Strategic Plan for Pediatric Urology

NIDDK – Research Progress Report

Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases

Strategic Plan for Pediatric Urology

NIDDK – Research Progress Report

Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases

NIH Publication No. 06-5879
February 2006

TABLE OF CONTENTS

III. Other Pediatric Urinary Conditions

IV. Research Methodologies

V. Training And Manpower

PLANNING COMMITTEE

Craig Peters, M.D.
Co-Chair

Barry Kogan, M.D.
Co-Chair

Anthony Atala, M.D.
Linda Baker, M.D.
Monica Liebert, Ph.D.
Sanjay Nigam, M.D.
John Park, M.D.

NIDDK Ex-Officio Members
Josephine Briggs, M.D.
Stuart Howards, M.D.
Marva Moxey-Mims, M.D.
Leroy Nyberg, Ph.D., M.D.
Elizabeth Wilder, Ph.D.

Publication Developer and Editor
Mark Geanacopoulos, Ph.D.

CONTRIBUTORS

Anthony Atala, M.D.
William Boyce Professor and Chair
Department of Urology
Wake Forest University School of Medicine
Winston-Salem, NC

Darius J. Bagli, M.D. C.M.
Associate Professor of Surgery
Department of Surgery
The Hospital For Sick Children, University of Toronto
Toronto, Ontario

Linda A. Baker, M.D.
Associate Professor
Department of Urology
University of Texas Southwestern Medical Center at Dallas
Dallas, TX

Laurence S. Baskin, M.D.
Chief, Pediatric Urology
Department of Urology
University of California, San Francisco Children's Medical Center
San Francisco, CA

Sheri A. Berenbaum, Ph.D.
Professor
Department of Psychology and Department of Pediatrics
The Pennsylvania State University
University Park, PA

Joseph G. Borer, M.D.
Assistant Professor of Surgery (Urology) and Assistant in Urology
Department of Urology
Harvard Medical School
Children's Hospital Boston
Boston, MA

Kevin T. Bush, Ph.D.
Assistant Project Scientist
Department of Medicine
University of California, San Diego
La Jolla, CA

Bartley G. Cilento, Jr., M.D.
Department of Urology
Children's Hospital Boston
Boston, MA

Martin J. Cohn, Ph.D.
Associate Professor
Departments of Zoology and Anatomy and Cell Biology
University of Florida
Gainesville, FL

Richard Czerw, Ph.D.
President
NanoTechLabs Inc.
Winston-Salem, NC

David A. Diamond, M.D.
Associate Professor of Surgery
Harvard Medical School
Children's Hospital Boston
Boston, MA

Jack S. Elder, M.D.
Director of Pediatric Urology
Department of Urology
Case Western Reserve University School of Medicine
Cleveland, OH

Michael Freeman, M.D.
Director
Urological Diseases Research Center
Children's Hospital Boston
Boston, MA

Kenneth I. Glassberg, M.D.
Professor of Urology
Department of Urology
Morgan Stanley Children's Hospital of New York-Presbyterian
New York, NY

L. Earl Gray
Research Biologist
Endocrinology Branch
Environmental Protection Agency
Durham, NC

Saul P. Greenfield, M.D.
Director, Pediatric Urology; Associate Professor of Clinical Urology
Department of Urology
State University of New York at Buffalo, School of Medicine and Biomedical Sciences
Buffalo, NY

Shuk-Mei Ho, Ph.D.
Professor of Surgery
Cell Biology and Physiology
Department of Surgery
University of Massachusetts Medical School
Worcester, MA

Alejandro Hoberman, M.D.
Associate Professor/Division Chief
Department of Pediatrics; General Academic Pediatrics
University of Pittsburgh School of Medicine
Pittsburgh, PA

Barry Kogan, M.D.
Professor, Surgery and Pediatrics
Division of Urology
Albany Medical College
Albany, NY

Bradley P. Kropp, M.D.
Associate Professor, Chief Pediatric Urology
Department of Urology
University of Oklahoma
Oklahoma City, OK

Peter A. Lee, M.D., Ph.D.
Professor
Department of Pediatrics
Penn State College of Medicine
Hershey, PA

Robert M. Levin, Ph.D.
Director of Research
Basic and Pharmaceutical Sciences
Albany College of Pharmacy
Albany, NY

Max Maizels, M.D.
Professor of Urology
Department of Urology
Children's Memorial Hospital
Chicago, IL

Cathy Mendelsohn, Ph.D.
Assistant Professor
Department of Urology and Pathology
Columbia University
New York, NY

Dawn S. Milliner, M.D.
Professor of Medicine; Professor of Pediatrics
Department of Internal Medicine; Department of Pediatric & Adolescent Medicine
Mayo Clinic
Rochester, MN

Sanjay Nigam, M.D.
Professor
Department of Pediatrics, Medicine and Cellular and Molecular Medicine; Division of Nephrology
University of California, San Diego
San Diego, CA

John M. Park, M.D.
Associate Professor, Director of Pediatric Urology
Department of Urology
University of Michigan Medical School
Ann Arbor, MI

David Penson, M.D., MPH
Associate Professor
Department of Urology and Preventive Medicine
University of Southern California
Los Angeles, CA

Craig Peters, M.D.
Professor
Department of Urology
University of Virginia School of Medicine
Charlottesville, VA

John C. Pope, M.D.
Assistant Professor
Surgical Oncology
Vanderbilt University
Nashville, TN

Alexandra Quittner, Ph.D.
Professor
Psychology Department
University of Miami
Miami, FL

Jonathon Ross, M.D.
Vice Chairman and Head of Pediatric Urology
Glickman Urological Institute
Cleveland, OH

Michael Sacks, Ph.D.
Professor
Department of Bioengineering
University of Pittsburgh
Pittsburgh, PA

David E. Sandberg, Ph.D.
Associate Professor of Psychiatry and Pediatrics
Psychiatry Department
School of Medicine and Biomedical Sciences,
University at Buffalo
Women and Children's Hospital of Buffalo
Buffalo, NY

Ellen Shapiro, M.D.
Professor of Urology
Department of Urology
New York University School of Medicine
New York, NY

Linda D. Shortliffe, M.D.
Professor and Chair of Urology, Chief of Pediatric Urology
Department of Urology
Stanford University
Stanford, CA

Shay Soker, Ph.D.
Associate Professor of Surgical Sciences
Institute for Regenerative Medicine
Wake Forest University Health Sciences
Winston-Salem, NC

T. Scott Stadler, Ph.D.
Assistant Professor
Molecular and Medical Genetics Department
Oregon Health and Sciences University
Portland, OR

Terry T. Turner, Ph.D.
Professor of Urology and Cell Biology
Department of Urology
University of Virginia School of Medicine
Charlottesville, VA

Margaret Vizzard, Ph.D.
Associate Professor
Department of Neurology and Anatomy and Neurobiology
University of Vermont College of Medicine
Burlington, VT

Julian Wan, M.D.
Clinical Associate Professor of Urology
Department of Urology
University of Michigan
Ann Arbor, MI

Valerie L. Ward, M.D.
Staff Radiologist, Instructor in Radiology
Department of Radiology
Harvard Medical School
Children's Hospital Boston
Boston, MA

Duncan T. Wilcox, M.D.
Associate Professor Pediatric Urology
Department of Urology
University of Texas, Southwestern Medical Centre at Dallas
Dallas, TX

Stephen A. Zderic, M.D.
Associate Professor of Urologic Surgery
Division of Pediatric Urology
Children's Hospital of Philadelphia
Philadelphia, PA

GRAPHIC DESIGN

Scott A. Kyle
The Scientific Consulting Group, Inc.

