RESEARCH NEEDS IN PEDIATRIC KIDNEY DISEASE

2000 and Beyond

Pediatric Nephrology Task Force Meeting
Washington, D.C.
January 27, 1999

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and
Digestive and Kidney Diseases

RESEARCH NEEDS IN PEDIATRIC KIDNEY DISEASE

2000 and Beyond

Pediatric Nephrology Task Force Meeting
Washington, D.C.
January 27, 1999

Sponsors
NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and
Digestive and Kidney Diseases
American Society of Pediatric Nephrology

NIH Administrative Publication
June 200

[NIDDK logo]
National Institute of Diabetes and Digestive and Kidney Diseases
American Society of Pediatric Nephrology
June 2000

CONTENTS

Executive Summary **1**

Introduction **9**

Research Opportunities **19**
Cluster 1 Genetic and Developmental Diseases **19**
Cluster 2 Acute Renal Failure **25**
Cluster 3 Immune-Mediated Diseases—
Glomerulonephritis and
Tubulointerstitial Diseases **27**
Cluster 4 Chronic Renal Failure and Its Treatment .. **30**

Tools, Methodologies, and Resources **39**

Challenges and Barriers **43**

Appendices
Congressional Action **45**
Task Force Members **47**

Executive Summary

Encouraged by Congress,[1] the American Society of Pediatric Nephrology and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a task force on January 27, 1998, to review current research and identify research priorities and barriers to progress.

The two organizations are commited to improving the diagnosis and treatment of kidney diseases in children and to preventing kidney failure among this most vulnerable segment of our population.

SCOPE AND IMPACT

Kidney disease is a major cause of illness and death among children, who make up about 25 percent of U.S. citizens. About 5,000 children who have kidney disease are on dialysis or have a kidney transplant because of end-stage renal disease, which is also called ESRD and kidney failure. Each year, 20,000 babies are born with kidney problems, 2,000 will die, and 1,000 will begin treatment for kidney failure. Medicare spends an annual average of $45,000 per person with kidney failure.

The most common childhood renal problems are:

- Urinary tract obstructions and reflux nephropathy;
- Genetic renal diseases;
- Missing or malformed kidneys; and
- Focal segmental glomerulosclerosis.

[1] Fiscal Year 1999 House and Senate Appropriations Reports. See appendix.

WHY STUDY CHILDREN?

Compared to adults, the young have different kidney diseases and face special challenges. Kidney disease disrupts somatic, developmental, and psychological maturation and may lead to learning disabilities and mental retardation. Children often need repeated transplants due to chronic rejection and are at greater risk for malignancy, steroid-induced bone disease, premature atherosclerosis, and serious infections, all associated with long-term use of immunosuppressive drugs.

WHO TREATS KIDNEY DISEASE IN CHILDREN?

Care is coordinated by a medical team led by a pediatric nephrologist, a doctor trained especially to consider and manage the needs of children.

CURRENT RESEARCH

NIDDK and other institutes at the National Institutes of Health (NIH) encourage and fund research on normal kidney development and on the causes and treatment of kidney disease. NIDDK's Pediatric Nephrology Program is a $24.6 million venture, funding individual research projects, large research and treatment centers, and training for people who will study childhood kidney diseases and care for children who have kidney problems.

Research. NIDDK invests in research proposed by scientists outside NIH and initiates selected projects in areas ripe with opportunity. The Institute has initiated research on IgA nephropathy, hemolytic uremic syndrome, chronic renal failure, polycystic kidney disease, and genetics. NIDDK has also established major research centers for pediatric and polycystic kidney diseases and renal morphogenesis, and clinical trials for IgA nephropathy, diabetic nephropathy, and hemolytic uremic syndrome. Concurrent with "bench" and "bedside" research, workshops on pediatric kidney disease, developmental nephrology, and hemolytic uremic syndrome have provided forums for researchers to present study results, receive feedback, and propose topics for future studies.

Research Training. Physician scientists play a key role in research on kidney disease in children. NIDDK's Pediatric Nephrology Program annually funds about 25 fellows at 10 U.S. institutions.

RESEARCH OPPORTUNITIES

Genetic and Developmental Diseases

- Abnormal ***Kidney Growth and Development*** are major causes of ESRD in children. Surgery is the only specific therapy. Better therapies will evolve only when molecular mechanisms controlling organ and functional development are understood. Basic research priorities are to (1) define the genetic programming of renal growth, development, angiogenesis; (2) neoplasias; (3) identify, clone, and maintain renal progenitor cells to elucidate differentiation of nephron cells; (4) define nephron growth in space and time; and (5) understand normal physiology of the developing kidney. Clinical research priorities are to (1) develop targeted pharmacological and gene therapies and (2) characterize children at risk.

- ***Systemic and Hereditary Diseases***, including nephrotic syndrome and Alport syndrome, focal segmental glomerulosclerosis, and polycystic kidney disease, would benefit from research to (1) identify and clone disease-causing genes, (2) analyze the structure and function of gene products, and (3) develop targeted tests and treatments.

- ***Epithelial Cell Physiology and Transport*** are central to nephrology and specifically related to disorders of water and electrolyte homeostasis, which are common in children. Basic research priorities are to (1) develop and integrate new with classic methods of studying embryonic kidney function, (2) identify molecular and physiologic causes of abnormal renal transport, and (3) study genes involved in sodium balance and genetic hypertension. Translational and clinical research should (1) establish a kidney tissue bank and an exceptionally secure database of families with inherited water and electrolyte transport disorders, (2) develop noninvasive tests to quantify expression of key transport proteins, and (3) determine target blood pressure

for children and test pharmacological treatments for children who have high blood pressure.

Acute Renal Failure

Acute renal failure is a sudden, sometimes reversible drop in kidney function, common among hospitalized children. Basic research priorities are to (1) develop cellular, transgenic, and knockout animal models that more closely resemble the disease in children, and (2) identify new strategies to improve acute dialysis and recovery of kidney function. Translational and clinical research priorities are to (1) develop criteria to test therapies and tools such as severity-of-illness scores; (2) identify the incidence, etiology, and outcomes in children; (3) identify markers of genetic and environmental susceptibility; and (4) develop noninvasive renal function tests.

Immune-Mediated Diseases—Glomerulonephritis and Tubulointerstitial Diseases

Despite important advances, the causes of pediatric renal diseases such as minimal change nephrotic syndrome and focal segmental glomerulosclerosis remain obscure. Basic research priorities are to (1) identify causal, susceptibility, and response genes; (2) identify exogenous and endogenous antigens that initiate immune responses leading to renal disease; and (3) determine the molecular and structural basis of proteinuria. Translational and clinical priorities are to (1) establish a collaborative network to evaluate treatments and (2) develop and validate markers of disease activity, severity, and progression.

Chronic Renal Failure and Its Treatment

- ***Preventing Complications and Progression.*** Childhood is the best time to begin interventions, as this is the time when disease processes and complications likely begin. And yet, interventions such as angiotensin converting enzyme inhibitors and strict glycemic control--proven to stall type 1 diabetic nephropathy in adults--have not been tested in children. Basic research priorities are to (1) study basic pathophysiologic mechanisms of growth failure and bone disease and (2) develop animal models that more closely resemble childhood renal diseases. Translational and clinical research priorities are to (1) test therapies for kidney

disease and complications such as growth retardation, malnutrition, bone disease, anemia, and infection; (2) identify early markers of disease activity, severity, and progression; (3) identify genes affecting disease severity and progression; and (4) identify incidence, prevalence, and risk factors for kidney disease.

- ***Dialysis.*** Children on dialysis experience growth retardation in spite of aggressive nutritional support, use of growth hormone, and treatment for anemia, acidosis, and bone disease. Dialysis dose and preserving the peritoneal membrane for children on peritoneal dialysis probably are important factors. Research priorities are to (1) improve the management of children on dialysis by understanding mechanisms of growth failure and by defining optimum doses of dialysis and growth hormone; (2) determine the role of the parathyroid hormone (PTH)/PTHrP receptor in bone metabolism and skeletal development; (3) correlate solute removal during dialysis with growth, cognitive development, and other outcomes; (4) identify and correct basic mechanisms that alter the peritoneum; and (5) define nutritional needs and cognitive alterations and develop methods to assess nutritional and cognitive status.

