3 Vascular Access

Description
Vascular access is the Achilles heel of hemodialysis. Improve techniques of creation of permanent and temporary vascular accesses. Develop the optimal model of vascular accesses in order to study the pathogenic mechanisms, prevention, and treatment of vascular access complications (such as neointimal hyperplasia, thrombosis, and infection) and failure. Of particular interest to hemodialysis are venous, rather than arterial, stenosis and the effects of mechanical trauma from repeated needle punctures and high blood-flow rates. Improve methodologies for assessing vascular access function and optimizing the timing and type of intervention for access stenosis and thrombosis.

Resources Needed
- Human and animal smooth muscle and endothelial cell cultures.
- Animal models.
- Development and adaptation of biomaterials and formatting of the biomaterials into optimal configuration for vascular access.
- Pharmacological and genetic modulation of hyperplasia.
- Hardware and algorithms to assess vascular access anatomy and function.

Patient Benefit
Improvements in temporary and permanent vascular access would allow adequate delivery of dialysis prescriptions while minimizing potentially fatal complications associated with vascular access.

#4 Uremic Toxins

Descriptions
Identify and determine of the kinetics of uremic toxins other than urea (such as beta-2-microglobulin and granulocyte inhibitory proteins). Assess and improve dialytic (high flux dialysis and hemofiltration) and non-dialytic (adsorbents) methods for selective removal of uremic toxins. Determine the biological effects and clinical outcome of their removal.

Resources Needed
1. Protein, lipid, and carbohydrate purification techniques.
2. Cell culture, isolated organ, and animal models to test the biological effects of isolated uremic toxins. Many of these can potentially be derived from other disciplines.
3. Membrane (semipermeable) and sorbent chemistry and biophysics.

Patient Benefit
Enhanced detoxification of the ESRD patient should lead to better quality of life and reduce mortality.

#5 Optimal Dialysis

Descriptions
Better define "optimal" and "adequate" dialysis, taking into account small solutes (e.g., urea) and middle molecules (uremic toxins that do not follow the dialytic kinetics of urea), in addition to salt and water. It is essential to address optimal dialysis for both acute and chronic renal failure.

Resources Needed
1. Surrogate markers for uremic toxins of various sizes.
2. Mathematical modeling.
3. Epidemiologic studies.
4. Clinical observation and intervention trials.

Patient Benefit
Patient morbidity and mortality would be reduced.

#6 Psychosocioeconomicosexual Aspects

Descriptions
Research in this area is very rudimentary. Develop or apply techniques to assess the psychological, socioeconomic, and sexual status of ESRD patients, and devise strategies to improve these states accordingly. Specific emphasis is placed on the psychological adaptation of patients and interventions to enhance compliance to dialytic and nondialytic treatment, as well as physical, psychological and vocational rehabilitation.

Resources Needed
Instruments to assess various aspects.

Patient Benefit
Patients would have enhanced quality of life and be more productive, and mortality and health care costs would likely be reduced.

#7 Factors Affecting Survival of Dialysis Patients

Description
Examine the multiple patient factors such as ethnicity, genetic predisposition, environmental influences and treatment factors such as hemodialysis versus peritoneal dialysis, hemodialysis membrane biocompatibility and flux that are associated with better outcome. This includes the evaluation of cause-specific mortality.

Resources Needed
1. Large data base of patient and sample registries.
2. Genotype and phenotype analysis.
3. Epidemiologic and biostatistical techniques.

Patient Benefit
Understanding these factors would help target areas needing special attention, application of specific dialysis techniques, and perhaps identify circumstances under which treatment would be futile.

#8 Extracellular Fluid and Plasma Volumes

Descriptions
Assess appropriate extracellular fluid and plasma volumes ("dry weight") in people on hemodialysis or peritoneal dialysis. Determine how these volumes and other parameters (e.g., sympathetic activity, diabetic status, ethnicity, and genetic predisposition) affect blood pressure and cardiovascular events.

Resources Needed
1. Hardware and software to assess volume in various body compartments noninvasively and conveniently.
2. Epidemiologic studies.
3. Clinical observation and intervention studies.

Patient Benefit
Maintenance of optimal volumes would promote patient compliance to dialytic treatment and reduce cardiovascular morbidity and mortality.

#9 Oxidant Stress

Descriptions
Determine the cellular source and pathogenic mechanisms of increased oxidative stress in dialysis patients. Assess how increased oxidative stress might adversely affect nutrition, atherosclerosis, amyloidosis, and other medical problems in ESRD patients. Devise intervention strategies.

Resources Needed
1. Cell cultures.
2. Biochemistry techniques to assess oxidation of proteins and lipids.
3. Epidemiologic studies.
4. Clinical observation and intervention studies.

Patient Benefit
Reduce end-organ damage such as atherosclerosis and skeletal diseases and improve body composition.