Executive Summary

Pediatric urology is a well-established area of clinical medicine that deals with the diseases of the urinary and genital tracts of children. These include a wide range of conditions that are both birth defects and acquired conditions, all having a spectrum of severity that ranges from causing early death or renal failure to the social burden of incontinence. Pediatric urology remains an underserved field in terms of research funding and activity relative to the health impact of pediatric urological conditions. Many of the conditions cared for by the pediatric urologist are relatively rare and unfamiliar—for example, posterior urethral valves—yet have profound impact on long-term health of the child and adult. Others are extremely common, such as urinary tract infection (UTI), yet may have a wide spectrum of severity that conveys the impression of relatively mild impact. Some conditions may have both direct health impact as well as potentially severe psychosocial impact, such as the intersex conditions and other congenital anomalies of the genitalia.

Much of the clinical challenge intrinsic to pediatric urology rests in the need to discriminate between children at risk for severe long-term complications and requiring intervention and the larger group who are not. The relative infrequency of many conditions necessitates development of multicentered clinical studies with the requisite infrastructure of database management, registries, and data analysis centers. The complexity and variety of the congenital anomalies seen in pediatric urology will require intensive basic science investigation to develop a clinically relevant understanding of the pathophysiological mechanisms of disease. This will require robust collaborative initiatives between clinicians and basic scientists in order to take advantage of modern scientific understanding and current technologies to develop such knowledge. Constraints to developing the necessary manpower infrastructure from both the basic scientific and clinical arenas are substantial and may represent one of the more formidable obstacles to maturation of the field of pediatric urological investigation. These obstacles must be overcome in order to elevate pediatric urology and the care given to many children by pediatric urologists above the increasingly archaic and reactive patterns of clinical care now in practice. Although the wide spectrum of conditions seen in pediatric urology may appear as yet another obstacle, the fact that they touch upon nearly every aspect of biology and medicine may make pediatric urology an ideal portal into the critical aspects of many disease processes and developmental anomalies.

Major Clinical Needs in Pediatric Urology

Key disease groups

Obstruction

Urinary obstruction is the major cause of renal failure in children and can be directly associated with abnormalities of kidney development producing dysplasia, another major cause of kidney failure. The wide range and severe impact of these conditions is well known, but the molecular mechanisms of these effects are unknown. As a result, the ability to predict clinical outcomes, select patients at risk or modify these effects specifically, is extremely limited. Integral to these goals will be a more thorough understanding of the developmental mechanisms in the kidney and urinary tract, since these are all influenced by obstructive processes. Understanding the basic mechanisms of the response to obstruction should permit development of biomarkers for these conditions that will facilitate identification and stratification of patients by their predicted outcomes. This would facilitate more specific therapy. These measures will clearly depend upon the development of clinical trial systems in obstructive uropathies to permit validation of potential diagnostic and therapeutic technologies.

Urinary Infection and Reflux

The frequency of urinary tract infections and their potential for causing kidney damage and other related morbidity make them a major challenge for pediatric urology research. The complex mechanisms by which bacteria infect the urinary tract and, in cases of pyelonephritis, cause renal injury, should be topics of investigation. Treatments to interfere with uropathogenetic colonization without prolonged antibiotic use and to prevent the complication of permanent renal damage are needed. Clinical management would benefit greatly from new methods that would permit immediate identification of infectious bacteria in patients as well as better technologies for imaging after a UTI, as well as identifying inflammation and renal scarring.

Vesicoureteral reflux (VUR) is a developmental defect in which abnormal insertion of the ureter into the bladder causes retrograde flow of urine into the ureter and the upper urinary tract. It may also be caused by lower urinary tract dysfunction. The most important complication of VUR, which affects 1 percent of children, is an increased risk of upper urinary tract infection leading to renal scarring and damage. The severity of the reflux and its complications range from cases where renal abnormalities are present at birth (these children account for most cases of subsequent renal failure) to the more prevalent mild and moderate cases where kidney damage is not present at birth and where the reflux is likely to resolve spontaneously. Milder cases are generally treated by antibiotic prophylaxis, which is effective in preventing UTI and its complications. The long-term individual and societal side effects of the antibiotics are unknown; indeed, there is increasing concern about the resulting emergence of resistant bacterial strains. New clinical trials will be needed to determine whether withholding of antibiotics until an infection is suspected is advisable. Another challenge is to determine optimal timing and type of therapy for children with VUR, whether this is open surgery, laparoscopic surgery, endoscopic injection, or observation. These decisions need to be based upon rigorous outcomes data based upon clinically relevant parameters over sufficiently long periods to capture the critical elements of reflux outcomes. It will also be essential for any clinical trials to be tightly integrated with a more complete understanding of the pathophysiology of critical events related to reflux, including renal growth, scarring, immune responses, and healing processes, as well as the genetic bases for these processes. Without this information, the ability to identify patients at risk, or to enhance therapeutic interventions, will be inadequate.

Bladder Dysfunction

Abnormalities of bladder function are wide ranging in causes and effects. They may produce quality of life challenges such as incontinence or bed-wetting (which has an extremely high prevalence), or they may produce a significant risk for infection and kidney injury when neurological abnormalities are the cause. The bladder's complexity is only now being recognized and presently knowledge of its normal, and abnormal, development and functional maturation is limited. Improved understanding is absolutely critical to our ability to identify patients at risk as well as to intervene for both quality of life and health issues. Research in this area will require indepth knowledge of developmental biology, neurobiology, and smooth muscle and epithelial cell biology.

Hypospadias and Genital Anomalies

Hypospadias is the second most common birth defect, and its incidence is increasing, according to the Centers for Disease Control and Prevention. Although there is increasing evidence that environmental factors such as maternal exposure to endocrine disruptors during pregnancy might explain the increased incidence, the etiology of hypospadias remains unknown in the majority of cases. A program of developmental genetic research leading to a better understanding of urethral development will provide insights into the causes of this congenital disorder and explanations for its increased incidence.

Congenital anomalies of the sex organs confront clinicians with urgent needs to assign sex and perform appropriate surgical reconstruction. Sex assignment decisions in which optimal gender was based on factors such as the potential for sexual function and reproductive potential have been highly contested; though studies are very limited, reports of affected individuals have indicated dissatisfaction with not only the gender assigned, but also resentment of the processes of decision-making and information sharing. Prospective studies of gender identity and reproductive function and quality of life are needed in this group of patients to guide clinicians and families in making decisions about gender assignment and surgical reconstruction. The relative infrequency of these conditions emphasizes the need for multicentered clinical studies with the requisite infrastructure of database management, registries, and data analysis centers.