- ***Transplantation.*** Compared to adults, children generally live longer and have the same or better graft survival. Ironically, longevity raises new problems in the form of chronic rejection, malignancy, atherosclerosis, serious infections, and lack of long-term compliance with complex therapeutic regimens. Basic research priorities are to (1) understand immunological mechanisms in acute and chronic rejection; (2) develop alternatives to whole-organ transplantation; and (3) understand the molecular basis of focal segmental glomerulosclerosis, a significant and recurring cause of kidney failure in children.

TOOLS, METHODOLOGIES, AND RESOURCES

Basic Research

Priorities are to develop and apply ***genomic and gene-expression technologies***, including (1) a database of expressed sequence tags (EST); (2) chip and high throughput analyses for nucleic acid; (3) bioinformatics to analyze EST and nucleic acid data; (4) methods to acquire and bank tissue and genetic material and information for this type of analysis.

Also of high priority are the development of ***animal models*** such as mouse, rat, zebrafish, and *C. elegans* to study genetics of kidney disease and mechanisms of action of disease genes. In addition, priority is given to developing micromethods to perform physiologic studies in small/young animals and imaging technologies to understand the intricacies of kidney development.

Clinical Research

Priorities are to (1) develop clinical databases of patients with specific renal diseases for genetic and other analyses, (2) develop new methods to deliver genetic and drug therapies to cells in the kidney, and (3) increase the development and testing of drugs and vaccines for children with kidney disease.

CHALLENGES AND BARRIERS

The NIDDK and the American Society of Pediatric Nephrology Task Force identified overarching challenges and barriers limiting progress:

Workforce Shortages. More pediatric nephrologists trained in basic or clinical research, more interdisciplinary collaborations, and more opportunities to transition from postdoctoral training to independent investigator are needed.

Bioinformatics. Researchers cannot fully utilize new information from human genome projects without effective bioinformatic resources and a central, shared database of patients, investigators, clinical trials, new methodologies, and tissue and other specimens.

Research Administration. Administrative and financial impediments such as indirect cost accounting impede collaborations between institutions, NIH, and industry.

Public Awareness. Lack of public awareness about the importance of genetic screening, clinical trials, and the treatment of kidney disease makes recruitment of patients for clinical trials more difficult.

INTRODUCTION

The U.S. House of Representatives and Senate (see appendix) encouraged the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to develop and implement plans to address the special needs of children with kidney disease. The Institute solicited the help of the American Society of Pediatric Nephrology (ASPN), a natural partner for this effort.

ASPN and NIDDK share a commitment to improve the diagnosis and treatment of kidney diseases in children and to prevent kidney failure among this most vulnerable segment of our population. NIDDK conducts and funds medical research on kidney disease, and ASPN is devoted to continuing education for pediatricians specializing in kidney disease, training future generations of pediatric nephrologists, and to basic and clinical research.

On January 27, 1998, NIDDK and ASPN convened a task force that reviewed current research and developed a long-range plan for research on kidney disease in children.

SCOPE AND IMPACT

Kidney disease is a major cause of illness and death among infants, children, and adolescents, who make up about 25 percent of the U.S. population.[2] Each year:

- An estimated 14,000 children have kidney disease. Of those, 5,000 have kidney failure and are on dialysis or have a kidney transplant; about 60 percent are 12 or younger. [3,4]
- 1.2 million children under age 7 develop urinary tract infections.[5] Left undiagnosed and untreated, infections can permanently damage the kidneys.

[2] Statistical Abstracts of the United States. 1996 Census, U.S. Bureau of the Census.
[3] North American Pediatric Renal Transplant Cooperative Study Database 1998.
[4] U.S. Renal Data System, USRDS 1998 Annual Data Report, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda MD, April, 1998, pp 105-120.

- 300,000 children require further testing after doctors find protein in the urine, an early sign of kidney disease.[6]
- An estimated 120,000 people under age 20 have diabetes[7]; 40 percent will eventually develop kidney disease.[8]
- 76,000 children are treated for hypertension, which often precedes kidney failure and cardiovascular disease.[9]
- 20,000 babies are born with kidney abnormalities.[10]
- 2,000 infants die from a disease of the genitourinary tract.[11]

The financial cost to society is enormous. Medicare alone spends an annual average of $45,000 for each person with kidney failure, more for those on dialysis.

WHY STUDY CHILDREN?

Medical treatments for children are often based on tests done only in adults. However, children are not tiny adults, do not physically respond to treatments like adults and, in the case of kidney disease, predominantly are affected by different diseases and face special growth and developmental challenges.

Kidney disease disrupts somatic, mental, and psychological maturation and may lead to learning disabilities and mental retardation. As a result, both dialysis and kidney

---

[5] 1.6 percent of boys and 7.8 percent of girls under age 7 will be treated for symptomatic UTI. From Rushton, HG. *Urinary Tract Infections in Children. Epidemiology, Evaluation and Management.* in Ped. Clin. of North Amer. 44: 1133-1142,1997. Using 1996 census data (ref. 1 above) there are 13,800,000 boys and 13,400,000 girls younger than age 7.

[6] Clark, AG and TM Barratt. *Steroid Responsive Nephrotic Syndrome* Chapter 45 in Pediatric Nephrology Fourth Edition Edited by TM Barratt, ED Avner and WE Harmon. Lippincott, Williams and Wilkins, 1999. pp 731-748.

[7] National Diabetes Data Group, National Institutes of Health. *Diabetes in America*, 2nd Edition. Bethesda, MD: National Institutes of Health, 1995. NIH Publication No. 95-1468.

[8] Feld, L. *Diabetic Nephropathy* Chapter 39 in Pediatric Nephrology Fourth Edition Edited by TM Barratt, ED Avner and WE Harmon. Lippincott, Williams and Wilkins, 1999. pp 633-640.

[9] Feld, L. and WR AZ. *Treatment of Hypertension* Chapter 63 in Pediatric Nephrology Fourth Edition Edited by TM Barratt, ED Avner and WE Harmon. Lippincott, Williams and Wilkins, 1999. pp 1031-1050.

[10] The incidence of renal anomalies is 3 to 6 per 1000 births@3,914,953 live births in 1996(ref. #1) or 11,742 to 23,484. Genitourinary disease accounts for 6.3 percent of all infant mortality (28,237 infant deaths in 1996 from all causes) equals 1,779. Ref. 91; Vital Statistics in Pediatrics, Pediatrics 1997; Limwongse, C, SK Clarren and SB Cassidy. *Syndromes and Malformations of the Urinary Tract* Chapter 25 in Pediatric Nephrology Fourth Edition Edited by TM Barratt, ED Avner and WE Hannon. Lippincott, Williams and Wilkins, 1999. pp 427-452.

[11] Ibid.

transplantation are individually tailored and continuously adjusted to meet the special requirements of the growing and developing young person.

Kidney transplantation is the best treatment for most people with kidney failure, including children. But again, it poses special problems for the young. Infants and children who receive renal transplants will often need subsequent transplants due to chronic, slow rejection of the transplanted organ. They also face long-term effects of immunosuppression, such as increased malignancy and steroid-induced bone disease.

Adults may actually benefit from what we learn from children. Diseases such as diabetes and hypertension cause permanent kidney failure in adults and may actually begin destructive processes during childhood—a time when treatment might prevent some of the devastating renal consequences seen later in adulthood. Better identification and management of diseases during childhood could greatly reduce subsequent Medicare and insurance costs and the financial, physical, and psychological burdens on families.

The reasons already stated argue the point well enough but, in addition, Congress mandated that the National Institutes of Health (NIH) increase research to benefit children.[12]

WHAT CAUSES KIDNEY DISEASE IN CHILDREN?