#10 Peritoneal Membrane

Descriptions
Examine factors that affect peritoneal membrane permeability (transport status). Determine the relationship between transport status of small solutes with that of larger solutes, including middle molecules and albumin. Determine the effects of the loss of plasma proteins on long-term clinical outcome. Determine the pathogenesis of filtration failure. Devise strategies to preserve peritoneal membrane integrity and function over time.

Resources Needed
1. Cell culture.
2. Animal models.
3. Morphometric, immunochemical, and other microscopic techniques; *in situ* Hybridization.
4. Protein analyses and assays.
5. Mathematical modeling.

Patient Benefit
Permits adequate removal of uremic toxins while preserving plasma proteins, thus improving body composition and health.

Other areas that the Dialysis Working Group considered extremely important but that do not usually fall into research:
1. Quality of general patient care
2. Patient education
3. Fellow education

Challenges and Barriers to Implementing Priorities

(Global and affect all 10 areas noted above)

Recognition
Funding agencies (e.g., special emphasis panel at NIH), academic leaders, nephrology researchers, and the general public do not realize that dialysis research is important and cost-effective--the majority of effort and expense in nephrology clinical care concerns dialysis and dialysis patients.

Money

1. The National Institutes of Health, National Science Foundation, and Veterans Affairs need to substantially increase funding for dialysis research.
2. Other funding sources are necessary and logical: HCFA, private foundations, dialysis and pharmaceutical industries, HMOs and third-party payers. The Health Care Financing Administration should pay for routine dialysis treatments in clinical studies and for alternative modalities such as daily hemodialysis.

Manpower

1. Related to money.
2. Foster interest from other scientists to collaborate.
3. Foster interest from medical and other science students and nephrology fellows.

Time

1. Related to money.
2. Provide more funding for principal investigator and trainee salary for basic and clinical research related to dialysis.

Communication

1. Provide incentives to encourage scientists who are not currently studying dialysis--from within and outside nephrology--to become involved in dialysis research.
2. Encourage dialysis researchers to seek assistance and collaboration from other fields (molecular biology, tissue engineering).

3. Establish project and data coordinating centers to foster communication among academic institutions, Federal agencies, and industry.
4. Relate information to the general public, renal patients, and their families, including providing more information and education through the Internet.
5. Improve communication and collaboration between:
    - Professional groups such as the Council of American Kidney Societies, vascular surgery, bioengineering, and chemical engineering;
    - NIH components such as the National Heart, Lung, and Blood Institute; National Institute of Mental Health; and National Institute on Aging;
    - Health Care Financing Admin.;
    - Industry;
    - HMOs;
    - Insurance companies; and
    - Venture capitalists.

Confidentiality

Ownership of intellectual properties and financial interests of industry may pose conflicts of interest or hinder collaborations.

Transplantation

Introduction

Renal transplantation is the treatment of choice for patients with end stage renal disease. There are two themes that govern research in transplantation: studies directed at optimizing the availability and function of the transplanted graft and understanding recipient-graft interaction. Since there are too few organs to satisfy the increasing recipient needs, strategies targeted at expanding the donor pool with optimal utility and outcome are critical. Studies to increase organ supply involve an understanding of the consent process, a consideration of the science of expansion of the donor pool by understanding the process of renal senescence and aging, the nature and potential reversal of retrieval injury, and the science and ethics of animal organ substitutes, xenotransplantation.

Even if all needed organs were to be available, understanding the mechanisms of graft dysfunction and failure is critical. Studies should target donor antigen specific responses, non-specific inflammatory responses to the graft, and graft tissue response. To accomplish these goals studies must be crafted to understand the processes of organ dysfunction and the markers that permit assessment of the health of the organ. Such studies drive the corollary experiments that seek to modulate those mechanisms to reverse dysfunction and failure including those targeting the non immunologic factors and immunomodulation to optimize therapies with increased specificity and decreased toxicity toward the goal of donor-specific tolerance.

The fruits of current transplant research have engendered the important accomplishments in the field while offering continued and new challenges. Ever more precise and powerful transplant immunosuppressive drugs have greatly increased both patient and graft survivals. However, despite our successes, almost half of renal grafts are eventually lost to premature patient death with a working transplant creating the challenge to understand the morbidity in pre-existing and concomitant illnesses such as cardiovascular disease, hypertension, infections, bone disease, diabetes, and malignancies. Strategies to induce donor specific tolerance in animal models hold promise. Strategies to hurdle xenogenic barriers using molecular genetic tools have begun. Expansion of these efforts taken together with experiments characterized above may bring the dream of successful replacement of a failed organ for the natural lifetime of a patient to fruition.

Progress

1. Development of new non-specific immunosuppressive drugs.
2. Prevention of early irreversible acute cellular rejection.
3. Identification of clinical risk factors of chronic allograft nephropathy.
4. Development of effective tolerance strategies in small animals.
5. Overcoming immunologic barriers of hyperacute rejection in xenotransplantation.