Developmental Andrology

Cryptorchidism requiring surgery occurs in approximately 1 percent of male births. While surgical therapy is highly successful, it does not always prevent impaired reproductive function. Given the very high incidence of these conditions, the research challenge is to determine the genetic and endocrinological basis of cryptorchidism and to develop strategies to prevent the loss of fertility. Varicocele is another condition associated with impaired fertility that develops in the early adolescent years. The underlying mechanisms of development and its effect on testicular function remain unclear, despite its occurrence in up to 15 percent of young men.

Key research themes

Molecular and Genetic Basis of Developmental Anomalies

Understanding the cellular and molecular basis of urinary tract development is a prerequisite for advancing the diagnosis and treatment of genitourinary tract disease in the post-genomic era. Exceedingly complex—and understudied—this area of developmental biology has important implications for congenital kidney and urinary tract disease, as well as the potential to provide critical insights into a variety of other developmental systems. The complexity of the urogenital system and the frequency of congenital abnormalities

suggest that an improved understanding of these processes will yield a broader understanding of other systems as well. This will be critical in both clinical diagnostics and therapeutics with a wide variety of methodologies, including tissue engineering, stem cells, gene therapy, and nanotechnology.

Formation of the genitalia is a complex developmental process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. Understanding the molecular mechanisms of normal development is critical if we are to be successful in elucidating the causes of abnormalities of both the internal and external genitalia. Basic research in this area will be vital for prevention and treatment of diseases such as hypospadias, epispadias, undescended testes, and uterine abnormalities. Specific priorities should include:

- Characterize the programs of gene expression that mediate the formation, function, and injury response of individual genitourinary tract structures using genetic models of mice, cell culture, biomechanical studies, and bioinformatics in a multidisciplinary manner.
- Establish the data-sharing platforms that will allow the productive integration of gene expression and proteomic data sets with three-dimensional morphometric data, as well as existing human and mouse genetic databases.
- Explore how *in vitro* developmental biology—including organ and cell culture, as well as stem cell technology—can be exploited for tissue engineering of genitourinary (GU) tract structures.
- Apply the insights into urinary tract development obtained from investigations in model systems to human malformations—such as renal dysplasia, renal ectopia, congenital hydronephrosis, reflux, and posterior urethral valves.
- Improve the description, diagnosis, and treatment of conditions of maldevelopment, with classification and diagnostic systems based upon multi-dimensional parameters.
- Develop systems to permit sharing of biological specimens and knowledge, linked with clinical registries using institutional arrangements that foster multidisciplinary investigation, as in Centers of Excellence for Pediatric Urology.
- Provide incentives and opportunities for investigators in developmental biology to enter into understudied aspects of genitourinary tract development, including (but not limited to) ureter and bladder formation
- Develop better treatments to prevent or correct conditions of maldevelopment: improve surgical success, both open and minimally invasive (endoscopic, laser, laparoscopic, and robotic), and develop potential drugs for treating the diseases without surgery.

Outcomes Assessments: Health and QOL

Throughout all aspects of pediatric urology, there is a significant need for enhanced tools to facilitate clinical research that can directly impact patient care. These limitations have hindered clinical progress to date and will limit the ability to apply novel technologies in a specific way. Without adequate systems to assess, compare, and monitor clinically relevant outcomes, new and promising technologies may not be able to be appropriately validated in pediatric urologic conditions. Steps critical to enhancing clinical research include:

- Establish standard definitions of pediatric urologic conditions for use in clinical practice and research.
- Develop a set of standardized objective and patient-centered outcomes for use in clinical research of various pediatric urologic conditions.
- Establish clinical research networks to undertake randomized clinical trials.

- Create pediatric urology disease registries for use in clinical research and improvement of quality of care.
- Develop systems to permit adequate training of clinical researchers with interest and experience in pediatric urology.

New Technologies in Research and Clinical Practice

Powerful new tools have become available to the researcher and the clinician during the last decade and with them an as yet unrealized capacity to improve our understanding of many more disease processes and ameliorate them in children. Pediatric urology is currently limited in its ability to tap into the new methodologies because of a variety of infrastructural, attitudinal, and financial limitations. To advance the care of children with Pediatric Urological diseases, these limitations must be overcome in the near future. The principle areas where important new knowledge and insight may be gained include:

- Systems Biology
- Bioinformatics
- Gene Chip Arrays
- Proteomics
- Genomics
- Metabolomics
- Nanotechnology
- Stem Cells and Tissue Engineering
- Biomechanics
- Bio-imaging Technology

In the clinical arena, novel technologies are emerging to enhance therapeutic interventions, and with increasing basic understanding of diseases, new technologies are certain to emerge. These include:

- Minimally Invasive Surgery and Robotics
- Tissue Engineering
- Imaging Technologies
- Technology Assessment

Each of these novel technologies is highlighted in this report, and all share similar needs to permit needed integration of their capabilities with pediatric urological needs and patients. Therefore, it is strongly recommended that efforts and funding be committed to:

- Arrange joint mentoring of researchers by mentors with extensive experience in pediatric urology and novel technologies.
- Fund new investigators taking a multidisciplinary approach to pediatric urology and aspects of novel technologies.
- Encourage multidisciplinary research efforts between scientists and clinicians experienced in these technologies, urologists, and industry.
- Establish regional resource centers for novel technologies and pediatric urology to assist with development and application of these technologies.
- Develop educational programs to acquaint the next generation of pediatric urological researchers with emerging technologies.
- Convene workshops to foster interaction between clinicians and scientists experienced in these new technologies and pediatric urological researchers.

Training and Manpower Infrastructure

A variety of institutional pressures make life exceedingly difficult for pediatric urologists contemplating a research career. We recommend new training mechanisms that would allow those with a strong commitment to immerse themselves in research under the mentorship of scientific leaders in the field.

The participation of Ph.D. investigators in research with direct applications to pediatric urology is inadequate. We discuss some cultural barriers to this participation and advocate training programs to support graduate students studying research problems centered on urologic disease, with urologists participating as advisors. Postdoctoral programs in urology research also are recommended.

We underscore the importance of collaboration between basic scientists and clinicians in pediatric urology research. If the number of collaborative projects is to grow, novel funding mechanisms may be needed to address the unique demands of the clinician scientist struggling to fulfill dual roles, as well as those of the basic scientist, as she or he attempts to maintain funding within, or in collaboration with, a clinical department.