According to a 1998 study by the North American Pediatric Renal Transplant Cooperative,[13] the leading causes of chronic renal failure in children are:

- Urinary tract obstruction (obstructive uropathy, 23 percent);
- Genetic renal diseases such as polycystic kidney disease (19 percent);
- Aplastic/hypoplastic/dysplastic kidneys (19 percent);
- Focal segmental glomerulosclerosis (FSGS, 12 percent). FSGS is two times more common in African American children compared to other groups; and
- Reflux nephropathy (9 percent).

[12] Fiscal year 1996 Appropriations Committee report.
[13] Statistical Abstracts of the United States. 1996 Census, U.S. Bureau of the Census.

Genetic and Developmental Diseases. Researchers are beginning to perform molecular and genetic analyses to link specific gene products to normal kidney growth and development and human kidney diseases.

In *congenital nephrotic syndrome,* a glomerular disease characterized by massive amounts of protein in the urine and progressive renal failure in infants, researchers have found mutations in a glomerular protein called nephrin. The glomerular diseases m*esangial sclerosis* and *Alport syndrome* are caused by inherited mutations in the Wilm's tumor transcriptional factor and by Type IV collagen genes, respectively. All three of these diseases of the glomeruli can lead to kidney failure.

Cysts growing from epithelial cells of the kidney tubules characterize *polycystic kidney disease (PKD),* inherited as either autosomal dominant (ADPKD) or recessive (ARPKD) diseases. About 85 percent of people with PKD have either ADPKD-1 or ADPKD-2, caused by mutations in proteins called polycystin-1 and polycystin-2. Research on both proteins is described under **Research Opportunities**. Scientists are also studying candidate genes for ARPKD, which causes ESRD in infants.

Mutations in genes coding for membrane transporter proteins in kidney epithelial cells cause many kidney diseases, including:

- *Hyperoxaluria*, which results in kidney stones;
- *Bartter's, Gitelman's, and Liddle syndromes*, which result in hypertension and the loss of sodium, potassium, and chloride in the urine;
- *Congenital nephrogenic diabetes insipidus,* which results in defective water transport; and
- *renal tubular acidosis,* which prevents normal acid and base handling by the kidney.

Inherited defects in specific metabolic pathways may also cause kidney failure in children. Such disorders include *cystinosis* and *oxalosis*, disorders of cysteine and oxalic acid metabolism, respectively.

Ureters are ramified tubular structures that carry urine from the kidney to the urinary bladder. O*bstruction* and *urinary reflux*, in which urine moves backward from the bladder to the

kidney can cause kidney infections and lead to renal disease and ESRD in children.

Finally, disorders affecting the growth, structure, and function of the kidneys during fetal development include *renal agenesis, dysplasia,* and *hypoplasia* and *tubulointerstitial diseases*. In these cases, babies born with no kidneys at all or with very little healthy kidney may need dialysis soon after birth.

Acute Renal Failure. Acute renal failure is common in hospitalized children, may require short-term dialysis, and substantially increases morbidity and mortality, apart from the original cause of hospitalization. Primary renal diseases such as glomerulonephritis, ischemic or toxin-induced renal injury such as hemolytic uremic syndrome (HUS), sepsis, and multi-organ failure all can result in acute renal failure. Many aspects of the pathogenesis of acute renal failure are unique to children, since both the insult and the kidney's response occur in an immature, still developing organ.

HUS, among the most common causes of acute kidney failure in infants and children, is a severe, life-threatening foodborne illness characterized by bloody diarrhea, vomiting, abdominal pain, hemolytic anemia, thrombocytopenia, and renal failure. The central nervous system and pancreas are also often affected. HUS is usually caused by the toxin-producing *E. coli* 0157:H7 bacteria and diagnosed in infants and children between the ages of 1 and 10 years. Moreover, up to 40 percent of children who initially appear to recover from HUS will later develop chronic renal disease.

Immune-Mediated Disorders. Immune system changes accompany kidney disease in many children and adolescents. In addition, some kidney diseases are caused by immune-mediated disorders, leading to massive loss of protein in the urine, scarring and destruction of glomeruli and, in some cases, renal failure. In diseases such as *post-infectious glomerulonephritis*, *human immunodeficiency virus* (HIV), immunoglobulin A *(IgA) nephropathy*, *Goodpasture syndrome*, and *Wegner's granulomatosis*, the underlying pathogenesis is known. In IgA nephropathy, this knowledge has led to clinical trials in children. In contrast, the underlying pathogenesis of kidney diseases such as *minimal change nephrotic syndrome* and *focal segmental glomerulosclerosis* are not known. Focal

segmental glomerulosclerosis is the most common acquired cause of ESRD in children and, tragically, can recur in transplanted kidneys.

Chronic Renal Disease—A Common Stage. Renal diseases may lead to kidney failure, requiring either dialysis or a kidney transplant to replace normal kidney functions.

Both therapies for kidney failure must be tailored to each child and continuously adjusted to meet the special requirements of growth and development. Often, in spite of exceptional efforts, these children do not grow and develop normally.

Several diseases that lead to chronic renal disease and ESRD in adults actually start damaging the kidneys during childhood. Diabetes is a notable example. Up to a third of children who develop type 1 (insulin-dependent) diabetes will develop ESRD in their twenties or thirties. Strategies to prevent kidney disease ideally should begin in childhood or late adolescence.

Successful kidney transplantation relies on chronically altering immune system responses. While survival rates for kidneys transplanted to pediatric recipients are equal to or better than rates for adults, many children lose kidney transplants from chronic rejection. Since children with renal transplants usually live for long periods of time, they often need multiple kidney transplants and are on immunosuppressive drugs longer than adults. Ironically, the success of transplantation and the extended use of immunosuppresive medications results in major complications such as infections, premature atherosclerosis, and malignancy.

WHO TREATS KIDNEY DISEASE IN CHILDREN?

Children who have kidney disease exhibit abnormalities in almost every organ system. They require coordinated care by multi-disciplinary teams led by pediatric nephrologists, doctors trained especially to diagnose and treat kidney disease in children. Pediatric nephrologists are also experts in growth and development, understanding pediatric drug dosages and nutritional requirements, and the unique aspects of dialysis and transplantation in infants, children, and adolescents.

Other vital members of the team are pediatric urologists and transplant surgeons, perinatologists, geneticists, radiologists, neurodevelopmental specialists, pediatric nurses specializing in renal disorders, dietitians specializing in pediatric nutrition and renal failure, and social workers and psychologists dedicated to the extensive management that children with a chronic disease require.

CURRENT RESEARCH

NIDDK's Pediatric Nephrology Program in the Division of Kidney, Urologic, and Hematologic Diseases funds research examining normal renal morphogenesis and development, underlying causes of diseases, and therapies. On cross-cutting issues NIDDK also collaborates with other NIH institutes, including the National Institute of Allergy and Infectious Diseases (NIAID), which is interested in both basic immunology and the immunology of organ transplantation, and the National Institute of Child Health and Human Development, which studies infant and neonatal health and diseases.

Major NIDDK initiatives related to pediatric kidney disease:

- Two new ***Centers of Excellence*** in Pediatric Kidney Disease Research.

- Six new grants were funded under the Request for Applications (RFA) *Progression of Renal Disease:* ***IgA Nephropathy in Childhood and Young Adults***. A clinical study funded under this RFA is identified below, under Clinical Trials.

- Twelve new grants were funded under the RFA ***Hemolytic Uremic Syndrome****: Pathophysiology and Treatment*

Interventions. NIAID funded another five projects under the RFA.

- Eleven new exploratory/developmental (R21) grants were funded under the RFA *Exploratory Grants in* ***Chronic Renal Failure in Children***. We anticipate that these grantees will apply for regular research grants (RO1) to continue and expand work begun under R21 projects.