New Frontiers and Priorities for Research

Transplanted Organs

1. Organ Availability:
   - Understand the consent process;
   - Estimate availability, performance; and
   - Expand the donor pool.
2. Optimal Utility:
   - Understand the mechanisms of organ senescence or aging and injury; and
   - Optimize outcomes with available organs.
3. Overcome the biological hurdles of xenotransplantation:
   - Immunological;
   - Physiological; and
   - Infectious.
4. Tissue Engineering/Cell Transplantation:
   - Develop biological alternatives to whole organ transplantation such as cell transplantation and bioartificial organs;
   - Bioartificial organs;
   - Stem cell biology;

- Organogenesis;
- Cell transplantation including islets; and
- Apply gene therapy to transplantation.

5. Patient Access
   Develop ways to access and monitor patients' access to transplantation.

Recipient/Host Response

1. Identify and understand the processes and measures of graft dysfunction and failure:
   - Antigen-specific factors;
   - Antigen-nonspecific inflammatory factors; and
   - Grafted tissue response.
2. Immunosuppressive strategies and tolerance:
   - Identify mechanisms of immune recognition and response to alloantigens;
   - Develop strategies to induce donor-specific tolerance; and
   - Develop more-selective immunosuppressive strategies.
3. Monitoring--Means to Measure Outcome and Guide Therapy:
   - Develop immunologic markers to predict graft outcomes;
   - Tissue-organ pathology; and
   - Measuring the drug kinetic and dynamic effects of therapies.

Patient/Recipient Survival and Quality of Life

1. Morbidity:
   - Complications of immunosuppression, such as infection, malignancy and toxicity;
   - Existing and new morbidities, such as cardiovascular, bone, and liver disease, diabetes, and bone disease;
   - Long-term access to care after transplantation;
   - Patient noncompliance (identification and prevention); and
   - Patient rehabilitation.

Top 10 Priorities for Transplantation Research

1. Mechanisms of immune recognition and response to alloantigens and development of strategies to induce donor-specific tolerance.
2. Identifying and understanding the processes and measures of graft dysfunction and failure, senescence, injury, and progression.
3. Development of immunologic (surrogate) markers to predict graft outcomes (rejection, dysfunction, and acceptance).
4. Development of more selective, more specific immunosuppressive strategies.
5. Optimizing immunosuppression while minimizing the risk of complications such as infection, malignancy and toxicity.
6. Identification and management of risk factors for patient morbidity and mortality (cardiovascular disease and HTN, diabetes, bone disease, liver disease).
7. Expand donor pool and optimal utility of available organs.
8. Overcoming the biological hurdles of xenotransplantation (immunological, physiological and infectious).
9. Improving quality of life: Patient access to care after transplantation, rehabilitation, identification and prevention of noncompliance.
10. Biological alternatives to whole organ transplantation (tissue engineering and cell transplantation).

The following research areas may dovetail with concerns of other renal scientists:

1. Understanding mechanisms of immune recognition and tolerance development are areas holding interest for the study of autoimmunity and renal disease.
2. Studying the processes and measures of graft dysfunction impacts on the mechanisms of progression in renal disease.
3. Identification of risk factors for patient morbidity and mortality is also of interest to understanding the factors leading to ESRD.

Tools, Methodologies, and Resources Needed

1. Small and large animal models, including novel gene knock-outs and transgenics for understanding the immune response to alloantigens, graft rejection, and tolerance.
2. New Technologies such as chip and informatics, MHC tetramers, and laser microdissection.
3. Agent/reagent bank to be able to study combination therapies not feasible with industry.
4. Computerized registries.
5. Biopsy tissue bank.
6. Support for multicenter clinical trials not ordinarily supported by industry.
7. Demonstration projects to test alternate models of organ retrieval and allocation.
8. Cutting edge epidemiologic tools for clinical trial design.

Challenges and Barriers to Implementing Priorities

1. Greater sharing and access of animals and technologies, agents and reagents, and information.
2. Cost of large animal models.
3. The capacity to combine experimental agents for clinical trials.
4. Collaboration between NIH and industry and between industry groups.
5. Collaboration between NIDDK and other institutes interested in transplantation.
6. Improve patient recruitment for clinical trials (collaboration with health providers, patient organizations and ESRD networks).
7. Lack of new trainees entering the field for both basic as well as clinical research.
8. Improve the peer review process for clinical research grants.
9. Lack of academic surgical trainees.
10. Facilitate and support academic foreign medical graduates to train and stay in the United States.

Overarching Issues and Concerns

1. Creation of an advisory group within the ASN that focuses on transplantation.
2. Creation of an Advisory Group on Transplantation to the National Institutes of Health director and/or to specific institutes such as the National Institute of Diabetes and Digestive and Kidney Diseases.
3. Consortia/Network of investigators to develop the particular priority and monitor the implementation – particularly important for the development of tolerance and xenotransplantation.
4. Collaboration with other disciplines: structural biologists, chemists, and social scientists.

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