I. The Urinary Tract

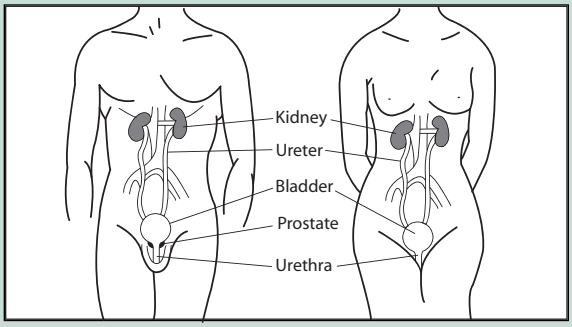
The urinary tract can be divided into upper and lower tracts: the upper tract refers to the kidneys and the ureters (production and transport of urine); the lower tract comprises the bladder and urethra (storage and emptying of urine). The kidneys continually filter the blood to maintain water and electrolyte balance, remove wastes and foreign chemicals, and perform a variety of hormonal functions, including the regulation of blood pressure. The ureters pump the urine produced by the kidneys into the bladder at low pressure without causing the holdup, or stasis, that might permit infections. The renal pelvis and the ureter pump urine in a similar manner, with an automatic pacemaker that controls the rate and force of contraction. The urine then passes into the bladder through the ureterovesical junction, which is configured in such a way as to prevent backwash, or reflux, of urine from the bladder into the ureter and kidney.

A. Upper Urinary Tract

1. Urinary Tract Development and Maldevelopment

Summary

Understanding the cellular and molecular basis of urinary tract development is a prerequisite for advancing the diagnosis and treatment of genitourinary tract disease in the post-genomic era. Exceedingly complex—and understudied—this area of developmental biology has important implications not only for congenital kidney and urinary tract disease, but also for devising new approaches to tissue engineering and organ repair and regeneration. What is required to advance the field is a multifaceted strategy that utilizes genetic investigation, organ culture, and cell culture, combined with multidisciplinary approaches. The collaborative efforts of cell and developmental biologists, clinicians, computational scientists, and tissue engineers will enable investigators to examine molecular and cellular mechanisms underlying the formation of individual genitourinary tract structures, their patterning, the fates of different cells in the genitourinary tract, and the way in which epithelial and mesenchymal cells interact in normal and disease states. The impact of such a research program on pediatric diseases such as obstructive and reflux uropathies, as well as end-stage kidney disease, could be profound.



Health Impact

Abnormal development of the urinary tract occurs in as many as 1.0 percent of all pregnancies and leads to a large and varied group of malformations, including those associated with obstruction and voiding dysfunction. As the use of fetal sonography provides earlier detailed anatomical information to parents, the challenge to the pediatric urologist is to reliably differentiate patients who have aberrant anatomy, but in whom these constitute incidental findings of no long-term significance, from those in whom a detailed workup and therapy are warranted. It should be noted that several urogenital tract abnormalities—of which renal dysplasia and hydronephrosis are the most important—can lead to end-stage renal disease (ESRD), thereby constituting a significant fraction of children and young adults requiring renal dialysis or transplantation. A clear understanding of the normal development of the urinary tract is a fundamental prerequisite to developing therapeutic or interventional treatments that prevent ESRD.

A Brief Description of Normal Urinary Tract Development

Kidney, renal pelvis, and ureter

Urinary tract formation depends on reciprocal interactions between epithelial and mesenchymal cell types. Development is initiated by the formation of the ureteric bud, an epithelial outgrowth of the Wolffian duct. The tip of the ureteric bud induces the kidney primordium to mature and begin to undergo successive branching to form the renal collecting system, which in humans consists of roughly 1 million collecting ducts. Meanwhile, the ureteric bud induces the formation of the nephrons. The mature kidney will be composed of a roughly 1 million nephrons, each consisting of a filtration unit (the glomerulus), a proximal tubule, the loop of Henle, and a distal tubule that connects with the collecting duct. Nephron function—maintaining the fluid composition of the body through the production of urine— is crucial for life; it depends upon the architecture of the kidney, in large part determined by the branching pattern of the ureteric bud.

Connecting the upper and lower urinary tract

The distal portion of the ureteric bud (i.e., that portion of the ureteric bud that lies outside the metanephric mesenchyme) will eventually differentiate into the ureter, a water-tight epithelial tube enclosed in a smooth muscle coat that propels urine to the bladder via rhythmic contractions of the smooth muscle (peristalsis). Defects in the development of the supravesical portions of the urinary tract include renal dysplasia, as well as malformations of the urinary tract distal to the kidney (e.g., megaureter, ureteropelvic junction obstruction, vesicoureteral reflux, ectopic/duplicated ureters, and posterior urethral valves). See "Renal Dysplasia" and "Ureteral Anomalies" below.

Bladder, trigone, and urethra

The bladder and urethra are thought to be formed from the urogenital sinus. The bladder trigone, the portion of the urogenital sinus between the bladder body and urethra, appears to derive from the intermediate mesoderm as the distal ureter inserts into the urogenital sinus. As development progresses, the bladder differentiates into a muscular structure lined by urothelium and begins to function in the collection, storage, and elimination of urine. Storage and emptying of the bladder requires coordination between the bladder and the urethra. Relatively little is known about the innervation of the urinary bladder that occurs during embryogenesis.

Common problems that affect the bladder and urethra include spinal cord defects (spina bifida), congenital bladder outlet obstruction (posterior urethral valves, ectopic ureterocele), acquired bladder obstruction (voiding dysfunction), and

congenital anatomic anomalies (bladder exstrophy, imperforate anus, prune belly syndrome, and ureteral ectopia). A significant number of children born with these defects will have morbidity directly related to their bladder dysfunction. Disorders of the urethra are discussed in a later section.

Major Disorders of Upper Urinary Tract Development

Renal dysplasia

While dysplasia is the leading cause of renal failure in children, it still has no universal definition. The term refers to a histologic diagnosis in which part or all of the kidney did not develop properly, causing a decline in kidney function. Associated conditions include obstruction (posterior urethral valves, ureteropelvic or ureterovesical junction obstruction), ureteral bud abnormalities (ectopic ureters, ureteroceles, and vesicoureteral reflux) and defects in genes and genetic pathways involved in normal kidney development and apoptosis. Renal dysplasia also is associated with certain developmental syndromes where multiple defects in other organs are found. The manifestation of dysplasia can range from small poorly functioning kidneys to large non-functioning, cystic ones (multicystic dysplastic kidney [MCDK]); it is likely that there are unique mechanistic pathways leading to each of the various forms of the condition. *A classification and grading system for dysplastic kidneys, based upon histological, molecular, and biochemical criteria, would facilitate research in his area.*

Upper urinary tract obstruction

Obstruction of the kidney is a major cause of kidney failure and other complications in children. Urinary tract blockage can occur at any level from the kidney to the urethral meatus; in congenital cases, the most common locations of obstruction include the ureteropelvic junction (between the kidney and ureter), the ureterovesical junction (between ureter and bladder), and the bladder outlet (here, in males, obstruction is often secondary to posterior urethral valves). The blockage causes urinary tract "ballooning" (dilatation) above the blockage — hydronephrosis refers to this dilation in the kidney, and is the cause of kidney failure in 16 percent of children who undergo transplantation. Urinary dilation, found in up to 2 percent of pregnancies, is the most common abnormality noted prenatally. *Current imaging methods (ultrasonography, radionuclide imaging, and pyelography), do not allow for differentiation of patients at risk for renal deterioration and those with little risk. New, non-invasive, accurate imaging methods for assessing and prognosticating renal function need to be developed.*

Hydronephrosis is usually accompanied by increased pressure in the kidney, and when severe and prolonged, can lead to kidney damage or destruction. In prenatal cases, cysts, kidney tissue malformation, and dysplasia can develop, replacing the normal kidney tissue. Growth of the kidney can be both augmented and impaired, and several growth factors have been implicated in dysplasia resulting from obstruction. (In a neonatal rat model, exogenous epidermal growth factor partially rescues changes induced by urinary tract blockage.) If hydronephrosis develops postnatally, the kidneys, especially in the presence of infection, may become scarred and damaged without associated dysplasia.