- In FY 1999, the NIDDK issued RFAs to advance research on kidney diseases in children:

  - *Diabetic and Non-Diabetic* ***Nephropathy Susceptibility Genes*** invited researchers to identify genetic regions, and ultimately genes, that could confer susceptibility to or protect against progressive renal disease. We anticipate that this work will lead to new strategies to combat kidney disease in both adults and children. Nine investigators at eight different institutions are collaborating on this study.

  - ***Polycystic Kidney Disease****: Innovative Imaging to Assess Progression* invited investigators to identify and test surrogate markers of disease progression, a tool that will help evaluate potential interventions. The most important clinical feature of PKD is the progressive enlargement of cysts in the kidney, a process that often results in gradual deterioration of renal function. Currently, there is no test to evaluate the effectiveness of experimental interventions, a major barrier to conducting clinical studies. Four institutions are collaborating on this project.

  - *Interdisciplinary Centers for* ***Polycystic Kidney Disease*** *Research* recruited investigators at four multi-disciplinary centers to expand the basic research infrastructure in PKD. This work will enable clinical studies to evolve more rapidly.

Clinical Trials. NIDDK is also funding clinical trials relevant to children:

- The multicenter *Phase II Randomized Study of Alternate Day Prednisone or Daily Fish Oil Supplements in Patients With* ***IgA Nephropathy*** is evaluating the efficacy of alternate-day prednisone and omega-3 fatty acids (fish oil).

- The multicenter ***Diabetic Nephropathy*** *Clinical Trial* is assessing whether blocking the renin-angiotensin system early in type 1 diabetes will prevent or slow the development of kidney disease.

- The multicenter ***HUS*** *Clinical Trial* is comparing Synsorb Pk to placebo in children newly diagnosed with enterohemorrhagic strains of *E. coli* bacteria associated with HUS. Synsorb Pk is an adsorbent agent designed to bind to and remove toxins from the intestine.

Workshops. Several NIDDK workshops have allowed scientists to share research results and propose topics for future investigations relevant to pediatric nephrology. Workshops have addressed developmental and pediatric nephrology and hemolytic uremic syndrome.

Training Future Generations of Researchers. NIDDK funds research training to draw individuals into scientific careers in both nephrology and pediatric nephrology. Recent reports from the American Society of Nephrology and American Academy of Pediatrics predict shortages in both subspecialties.

While NIDDK's Pediatric Nephrology Program funds research training for about 25 people a year, the decline in number of both nephrologists and pediatric nephrologists, along with the expectation that the later group will be asked to care for more and older adolescents and young adults, means that pediatric nephrologists are likely to spend less time on research overall.

How Productive is the Research? Based on one measure of success--the number of papers in top-ranked peer-reviewed journals--NIDDK-funded researchers are effective. In 1998, 29 of 252 papers by pediatric investigators appeared in widely read international journals, including the highly esteemed *Nature Medicine*, *Nature Genetics*, the *Proceedings of the National Academy of Sciences*, and *Science*.

RESEARCH OPPORTUNITIES

CLUSTER 1
GENETIC AND DEVELOPMENTAL DISEASES

A. Renal Morphogenesis, Growth and Development

Abnormal kidney development is a major cause of ESRD in children. Kidney morphogenesis is complex and studied not only by pediatric nephrologists but also by cellular and molecular biologists who favor the kidney as a model for understanding how all organs form.

Kidney development begins when stem cells commit to a kidney cell line that will differentiate and eventually assemble into the various segments of the nephron under the influence of the appropriate molecular signals. In humans and other mammals, nephrons develop in the mature kidney by the reciprocal, inductive interactions of the ureteric bud with the metanephric mesenchyme. Nephron development is also tightly coordinated with vascularization of the kidney such that the interaction of vascular precursors, epithelial progenitors, and mesenchymal cells is highly integrated. This overall process culminates in the formation of mature kidneys and ureters that are architecturally and functionally ready for the demands of life outside the womb.

While researchers have identified more than 300 genes linked to kidney and ureter morphogenesis, the specific genetic "programming" governing the production of the unique three-dimensional structure of the kidney and ureters remains to be elucidated. Similarly, molecular pathways that commit and differentiate renal stem cells are unclear.

Alterations in kidney and urinary tract morphogenesis are thought to cause a variety of inherited and acquired kidney abnormalities in infants and children. Abnormalities include renal ***dysplasia, agenesis, and hypoplasia***; renal ***tumors*** such as Wilms' Tumor; multiple ***cystic and fibrotic***

disorders; and ***urinary tract malformations*** causing problems such as urinary reflux.

Kidney transplantation and surgery to correct some anatomical problems are the only specific therapies available for abnormally developed kidneys. Research to reveal molecular mechanisms mediating both the organogenesis and functional development of the kidney provide hope for improving treatments.

Priorities for Basic Research

1. *Define the genetic programming of renal morphogenesis, growth, development, and angiogenesis.* Link patterns of gene expression in the kidney to critical functional parameters (renal genomics).

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

3. *Define how the nephron grows in space and time.* Define the inductive mechanisms that 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 and the cell-cell and cell-matrix interactions that determine the structure, location, and differentiated functions of various nephron cells.

4. *Understand the normal physiology* of the embryonic and fetal kidney.

Priorities for Translational and Clinical Research

1. Use genetic programming data to *develop new therapeutic targets* and to *characterize patients at risk*.

2. *Target therapies to the diseased, developing kidney.* Develop methods to express exogenous gene products to replace missing functions, to modify existing functions, or to introduce new functions in the kidney (renal gene therapy).

Develop methods to target pharmacological therapies to specific cell types in the kidney. Develop unique systems to deliver exogenous factors, compounds, proteins, and genes to the kidney.

B. Systemic and Hereditary Diseases

Systemic and hereditary diseases encompass a heterogeneous group of disorders that affect specific kidney structures and functions. Abnormalities in the kidney's glomeruli result in a massive loss of protein in the urine (nephrotic syndrome), an element responsible for the eventual destruction of the filtration function in the kidney and ESRD. Some of these disorders are ***congenital nephrotic syndrome***, ***idiopathic childhood nephrotic syndrome***, ***Alport syndrome***, ***focal segmental glomerulosclerosis***, and ***mesangial sclerosis***.

Abnormalities in the structure and function of the kidney's tubules are found in ***ARPKD***, ***ADPKD***, and ***nephronophthisis***. Cysts growing in the kidneys destroy functioning renal tissue and result in hypertension, kidney infections, alterations in body fluid and electrolyte composition, and growth disorders in children.

Structural and functional abnormalities in the ureters can obstruct the normal flow of urine, as in ***ureteral obstruction***, ***posterior urethral valves***, and ***vesicoureteral reflux***.

Certain metabolic diseases also profoundly alter kidney function and, if untreated, may result in ESRD. These abnormalities include defects in specific metabolic pathways, as in ***oxalosis*** and ***cystinosis***, and abnormal handling of calcium, causing kidney stones and renal calcification.

Essential hypertension is a major cause of morbidity and mortality in adults living in industrialized countries and an independent risk factor for stroke, myocardial infarction, and ESRD. While the genetic cause(s) of essential hypertension is unknown, it is important to note that hypertension often begins in childhood.

Effective diagnoses and therapies for systemic and hereditary disorders can best be developed by first understanding the fundamental molecular mechanisms responsible for the

pathogenesis of each disease. The following paradigm could be followed for all of the diseases described:

1) Identify and clone disease-causing genes;
2) Analyze the structure and function of gene products; and
3) Based on 1 and 2, design diagnostic tests and treatments.

Priorities for Basic, Translational, and Clinical Research

1. *Identify and clone disease susceptibility genes for monogenic and polygenic disorders.* Identify defective genes in Mendelian disorders, genes that modify the phenotype of monogenic diseases (quantitative trait loci, QTL), and/or genes involved in the development or progression of multifactorial traits (e.g., focal glomerulosclerosis, diabetic nephropathy). Although rare, monogenic disorders represent "experiments of nature" that allow precise delineation of molecular pathways. Concepts learned from these disorders can be applied to analyzing complex physiologic processes. QTL analysis and identifying genes involved in multifactorial traits are particularly important in diseases that progress over time and in pediatric kidney diseases. Identifying these genes and the genetic pathways in which they operate and delineating their biochemical and physiological functions will provide the necessary reagents and understanding to guide the development of early interventions.

2. *Characterize the function of cloned genes.* Determine the biochemical structure of proteins encoded by disease susceptibility genes and the effect of specific mutations on the biochemical and functional properties of these molecules (protein folding, functional domains, physiologic effects, etc.). Determine the molecular pathways of these proteins and how they affect the function of other genes.

3. *Design and implement rational therapy*. Once the molecular bases for specific disease processes are understood, researchers will be able to develop appropriate therapies.

C. Epithelial Cell Physiology and Transport

Epithelial cell physiology and membrane transport of solutes and water are topics central to the discipline of nephrology. ***Disorders of water and electrolyte homeostasis*** are common in infants and children compared to adults. Moreover, alterations in how the kidneys handle sodium now appear central to the pathogenesis of many forms of primary human hypertension. Childhood disorders of epithelial cell physiology and membrane transport may be caused by either inherited or acquired abnormalities of epithelial cell function. Inherited disorders are rare in children but provide prime opportunities to understand the normal physiology of solute and water transport in the developing and adult kidney. The molecular cloning of major epithelial cell transport proteins has significantly expanded our research capabilities in this area. Elucidation of specific mutations within membrane transporters, combined with current efforts to determine the molecular structure of these proteins, promises to yield a molecular understanding of most basic aspects of solute and water transport within the kidney. Knockout mice that lack specific, functioning transporters have provided further insights into the pathophysiology of water and electrolyte disorders in humans.

Integrating physiologic study results with details on epithelial cell control of membrane transport and function is crucial to developing new drugs to treat inherited and acquired human diseases such as ***hypertension, diabetes, and chronic renal failure***. Current research on epithelial cell physiology and membrane transport also suggests that the expression and differentiation of transport processes contribute to overall morphological development of the kidney. Endocrine, paracrine, and autocrine mechanisms such as angiotensin and thyroid hormones that regulate transport proteins should be explored in more detail. Studies combining what we know about embryonic kidney development and maturation of kidney transport function in both normal and abnormal epithelial cells, such as in polycystic kidney disease, will impart a more complete understanding of complex developmental physiology in infants and children.

Priorities for Basic Research

1. *Define the basis for acquiring and maintaining differentiated renal function throughout ontogeny and the developmental interactions of membrane transport proteins and epithelial cell development.* These efforts should focus on new methods to study embryonic kidney function and to integrate those methods with classic physiological renal techniques.

2. *Identify the molecular etiologies and physiologic bases of inherited and acquired diseases of renal transport.* Combine research to define the molecular signaling networks controlling membrane transport processes with the structural biology of membrane transport proteins. Using both model systems, study transport/cell physiology in differentiating cells, embryonic kidneys and non-mammalian systems such as zebrafish and *C. elegans* and appropriate cell lines representing nephron segments that can be phenotypically modulated to the appropriate developmental stage.

3. *Investigate genes that control sodium balance and appear important in the pathogenesis of genetic hypertension.*

Priorities for Translational and Clinical Research

1. *Create and maintain a database on families suspected to have inherited abnormalities of epithelial cell function and/or transport and a repository of human kidney tissues.* The database should be highly secure and, if possible, integrated with other human pediatric databases.

2. *Develop noninvasive assays* to quantify expression of key epithelial cell transport proteins for studies in children with solute and water homeostasis abnormalities.

3. *Determine target blood pressures for children,* as has been done for adults, and *study the pharmacological treatment of childhood hypertension.*

CLUSTER 2
ACUTE RENAL FAILURE

Acute renal failure is common in hospitalized children and causes substantial illness and death aside from the original cause of hospitalization. Acute renal failure may result from primary renal diseases such as acute glomerulonephritis, interstitial nephritis, hemolytic uremic syndrome, and from secondary causes such as ischemic injury, toxin-induced renal injury, sepsis, and multi-organ failure.

In hospitalized adults, a small rise in serum creatinine is associated with substantially increased mortality; higher increases in serum creatinine greatly increase the mortality rate. The consequences of similar declines in renal function in pediatric patients are entirely unknown. Studies describing the etiology and outcome of acute renal failure in children were done 10 to 20 years ago; the current causes, therapy, and outcomes in a broad-based group of pediatric patients are entirely unknown. With improved intensive care support of pediatric patients, acute renal failure associated with sepsis, multi-organ failure, cardiac surgery, and solid organ transplantation is an important contributor to morbidity and mortality.

Several diseases that cause acute renal failure in children are atypical causes in adults. Hemolytic uremic syndrome typically occurs during the first decade of life, causes substantial illness and death, and causes permanent kidney damage in up to 40 percent of children who initially appeared to recover from HUS. The immature and growing pediatric kidney is likely to respond to injury much differently than the mature, adult kidney, a particularly important difference in the premature newborn. Ischemic and toxic insults before renal development is complete at about 32 to 36 weeks' gestation may interfere with nephrogenesis and eventually lead to complications.

Over the past decade, animal and human studies have established the role of alterations in epithelial polarity and cytoskeletal changes, cell adhesion molecules, oxidants and protease enzymes, and the inflammatory response in the pathogenesis of acute renal failure. However, important questions remain:

- What are the contributions of vascular and endothelial abnormalities in human disease?
- To what extent do tubular injury and obstruction contribute to the pathophysiology of human disease?
- What are the roles of proximal or distal tubules in the initial and subsequent phases of ischemic acute renal failure?
- What are the roles of inflammatory mediators in the pathogenesis of acute renal failure?
- How do pathogenetic factors affect the immature and growing kidney's response to injury?

Priorities for Basic Research

1. *Develop animal and cellular models that more closely resemble acute renal failure in humans, including models that consider the immature and growing kidney's response to injury.* Animal models should reflect the complexity of the human condition, including the role of inflammation. Cellular models should reflect endothelial-tubular and tubular-tubular cell interactions. Transgenic and knockout animals will allow researchers to explore candidate mechanisms leading to injury and/or tolerance to injury.

2. *Establish new approaches to enhance or accelerate recovery from established acute renal failure.* Possibilities include identifying new molecules to enhance recovery, gene therapy, and strategies to improve renal replacement therapy.

Priorities for Translational and Clinical Research

1. *Conduct cooperative multicenter studies to define and develop criteria for testing potential therapies in children.* Collaborative networks could evaluate and validate markers of injury, provide technology, and design and conduct clinical trials. Networks could also develop severity-of-illness scores and provide pathologic and other samples.

2. *Conduct epidemiological studies of incidence, etiology, current therapy, and outcomes of acute renal failure in newborns, infants, young children, and adolescents.* Investigate short- and long-term consequences of acute deterioration in renal function due to ischemic/reperfusion injury, toxic nephropathy, and other insults in premature neonates born before nephrogenesis is complete.

3. *Determine markers of genetic and/or environmental susceptibility* to nephrotoxic acute renal failure, hemolytic uremic syndrome, ischemic renal injury, and acute renal failure associated with sepsis and multiorgan failure.

4. *Develop noninvasive tests of renal function.* Investigate possibilities such as PET scans to assess regional metabolism after specific renal insults, MRI to detect blood flow changes, radiopharmaceutical markers of renal dysfunction, and gene/protein methods to detect changes in renal function.

CLUSTER 3
IMMUNE-MEDIATED DISEASES–GLOMERULONEPHRITIS AND TUBULOINTERSTITIAL DISEASES

Immune-mediated glomerular diseases are a major cause of morbidity in children. While some children develop ESRD, many more suffer major illness from the immune-mediated renal disease and/or from therapy itself. A decade of basic research has elucidated the role of complement, cytokines, oxidants, protease enzymes, adhesion molecules, and growth factors in immune-mediated renal disease. Despite these important advances, the pathogenesis of many pediatric renal diseases remains obscure.