A hallmark of obstruction is the development of interstitial renal fibrosis, a phenomenon that has been extensively examined in non-obstructive models, yielding insights with potential relevance to obstruction. Molecular mediators of fibrosis include the renin-angiotensin system (already implicated in obstructive changes), cytokines such as TGFß1, as well as direct regulators of extracellular matrix homeostasis, MMPs (metalloproteinases) and TIMP (tissue inhibitors of metalloproteinases). It should be noted that the highly specialized functions of the various

kinds of renal cells can be affected by obstruction beyond obvious growth and injury responses. Functional consequences of obstruction can include impairment of glomerular and tubular function, with clinical implications such as azotemia (renal failure), diabetes insipidus, and renal tubular acidosis.

Hydronephrosis is a condition that can significantly impair the developing kidney. *One focus of research should be intercellular signaling within the tubules and between the epithelia and mesenchymal compartments of the developing kidney; altered epithelium-mesenchyme transitions, which are a critical part of normal kidney development, are very likely to play a key role in obstructive nephropathy. The signal transduction mechanisms underlying these processes are being elucidated, and they need to be understood in the context of obstruction. The complex integrative functions of the kidney cannot be neglected, particularly the impact of obstruction on renal innervation and humoral regulation, as well as angiogenesis and the development and regulation of the renal vasculature.* Obstruction also has been demonstrated to affect apoptosis through well-characterized molecular mediators of this process. *The regulation and role of apoptosis in the developing kidney, and its involvement in the kidney damage accompanying hydronephrosis, need to be further investigated.*

Other ureteral anomalies

Many anomalies of the ureter—including vesicoureteral reflux and abnormal entry of the ureters into the bladder (ectopic ureter or ureterocele)—result from abnormal ureteral budding. Abnormal ureter locations can lead to ureteral blockage, and in rare cases, ureteral communication with other structures such as the seminal vesicle, *vas deferens*, and vagina.

The best described ureteral anomaly, megaureter, can be classified in three general categories: (1) obstructed megaureter, (2) refluxing megaureter, and (3) non-obstructed, non-refluxing megaureter. All are presumed to be caused by an abnormality at the junction of the ureter and the bladder. In obstructed megaureter, the junction appears to be thickened and narrowed so that the normal flow of urine from ureter to bladder is impeded; this causes the ureter to distend and become quite enlarged. In refluxing megaureter, the ureters join the bladder in such a way that extensive vesicoureteral reflux occurs causing the ureter to become very enlarged.

Prune belly syndrome (PBS) is a complex congenital anomaly characterized by abnormal abdominal muscles, undescended testes, infertility, and massive urinary tract dilation. Bilateral massive megaureters are typically present. While there is no evidence of obstruction, these ureters typically drain very poorly, and this can result in urinary tract infections and kidney failure. *Very little is known about the cause of this disease or why the urinary tract is so abnormal.*

The diagnosis of renal dysplasia and ureteral anomalies is typically performed by ultrasound to detect ureter and kidney dilation; voiding cystography can detect vesicoureteral reflux, and nuclear renography is used to determine kidney function and establish whether there is a blockage present in the system. Newer modalities such as magnetic resonance imaging (MRI) have recently been reported to enhance both anatomic and functional detail. MRI may permit the clinician to obtain an accurate anatomical picture of the entire urinary tract and determine the obstructive nature of megaureter in a single test. Radiation is avoided, and the contrast reagent does not harm the kidney, while the imaging quality is excellent. The disadvantages are high costs and the possible need for anesthesia in younger children.

Priorities for Basic Research

1. Clarify the mechanisms by which the normal GU tract development is regulated—to include the glomerulus, proximal and distal tubules, collecting ducts, renal pelvis, ureter, bladder, and urethra.

- Characterize the program of gene expression that mediates formation of individual GU tract structures.
- Determine how collecting ducts, renal pelvis, and ureter derive from the Wolffian duct and ureteric bud.
- Identify the reciprocal epithelial-mesenchymal signals required for patterning of GU tract tissues.
- Generate the mouse strains that will permit the conditional and tissue specific expression of molecular markers of cell origin that can define cell lineage in development of the upper urinary tract. Elucidate the origin of cells comprising the epithelial and mesenchymal structures of the GU tract (e.g., formation of the bladder trigone).
- Encourage multidisciplinary approaches, bringing together those who investigate the development of the GU tract through organ culture, murine genetic models, cell culture systems, biochemical approaches, and bioinformatics.
- Establish the data sharing platforms that will allow the productive integration of gene expression and proteomic data sets with three dimensional morphometric data as well as existing human and mouse genetic databases.

2. Clarify the molecular and cellular mechanisms of urine transport in the upper GU tract and the voiding reflexes in the lower GU tract.

- Identify and characterize the molecular and cellular mediators that regulate pyeloureteral peristalsis.
- Identify cell populations that form the pacemaker cells and sympathetic nerves that control muscle contraction in the renal pelvis and ureter.
- Understand formation and function of neurons that control the voiding reflexes.
- Identify the developmental switching mechanism(s) that convert the voiding reflexes from the neonatal to the adult pattern.
- Define the relationship of ureteral muscle function (contractility) to the microscopic findings.

Priorities for Translational and Clinical Research

1. Determine how knowledge of the developmental biology of the GU tract can be applied to tissue engineering purposes.

- Explore how *in vitro* developmental biology (including work in organ and cell culture) can be exploited for tissue engineering of GU tract structures.
- Combine stem cell approaches with *in vitro* developmental systems to devise new strategies for engineering GU tract structures.

2. Apply the insights into urinary tract development obtained from investigations in model systems to human malformations such as renal dysplasia, renal ectopia, congenital hydronephrosis, reflux, and posterior urethral valves.

- Identify candidate genes for GU tract malformations through transcriptional profiling of developing urinary structures and subsequent analysis using sophisticated informatics approaches.
- Establish national human tissue banks and repositories of human specimens to more effectively investigate whether results in

mutant mice or *in vitro* developmental systems are applicable to diseases seen in humans.

- Develop appropriate murine models for renal dysplasia, hydronephrosis, and ureteral anomalies and other diseases of maldevelopment.
- Evaluate genetic pathways implicated in human disease and murine models of disease in animals amenable to detailed physiological studies and, where applicable, in organ culture systems.

3. Characterize the developmental determinants of renal dysplastic syndromes and chronic bladder dysfunction.

- Investigate the role of epithelial-mesenchymal interactions in development—in injury, fibrosis, dysplastic syndromes, and childhood malignancy.
- Elucidate the developmental origins of bladder disease in children and adults (e.g., interstitial cystitis, voiding dysfunction in childhood, and reemergence of primitive reflexes after spinal cord injury).

4. Improve the description, diagnosis, and treatment of conditions of maldevelopment.

- Improve the diagnosis, classification, and histopathological description of dysplasia and other developmental disorders.
- Conduct trials to establish the true natural history of the varying degrees and causes of renal obstruction.
- Develop tests using novel technologies (from bioengineering, proteomics, etc.) for the purposes of determining the severity of disease and identifying which patients would benefit from surgery or drug treatments. New imaging methods or biomarkers to identify those at risk for renal deterioration among patients with obstruction and other conditions are critically needed.
- Develop better treatments to prevent or correct conditions of maldevelopment: improve surgical success, both open and minimally invasive (endoscopic, laser, laparoscopic, and robotic), and develop potential drugs for treating the diseases without surgery.

Infrastructural Needs

- Unimpeded sharing of mouse strains relevant to urological disease; central human tissue banks and repositories; clinical registries
- Institutional arrangements that encourage multidisciplinary approaches, including Centers of Excellence for Pediatric Urology
- Incentives and opportunities for investigators in developmental biology to enter into understudied aspects of GU tract development, including (but not limited to) ureter and bladder formation

2. Nephrolithiasis

Summary

Kidney stones in children are increasing in prevalence and often require a lifetime of dietary changes, medication, and hospitalizations. The condition is often painful and frequently requires surgery. It should be noted that the rare inherited diseases like primary oxaluria that cause kidney stones are life threatening because of the risk of kidney failure, and these inherited diseases cannot be adequately addressed with current therapies. Multi-center trials are needed to compare the effectiveness of extracorporeal shock wave lithotripsy and percutaneous nephrolithotripsy for stone removal and to evaluate the use of medications to aid spontaneous passage. Critical goals for basic research include a detailed understanding of the metabolic basis of the stone diseases, identifying the genetic determinants of susceptibility, and understanding the mechanism of crystal attachment and stone formation in the urinary tract.

Health Impact

Stones of the kidneys and urinary system (urolithiasis) are a growing problem in pediatric urology and now account for one in 7,600 to 10,000 hospital admissions. In developing countries where diet is poor and dehydration common, pediatric urolithiasis is endemic. In the United States, hospitalizations, surgery, parental time away from work to care for the affected child, and chronic medications all add to the economic burden. Children with stone disease may be faced with a lifetime of medical issues, as many will become adult stone formers. Dietary restrictions and vigorous fluid intake are typically needed to prevent recurrence. Kidney stones are often extremely painful to pass and may be accompanied by urinary infection. Hospitalizations and surgery are frequently required. Children whose kidney stones are symptomatic of rare diseases due to inherited defects in metabolism—distal RTA, cystinuria, and primary hyperoxaluria—may suffer kidney damage or failure and require dialysis and/or organ transplantation.

Clinical Presentation and Treatment

Formation of stones in a child is a manifestation of abnormal metabolism in the majority of cases, although sometimes it is related to abnormal structure of the urinary tract. In approximately one-half of pediatric cases, urinary stone disease is familial. Typically, specialized blood and urine testing is performed to identify the root cause of the stone production. In 80 percent of cases, stones are composed predominantly of calcium compounds with calcium oxalate stones being the most common subtype. Infection stones, uric acid stones, and cystine stones can also affect children.

Once a stone is identified, it can be monitored for spontaneous passage if no complicating issues arise. However, stones greater than 5 mm rarely pass unaided. Three main avenues of surgical treatment exist—extracorporeal shock wave lithotripsy (ESWL), ureteroscopic lithotripsy, and percutaneous nephrolithotripsy (PCNL). Open surgery is rarely required.

ESWL is typically the first choice of therapy for fragmenting a urinary stone and is about 80 percent successful, but sometimes the stone is too hard to break or the fragments do not pass out in the urine. *Short-term studies suggest there are no lasting effects of the shock waves on the growing pediatric kidney, but long-term studies to verify this are lacking.*

Ureteroscopy is a surgical procedure in which tiny long telescopes (ureteroscopes) are passed into the urinary system through the urethra, into the bladder and up the ureter to the stone. Specialized devices (including lasers) are then

passed through the ureteroscope to fragment the stone. Subsequently, some or all of the stone fragments can be removed from the body with the ureteroscope. Performed under anesthesia, this technically challenging procedure is generally safe but somewhat riskier than ESWL, and 90 percent effective at stone removal in children.

In percutaneous nephrolithotripsy, a special hollow tube is passed through the skin of the back directly into the affected kidney. Under anesthesia, special telescopes (endoscopes) are passed to fragment and remove the stones. This procedure is typically performed for larger or hard-to-break kidney stones or in other special situations. In rare cases, blood transfusion is required. The stones are eliminated in 90 percent of cases. Open stone surgery is rarely needed and now is used only for the most complex cases with large stone burden.

Priorities for Basic Science Research

- Obtain a thorough understanding of the metabolic basis—in the kidney, intestines, and bone—of stone formation in children.
- Characterize the genetic determinants of increased susceptibility to stone formation in certain individuals. Conduct additional familial studies to identify the genetic basis of inherited diseases that cause stone formation.
- Determine how crystals and stones attach to the surfaces of cells in the urinary tract.

Priorities for Translational and Clinical Research

- Study the long-term effect of excess urine calcium in childhood, including the risks of recurring stone formation and osteoporosis.
- Validate pediatric standard reference ranges (stratified for age and sex) for lithogenic and stone-inhibiting urine solutes and metabolites.
- Use proteomics methodologies to identify factors that promote and prevent stone formation.
- Perform multicenter outcomes analyses of ESWL versus PCNL for large stone burden in children. Evaluate the long-term effects of ESWL on the pediatric kidney.
- Perform a prospective, double-blind, randomized clinical trial investigating the usefulness of medications to help spontaneous passage of symptomatic distal ureteral stones in children. Possible medications could include alpha-blockers, steroids, and calcium-channel blockers.
- Develop stone-imaging techniques that minimize X-ray exposure.
- Develop improved miniaturized instrumentation for pediatric lithotripsy.

B. Lower Urinary Tract

3. Lower Urinary Tract Obstruction

Summary

Mechanical lower urinary tract obstruction (i.e., of the bladder outlet) occurs predominantly in male children and the most common cause is posterior urethral valves. Prenatal prognosis is poor, and while the condition can be addressed surgically in neonates, these children are at long-term risk for renal failure and urinary incontinence. Improved methods for both prenatal diagnosis and predicting risk for later complications are needed. Clinical trials will be required to assess the value of therapeutic approaches such as upper urinary tract diversion, intermittent catheterization, and pharmacologic interventions. More research is needed to understand how pressure and ischemia attributed to obstruction cause long-term decline in neuromuscular control of the bladder.