The pathogenesis of ***minimal change nephrotic syndrome***, the most common form of the syndrome, and of ***focal segmental glomerulosclerosis***, the most common form leading to ESRD, is entirely unknown. While steroids are standard treatment for minimal change nephrotic syndrome, there is no standard alternative for patients who are not helped by steroids. Also unknown is the pathogenesis of other common glomerular diseases such as ***IgA nephropathy***, ***Henoch-Schonlein purpura***, and ***membranoproliferative glomerulonephritis***. The absence of established therapies is partly a reflection of not knowing what causes these kidney disorders and not knowing genetic and environmental contributors.

Although acquired ***primary tubulointerstitial disease*** is relatively uncommon in children, it has become increasingly

clear that the disease plays a critical role in the progression of all renal diseases.

Overarching research priorities include identifying causal, susceptibility, and response genes for immunological renal diseases, developing murine models that imitate human glomerular and interstitial renal diseases, and identifying exogenous and endogenous antigens that initiate an immune response leading to immunologic renal disease. Furthermore, research should focus on developing and validating non-biopsy markers of disease activity, severity, and progression; establishing collaborative networks to study and treat immunologic kidney disease; and understanding better the molecular and structural basis of proteinuria. Within this broad net of research priorities, several specific areas of research should lead to important advances in understanding the pathogenesis of kidney disease and expanding therapeutic options for children with immune-mediated renal diseases.

Priorities for Basic Research

1. *Identify causal, susceptibility, and response genes for immune-mediated renal diseases.* Genetic and environmental factors combine to cause most immune-mediated renal diseases. With current molecular genetic tools, identify disease susceptibility genes in children with specific glomerular diseases and in homogenous populations or families with more than one affected member. Elucidate the molecular and genetic bases of the host's response to immunologic renal disease. This research approach might prove most fruitful in studies of minimal change nephrotic syndrome, focal glomerulosclerosis, and IgA nephropathy. Another important goal is to identify families with such diseases and examine members for subclinical features of the diseases.

2. *Identify exogenous and endogenous antigens that initiate an immune response leading to immunologic renal disease.* Most forms of acquired glomerulonephritis are immune-mediated. Yet, with few exceptions, the nephritogenic antigen remains unknown. Tightly coupled to identifying the triggering antigen is the question of why most children exposed to the putative antigen are either immunologically tolerant or mount a successful defense that fails to trigger a nephritogenic response. Studies in this area may hold greatest promise for preventing kidney

disease or for developing early, targeted treatments. Many new technologies could be used to identify renal antigens at the molecular level. Studies in animal models and using human biopsy material could be very informative.

3. *Determine the molecular and structural basis of proteinuria.* Proteinuria is the functional hallmark of glomerular disease. Despite that, our understanding of the fundamental pathogenetic mechanisms of proteinuria is incomplete. Identifying and purifying a circulating factor(s) that directly modifies glomerular permselectivity would be a major advance that could open many new doors to potential therapies. The recent identification of the glomerular epithelial slit diaphragm protein—nephrin—as the mutant gene in congenital nephrotic syndrome should lead to significant advances in understanding the pathogenesis of proteinuria. The possibility that genetic or acquired mutations in other cellular structures of the glomerular capillary might be involved in proteinuria deserves consideration.

Priorities for Translational and Clinical Research

1. *Develop a collaborative network to study immune-mediated kidney diseases.* A major goal over the next 5 to 10 years must be to develop standard protocols to treat chronic glomerular diseases in children, modeled on the approach developed by pediatric oncologists. With few exceptions, well established, controlled therapies for chronic glomerular diseases do not exist. The number of children with specific diseases in a single academic center is too small to design local treatment studies. Results of studies performed in experimental kidney disease models over the past decade have identified candidate disease mediators. Clinical trials targeting these mediators are beginning and could revolutionize the treatment of glomerular disease in children.

2. *Develop and validate both biopsy-based and non-biopsy markers of disease activity, severity, and progression.* Similar studies investigating candidate cytokines and molecules in surveillance transplant biopsies are under way and may validate techniques. Develop better methods to identify children at risk for progressive renal injury. Advances in renal imaging may be most informative, but monitoring sensitive markers in urine deserves further

consideration. Use new DNA, RNA, and protein technologies in biopsy material to identify reliable markers of disease activity, severity, and progression.

CLUSTER 4
CHRONIC RENAL FAILURE AND ITS TREATMENT

A. Preventing Progression of Renal Disease

In 1997, approximately 5,000 children were on dialysis, according to NIDDK's U.S. Renal Data System. Many more children have chronic renal insufficiency, defined as a glomerular filtration rate less than 75-80 ml/minute/1.73 M2 of body surface area, and will eventually need dialysis or a kidney transplant.

Growth retardation, malnutrition, bone disease, anemia, and increased susceptibility to infection are serious complications of chronic renal insufficiency in children. Growth failure, bone disease, and anemia may each become advanced before symptoms of renal disease develop. While erythropoietin, growth hormone, 1,25 vitamin D, improved nutrition, and other measures have substantially improved the care of children with chronic renal failure, basic and clinical research could improve treatment even more.

Current therapies to prevent progression of chronic renal disease are relatively nonspecific and have not been tested in pediatric patients. For example, angiotensin converting enzyme inhibitors, which effectively slow the progression of diabetic nephropathy in adults who have type 1 diabetes, have not been tested in children, when the damage likely begins. In addition, glycemic control and strong evidence for a genetic predisposition to diabetes complications have not been tested in pediatric patients.

While many slowly progressive renal diseases first manifest in adulthood, the disease process often exists in childhood. Therapies for such diseases as polycystic kidney disease, IgA nephropathy, Alport syndrome, focal segmental glomerulosclerosis, and diabetes are likely to be most beneficial in the early stages of disease.

Other issues important in children with renal disease are environment and genetic contribution to disease progression.

For example, epidemiological data suggest that both African American and Hispanic children who have focal segmental glomerulosclerosis advance to end-stage renal disease in significantly greater numbers compared to Caucasians.

Recruiting children for clinical trials is difficult and a major barrier to conducting multicenter studies. Sufficient resources to promote patient recruitment will be critical if multicenter studies are to succeed.

Priorities for Basic Research

1. *Investigate basic pathophysiologic mechanisms of growth failure and bone disease in children with chronic renal insufficiency.* Study insulin-like growth factor (IGF) proteins and IGF binding proteins since these receptors are potential therapeutic targets. Investigate the affects of chronic renal failure on normal differentiation of bone, altered bone metabolism, and skeletal development in children. Expand current pilot studies (R21 grants) on these issues.

2. *Develop animal models that more closely resemble progressive renal disease in humans.* Reliable animal models of human disease would facilitate progress in understanding the pathophysiology of progressive renal scarring. Molecules that may play a role in the progression of renal disease include cytokines, platelet-derived growth factors, fibroblast growth factor, and transforming growth factor-P. Better understanding cytokine and hormonal control of extracellular matrix turnover would facilitate progress in understanding the pathophysiology of progressive scarring. Develop and use transgenic animals. Study the basic mechanism of renal extracellular matrix deposition and removal in human and animal models of renal diseases such as diabetic nephropathy to understand the cell/matrix communication and regulatory systems that result in deposition following injury and removal during healing.

Priorities for Translational and Clinical Research

1. *Establish protocols to study interventions in children with chronic renal disease.* Investigate therapies to slow the progression of chronic renal disease and to prevent or

lessen complications. For example, the best treatment for renal osteodystrophy and to avoid hyperparathyroid bone disease and aplastic or low turnover osteomalacia are unknown. Similarly, the best dose and duration of growth hormone are unknown.

2. *Develop markers of progressive renal disease that reliably predict disease activity, severity, and progression at an early stage.* Investigate serologic or histologic markers of disease activity, severity, and progression as well as cytokines, transforming growth factor-P, and others. Use new DNA, RNA, and protein technologies to identify reliable markers of disease activity, severity, and progression in biopsy material. Develop new methods, including imaging techniques, to detect early structural and functional changes and to assess disease activity, severity, and progression at an early stage.