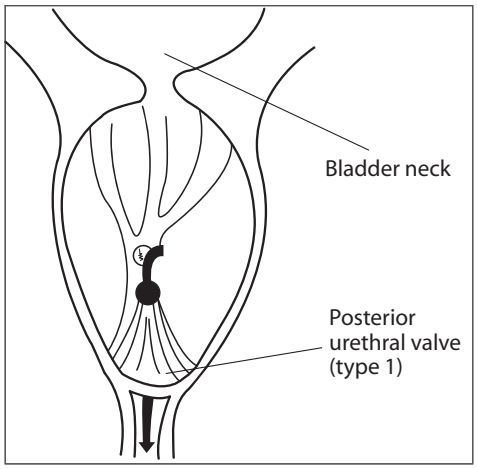
Health Impact

Prenatal diagnosis of bladder outlet obstruction confers a poor prognosis with a large number of fetuses succumbing before birth. Among the one in 5,000 to 8,000 males born with the most common cause of bladder outlet obstruction in children—posterior urethral valves (PUV)—25 percent will experience renal failure. Many more will have the burden of significant long-term lower urinary tract dysfunction requiring costly treatments, including intermittent catheterization and surgical augmentation of bladder function.

Clinical Presentation and Treatment

Bladder outlet obstruction is defined as obstruction at the bladder neck or urethra resulting in impairment of urine flow. Anatomic obstruction is more frequent in males; the most common cause is PUV, a developmental anomaly resulting in membranous folds in the posterior urethra that occurs in approximately 10 percent of prenatally diagnosed uropathies. Acquired voiding dysfunction and neurological disease are also causes of outlet obstruction.

Neonates with PUV may exhibit underdevelopment of the lung caused by oligohydramnios, and morbidity and mortality associated with pulmonary hypoplasia are significant. Renal impairment—that resulting from primary renal dysplasia and that which is secondary to bladder dysfunction—occurs in 20 to 65 percent of boys with PUV and often leads to kidney failure. Persistent urinary incontinence is present in as many as 50 percent of patients. Urodynamic studies indicate that bladder function deteriorates with time: in early life, the



bladders are hypercontractile—characterized by small capacity, high-pressure detrusor contractions, and high voiding pressures. Subsequently, the patterns change with PUV patients developing abnormally large capacity bladders and experiencing emptying difficulties, indicating an evolving bladder decompensation. The degree of bladder dysfunction in patients is correlated with loss of renal function.

Numerous approaches have been tried to improve postnatal outcomes in PUV patients. *The possible*

benefit of early delivery to improve renal outcome needs to be weighed against the risk of pulmonary immaturity, and to date, there have been no studies documenting the actual benefit of early delivery. Vesico-amniotic shunts have been placed for many years with little positive impact on kidney function, although the disappointing results might reflect overly stringent patient selection. Overall, *fetal intervention is plagued by the lack of both an accurate diagnosis of bladder outlet obstruction and a reliable indicator of postnatal renal function.*

Postnatal treatments consist of immediate bladder drainage, followed by endoscopic valve ablation. These children often still have a poor prognosis for both renal function and urinary continence. Consequently, a more proactive management is now being advocated. Some clinicians suggest upper urinary tract diversion when early bladder drainage does not improve renal parameters, while others advocate the early use of clean intermittent catheterization or overnight drainage, similar to that used with neuropathic bladder. *Pharmacologic intervention to relax the bladder outlet or bladder muscle have been helpful in some cases; why only some patients respond to this approach is not known.*

Pathophysiology of Bladder Obstruction

Proper urine storage and evacuation by the bladder depends on: (1) appropriate tissue viscoelasticity, (2) reflex peripheral-spinal neuromuscular control, and (3) central nervous system modulation of neuromuscular reflexes to coordinate bladder and sphincter function. These three elements undergo progressive integration during development and postnatal maturation, and by late development *in utero*, the bladder is already filling and emptying. At birth, reflex voiding is occurring between one and two dozen times per day. Maintaining a normal frequency and volume of bladder filling and emptying may be important to long-term bladder function.

Obstruction leads to complex changes in the dynamic properties of the bladder, including increased voiding pressures, and a decrease in the volume required to trigger the voiding reflex, or an uninhibited voiding reflex. Later changes may lead to bladder decompensation. Sensory nerve changes that occur with obstruction may cause urinary frequency or urgency, and decreased appreciation of bladder filling. The variability in observed bladder pathology suggests that the obstructive process—and perhaps the possibility of its reversal—may be quite different in the developing bladder as contrasted with the mature bladder. *The cellular mechanisms by which obstruction leads to changes in bladder function are largely unknown*, but results from some initial investigations have suggested several promising lines of research. The stretched bladder urothelium secretes signaling molecules that could mediate broad effects on surrounding tissues, including proliferative effects on bladder muscle. Obstruction damages peripheral nerves, thereby altering peripheral and CNS pathways mediating bladder function. The contractility of smooth muscle bundles is greatly reduced following obstruction. Other *important topics for investigation include the role of extracellular matrix in the bladder's response to obstruction and the consequences of damage to the vasculature perfusing the bladder.*

Priorities for Basic Research

- Determine how the urothelium functions as a pressure sensor; characterize the relevant cellular signal transduction mechanisms.
- Investigate how and to what extent obstruction causes peripheral and central nervous system damage, and how it affects the vasculature.
- Elucidate cholinergic and adrenergic function in obstructed bladder muscle.
- Characterize the dynamic composition and structure of the bladder extracellular matrix. Define the role of the ECM in pathogenesis caused by obstruction.

- Define the role of angiogenesis as a response to, or as a mediator of, fibroproliferative change and ECM remodeling.
- Determine the impact of ischemia on the smooth muscle cells of the bladder.

Priorities for Translational Clinical and Research

- Determine how developmental timing of obstruction determines pathology.
- Develop obstruction models that are more appropriate to human disease in terms of severity, duration, and location of the obstruction. Use existing transgenic animals to study the role of specific genes in bladder obstruction.
- Develop methods for more accurate diagnosis of prenatal PUV and prediction of long-term renal function.
- Conduct randomized, controlled trials to assess fetal interventions.
- Define the relationship between the development of oligohydramnios and postnatal pulmonary function and how a finding of oligohydramnios should guide prenatal intervention.
- Conduct trials to evaluate new methods of managing the obstructed bladder to improve bladder and renal function.
- Assess the quality of life in PUV patients and families.