3. *Investigate environmental and genetic factors in progressive renal disease using population and molecular genetic techniques to identify genes contributing to disease severity and progression.* For example, study sibling pairs to elucidate the relationship between genetics and other factors and progression of diabetic nephropathy. Similarly, understanding the role of environment and genetics in the pathogenesis of hypertension and the progression of kidney disease could lead to new therapies for progressive renal disease.

4. *Conduct epidemiological studies of patients who have chronic renal disease, including incidence, prevalence, and risk factors such as genetic, biochemical, and toxic mechanisms.* For example, focal segmental glomerulosclerosis appears to be more common, more severe, and more resistant to therapy in African Americans.

B. Dialysis

Infants, children, and adolescents have requirements unique from adult counterparts. Growth retardation in children on dialysis is significant and persistant despite correction of anemia, acidosis, aggressive nutritional support, treatment of bone disease, and treatment with recombinant human growth hormone (rhGH). Although rhGH improves growth, children on dialysis respond less well despite correction for age, height deficit, and growth velocity. Current recommendations for vitamin D therapy are based on studies done nearly 20 years ago. Calcitriol is a potent antiproliferative hormone, and, indeed, over-suppression of parathyroid hormone (PTH) and the subsequent development of adynamic bone are associated with more-severe growth retardation. The nutritional status of pediatric patients on dialysis is also marginal and further contributes to anemia, bone disease, and chronic renal failure.

Recent studies in adults have suggested that the quantity and duration of dialysis is important in short- and long-term morbidity and mortality. However, the optimal dialysis dose for pediatric patients has not been defined. Research must define the optimal dialysis dose in pediatric patients by correlating dose with outcomes in children, including growth, development, nutrition, and cognitive function.

Most children with ESRD are on peritoneal dialysis, while most adults are on hemodialysis. Studies have shown that the longevity of the peritoneal membrane declines with the duration of peritoneal dialysis, and membrane failure is associated with peritonitis. Thus, understanding how peritonitis injures the peritoneal membrane could lead to prevention or treatment measures to improve its longevity and improve dialysis for children.

Priorities for Basic, Translational, and Clinical Research

1. *Determine the optimal management of growth failure in children of all ages.* Conduct basic and clinical studies of the mechanisms of growth failure and clinical studies to determine the optimal dose of growth hormone in different age groups and at each time-interval of growth hormone therapy.

2. *Determine the role of the recently cloned PTH/PTHrP receptor in altered bone metabolism and skeletal development in children with chronic renal failure.* Little is known about the pathogenesis and molecular biology of renal osteodystrophy. Redefine indications for vitamin D therapy in children on hemodialysis and peritoneal dialysis. Develop and test treatment strategies using vitamin D analogues to prevent and optimally control renal osteodystrophy and prevent adynamic bone disease.

3. *Conduct prospective studies to correlate solute removal during dialysis with outcomes in children, including growth, development, and cognitive development.* Accurate estimates of body fluid compartments in children on dialysis would help accurately quantify urea transport and optimize dialysis prescriptions.

4. *Determine basic mechanisms that alter peritoneal membrane function, and improve measures to treat and prevent destruction of the peritoneal membrane.* Basic and clinical studies are needed to identify mechanisms of mesothelial cell and membrane injury that contribute to ultrafiltration and membrane failure. Studies to preserve membrane function and decrease illness and death in children on dialysis are also needed.

5. *Define both the nutritional needs and cognitive alterations in children on hemodialysis and peritoneal dialysis, and determine optimal methods to assess both nutritional and cognitive states.* Study the potential application of bioimpedance, DEXA, and subjective global assessment. Correlate results with data on outcomes.

C. Transplantation

Renal transplantation is the treatment of choice for children with kidney failure. At present, optimal therapy involves specific temporal targets of childhood age for very young children who require renal transplants. Compared to adults, graft survival rates are either the same or better in all but very young children, and patient survival rates are substantially higher. Ironically, this success has brought new challenges.

Chronic rejection is the greatest challenge. It is the leading cause of graft loss in children, requiring multiple transplants

and exacerbating the organ shortage. Little is understood about the pathophysiologic mechanisms of chronic rejection. Research should be devoted to identifying immune- and non-immune-dependent mechanisms in chronic rejection and the molecular/genetic basis underlying its development and progression. Clearly, basic and patient-oriented research must focus on improving short- and long-term graft survival and expanding the donor pool.

Children with kidney transplants receive immunosuppression over a long time and are prone to complications such as cancer, premature atherosclerosis, and serious infections. The best long-term treatment would be to induce donor-specific tolerance and either eliminate or drastically reduce immunosuppressant drugs. Further research is needed to promote graft tolerance and develop methods to detect this state.

The long-term risk of malignancy and chronic infections such as Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) during the transition to adulthood is not clearly understood. It is imperative to develop more-selective immunosuppressive strategies and to learn which patients will do well on less medication. In addition, vaccines should be developed against EVB and CMV to decrease infectious and lymphoproliferative diseases.

Focal segmental glomerulosclerosis is the most common acquired cause of ESRD in children. The disease appears to be immunologically mediated, and it progressively scars and destroys the glomeruli. Understanding of the primary pathogenesis of FSGS is limited, but the disease recurs in transplanted kidneys. It seems clear that understanding molecular events causing the disease in both native and transplanted kidneys will greatly improve our ability to prevent and treat FSGS.

Another serious problem resulting in significant morbidity, graft loss, and mortality is lack of patient compliance to the complex, post-transplant medication regimen. Clinical studies are needed to understand and overcome this phenomenon and to assess the impact of kidney failure and transplantation on quality of life, including social adjustment, graduation from high school, employment, and establishing families.

Priorities for Basic Research

1. *Understand the immunological mechanisms involved in acute and chronic rejection.* Investigate non-immunological factors and strategies to induce donor-specific tolerance. Develop animal models, including transgenic and gene-targeting approaches, to understand immune responses to alloantigens, graft rejection, and tolerance.

   Using microarrays and informatics, uncover patterns of gene activation that might be markers of the immune response to detect acute and chronic rejection and progression, predict outcome, and guide therapy.

2. *Develop strategies to expand the donor pool by maximizing the use of recovered organs.* Develop alternatives to whole-organ transplantation with knowledge from renal stem cell biology and xenotransplantation.

3. *Understand molecular events underlying recurrence of FSGS.* Establish multicenter networks that would share information and data, including renal biopsies and computerized registries.

Priorities for Clinical and Translational Research

1. *Evaluate children's access to transplantation, and identify factors that improve patient compliance and quality of life.*

2. *Establish multicenter trials that are not traditionally supported by industry.* Consider grants or cooperative agreements with for-profit entities to study access to transplantation, risk factors, strategies to increase the donor pool, quality of life, patient compliance, and drug development and testing.

TOOLS, METHODOLOGIES, AND RESOURCES

The Task Force identified tools, methodologies, and resources needed to effectively extract information that might improve the diagnosis and treatment of childhood kidney diseases.

BASIC RESEARCH

1. Genomic and Gene-Expression Technology

a) Develop a kidney-derived, developmental, stage-inclusive expressed sequence tag database (human and murine).
b) Develop chip and high throughput technology for nucleic acid analyses.
c) Use the new bioinformatics technology to analyze data from *a* and *b* above.
d) Develop methods such as laser microdissection to acquire tissue for microanalysis (high throughput technology).
e) Develop methods to acquire genetic material from archival samples.
f) Establish banks of DNA, cells, and fresh and fixed tissues from patients and families with various pediatric renal diseases.
g) Exploit newer technologies such as SAGE, differential display, single-cell PCR, and cDNA microarrays.
h) Use microarrays and informatics to reveal patterns of gene activation that may be used as markers of the immune response to detect acute and chronic rejection, to follow progression, to predict outcome, and to guide therapy.
i) Construct databases of cell- and segment-specific genes and of mouse and human mutations with defined renal transport defects.

2. Genetic and Animal Models

a) Develop and study mouse, rat, zebrafish, *C. elegans,* and other animal models of childhood renal diseases, and study groups of people with circumscribed gene pools. For example, Pima Indians are disproportionately affected by diabetic nephropathy.
b) Develop animal models, including transgenic and gene targeting approaches, to understand immune responses to alloantigens, graft rejection, and tolerance.
c) Develop alternatives to whole-organ transplantation. Explore tissue and organ engineering using information from renal stem cell biology and advances in tissue culture and engineering.
d) Develop micromethods for physiologic studies in small animals and kidney structures.
e) Implement model systems to study both transport/cell physiology and renal injury in differentiating mammalian cells, embryonic kidneys, and non-mammalian systems such as zebrafish and *C. elegans*. Develop and maintain renal and non-renal stem cell cultures. Develop cell-specific markers and antibodies to facilitate lineage analyses.
f) Develop new organotypic *in vitro* culture models.
g) Develop new reporter molecules for advanced 3-D imaging. Develop new computerized imaging technologies for 3-D modeling of the developing kidney.
h) Generate appropriate cell lines representing various nephron segments that can be phenotypically modulated to the appropriate developmental stage.

CLINICAL RESEARCH

1. Clinical Databases and Therapeutic Trials

a) *Develop databases of patients with specific renal diseases* such as acute renal failure and hereditary renal disorders. Perform genetic analyses of inherited kidney diseases that may be linked to a human kidney-based genome program.

b) *Improve compliance* of children receiving established therapies for renal diseases.

c) *Develop biological or mechanical systems to deliver genetic and pharmacological therapies* to specific cells in the kidney.

d) Support studies on transplantation issues such as access, risk factors, strategies to expand the donor pool, quality of life, and compliance.

2. Drugs and Vaccines

a) With industry partners, develop and test more-selective immunosuppressive drugs and vaccines for EBV, CMV, and others.

b) Collaborate with clinical pharmacologists and toxicologists to study the pharmacokinetics, efficacy, and safety of new compounds in young children.

CHALLENGES AND BARRIERS

WORKFORCE

Training Pediatric Nephrologists

To meet the research goals identified in this report, the pool of physician-scientists trained in pediatrics and nephrology must be strengthened and expanded.[14] Optimal progress toward understanding the etiology and treatment of renal diseases in children will occur when well-trained pediatricians contribute their comprehensive knowledge of childhood development to research.

Two major challenges impede advances in pediatric renal disease research:

1. Too few investigators are entering pediatric nephrology; and

2. Young investigators have inadequate opportunities to move from postdoctoral trainee to independent investigator.

Possible solutions include recruiting more basic and clinical research trainees; increasing cross-disciplinary training to attract researchers from other fields; and increasing collaborations with investigators from such disciplines as embryology, biomedical engineering, chemistry, pharmacology, and computer science.

[14] Stapleton FB, Andreoli SP, Ettenger R, Kamil E, Sedman A, Chesney R. Future workforce needs for pediatric nephrology: an analysis of the Nephrology Workforce Training Requirements by the Workforce Committee of the American Society of Pediatric Nephrology. **Journal of the American Society of Nephrology** 8:S5-S8, 1997.

DATABASES

Pediatric nephrology lacks a centralized national or international database linking patients, investigators, tissues, biopsies, reagents and information on clinical trials, new methodologies, etc. Researchers need bioinformatic resources, including computer programs, to fully utilize and link new information from genome research to functional information and available patients, DNA, tissues, etc.

OTHER

1. Collaboration between NIH and industry is difficult.

2. Recruiting patients for multicenter clinical trials is difficult.

3. Indirect cost accounting and other financial and administrative barriers impede inter-institutional research collaborations.

4. Improved technologies, reagents, and information are not being shared.

5. Pediatric nephrologists are spending less time on research because they are required to see more patients and teach more classes.

6. Patients, doctors, and the public are generally unaware of the importance of genetic screening and participating in clinical trials and of the potential to slow or prevent progression of renal disease.

APPENDIX 1
CONGRESSIONAL ACTION

From the House of Representatives' Committee on Appropriations report on the Fiscal Year 1999 budget for the Department of Health and Human Services (House Report No. 105-635, page 72):

> While kidney disease research has led to advances in the care and management of children and adolescents, these diseases persist as a major cause of illness and death among the most vulnerable population. In last year's report, the Committee encouraged the NIDDK to develop and implement an interagency action plan for adult and pediatric kidney disease research. The Committee specifically made the distinction between adult and pediatric research because of the unique problems encountered by infants, children and adolescents. The Committee, therefore, urges NIDDK to submit a status report prior to the fiscal year 2000 appropriations hearing outlining specific actions to address the specific research needs of children and adolescents suffering from kidney diseases.

From the Senate's Committee on Appropriations report on the Fiscal Year 1999 budget for the Department of Health and Human Services (Senate Report No. 105-300, page 98):

> In the fiscal year 1998 report, the Committee urged the NIDDK to develop and implement an interagency action plan for adult and pediatric kidney disease research. The Committee made that distinction because young people are especially vulnerable to problems not encountered by adults, involving growth and development, a higher potential for learning disabilities, and the effectiveness of immunosuppressive drugs. The Committee, therefore, urges NIDDK to submit a status report prior to next year's hearings, outlining specific actions taken to address the special research needs of children and adolescents suffering from kidney disease.

APPENDIX 2
TASK FORCE MEMBERS

Sharon Andreoli, M.D.
Indiana University, Indianapolis

Ellis D. Avner, M.D.
Rainbow Babies & Children's Hospital, Cleveland

Eileen D. Brewer, M.D.
Texas Children's Hospital, Houston

Robert L. Chevalier, M.D.
University of Virginia, Charlottesville

Allison Eddy, M.D.
Children's Hospital and Medical Center, Seattle

Barbara Fivush, M.D.
Johns Hopkins University, Baltimore

Aaron L. Friedman, M.D.
University of Wisconsin Children's Hospital, Madison

Ariel Gomez, M.D.
University of Virginia, Charlottesville

Ira Griefer, M.D.
Montefiore Medical Center, Bronx, New York

Alan B. Gruskin, M.D.
Children's Hospital of Michigan, Detroit

Lisa Guay-Woodford, M.D.
University of Alabama, Birmingham

William E. Harmon, M.D.
Children's Hospital, Boston

H. William Harris, M.D., Ph.D.
Harvard University Children's Hospital, Portland, Maine

Pedro A. Jose, M.D., Ph.D.
Georgetown University Medical Center, Washington, DC

Clifford Kashtan, M.D.
University of Minnesota Medical School, Minneapolis

Frederick J. Kaskel, M.D., Ph.D.
Montefiore Medical Center, Bronx, New York

Alan M. Krensky, M.D.
Stanford University, Stanford, California

Craig B. Langman, M.D.
Children's Memorial Hospital, Chicago

John E. Lewy, M.D.
Tulane Medical School,

New Orleans

Michael Mauer, M.D.
University of Minnesota, Minneapolis

Marva M. Moxey-Mims, M.D.
Children's National Medical Center, Washington, DC

Jeffrey Platt, M.D.
Mayo Clinic, Rochester, Minnesota

Jean Robillard, M.D.
University of Michigan, Ann Arbor

Dominic Ruscio
Washington, DC

Isidro Salusky, M.D.
UCLA School of Medicine, Los Angeles

Lisa M. Satlin, M.D.
Mt. Sinai School of Medicine, New York

H. William Schnapper, M.D.
Northwestern University Children's Memorial Hospital, Chicago

Norman J. Siegal, M.D.
Yale University School of Medicine, New Haven, Connecticut

F. Bruder Stapelton, M.D.
University of Washington Children's Hospital, Seattle

Amir H. Tejani, M.D.
New York Medical College, Hawthorne

Bradley A. Warady, M.D.
The Children's Mercy Hospital, Kansas City, Missouri

Sandra L. Watkins, M.D.
University of Washington Children's Hospital, Seattle