Infrastructural Needs

- Unimpeded sharing of mouse strains relevant to urinary tract obstruction
- A clinical registry of PUV patients and banking of PUV patient tissue samples

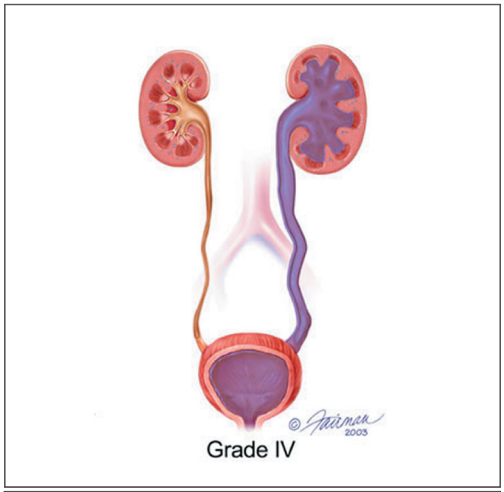
4. Vesicoureteral Reflux

Summary

Vesicoureteral reflux (VUR) affects 1 percent of children and is a developmental defect in which an abnormal attachment of the ureter to the bladder causes retrograde flow of urine into the ureter and kidney. The most important complication of VUR is an increased risk of a urinary tract infection leading to renal damage or scarring. The severity of the reflux and its complications varies from cases where renal scarring is present at birth (these children account for most cases of subsequent renal failure) to the more prevalent mild and moderate cases where kidney damage is not present at birth and where the reflux is likely to resolve spontaneously. Milder cases are generally treated by antibiotic prophylaxis, which is effective in preventing UTI and its complications. The long-term side effects of the antibiotics are unknown; there is also concern about the resulting emergence of resistant bacterial strains. New clinical trials will be needed to determine if withholding of antibiotics until an infection is suspected is advisable. Another challenge is to determine in which cases a surgical procedure (e.g., open surgery to recreate the valve between the ureter or bladder or cystoscopic treatment by subureteral injection of a bulking agent) is recommended instead of medical therapy.

Health Impact

It is estimated that 1 percent of children have VUR and approximately 50,000 new cases are diagnosed annually, making it the most common inherited anomaly of the urinary tract. VUR may predispose an individual to kidney infection, which can cause kidney damage or scarring and significant related morbidity, including reduced renal function,



In relatively severe type IV vesicoureteral reflux, urine refluxes all the way up the ureter, with marked dilation of the ureter and calyces. (© Fairman Studios LLC 2003)

hypertension, and impaired growth. In the past, kidney failure in children was attributed to VUR in as many as 20 percent of cases. Currently, only 3 to 5 percent of children with kidney failure have VUR, with the decreased incidence attributed to improved diagnosis and treatment of both VUR and UTI. However, *the long-term effects VUR in terms of reflux-related kidney damage are not well documented, as national renal transplantation registries do not accurately identify reflux as the underlying cause of renal failure.* While antibiotic prophylaxis has been shown to be effective in preventing UTI and its complications, the treatments are costly and may require many years of observation, including surveillance of urinary cultures and periodic cystography. *There is concern about the possible adverse side effects of long-term antibiotic usage and the accompanying emergence of resistant bacterial strains.*

Clinical Presentation and Treatment

Pathogenesis of Renal Scarring

Kidney damage associated with VUR can be present at birth or it may occur after a UTI. Children with the most severely affected kidneys at birth account for the majority of individuals who develop kidney failure. Unfortunately, the etiology of prenatal kidney damage is unknown. Children born with VUR without renal complications are at significant risk for subsequent kidney damage as a result of UTI. *The mechanism of scar formation is incompletely understood, and predicting which children with VUR are most likely to develop kidney scarring is not possible at present.* Factors such as age, gender, reflux grade, ethnicity, voiding dysfunction, and genetic determinants may play a role. Other than antibiotic treatment, methods to minimize the severity of kidney damage following UTI are unknown.

Detection and Evaluation

Currently, the diagnosis of VUR can be made only by voiding cystography (voiding cystourethrogram or radionuclide cystogram) in which a catheter is inserted through the urethra into the bladder, and images of the bladder are obtained during filling and voiding. The severity of VUR is graded on a scale of I (least severe) to V (most severe). The procedures produce discomfort, and for some children they are traumatic; in some centers, mild sedation or conscious sedation has been utilized to reduce the trauma of the catheterization. Cystography exposes the ovaries or testicles to radiation. Typically, many children with VUR will undergo serial cystography to monitor the status of the reflux condition.

Kidney imaging includes an ultrasound to assess hydronephrosis and kidney size, and some children undergo an intravenous pyelogram or radionuclide kidney scan to determine whether there is kidney damage. In complex cases in which there are questions regarding urinary tract anatomy, CT or MR scans are used. Abnormal kidney imaging does not predict the presence or absence of VUR.

Screening

Reflux is usually diagnosed in children after a UTI and in their siblings and offspring. Although the genetic basis of the condition is not known, 40

to 50 percent of siblings will have asymptomatic VUR. Diagnosis of VUR in asymptomatic children can prevent its infection-related complications, however, *the advantage of preventive management is unproven.* VUR also is found in infants with dilatation of the kidneys *in utero* and is the most common treatable cause of prenatal dilation of the kidney. In these cases, it is more likely to be severe and involve both kidneys.

Medical Therapy

The primary goals of therapy in children with VUR are to prevent UTI and kidney damage. Many, although not all of those with mild or moderate VUR, have spontaneous resolution in later childhood. Factors such as gender, age, voiding dysfunction, reflux grade, and circumcision status may determine the risk of VUR-related morbidity. In prospective randomized trials, continuous low-dose antibiotic prophylaxis has been shown to be generally effective in the prevention of both urinary infection and the development of new renal scars. Consequently, most children with VUR are managed initially with daily antibiotic prophylaxis. However, the medical regimen is costly and may require many years of observation, surveillance of urinary cultures several times per year, and periodic cystography. Recent studies have implied that some children with VUR, particularly those with less severe VUR, may not need daily antibiotic prophylaxis. However, the general validity of these studies has been questioned, and discontinuing prophylaxis has not become common practice in the United States.

Voiding Dysfunction

There is an association between lower urinary tract (bladder and sphincter) dysfunction and congenital VUR. *In utero* voiding dysfunction may account for the high grade of neonatal reflux seen predominantly in male infants. In older children, voiding dysfunction as well as abnormal bowel habits may develop during the toilet training years, and the untreated condition has been associated with increased rates of breakthrough UTI, kidney scarring, and surgical failure. *Evaluation and management of voiding function should be an integral part of the treatment of every child with VUR, but currently no standard definitions or validated symptom scores for it exist. The appropriate role of invasive bladder testing in VUR patients with voiding dysfunction is unclear, and the benefits of medications for bladder function, biofeedback, and bladder training are unknown.*

Surgical Therapy

Surgical therapy—to eliminate VUR and thereby minimize the risks of kidney infection and damage—is often recommended for individuals who have breakthrough infection or have persistent high-grade reflux. The procedure recreates the valve between the ureter and bladder and has a success rate of more than 95 percent. In recent years, improvements in perioperative management have reduced hospital stays to 1 or 2 days in many centers. Laparoscopic ureteral reimplantation has been studied at a few pediatric urology centers. A new outpatient approach not requiring an incision is cystoscopic treatment by subureteral injection wherein a bulking agent with the consistency of toothpaste is slowly injected into the ureteral opening, changing its shape and providing improved backing to the ureter. The success rate is up to 85 percent, although some children need two or three injections. *There are ongoing concerns regarding the durability of bulking agents. Children treated with FDA-approved Deflux (dextranomer/hyaluronic) have a 10 percent VUR recurrence rate at 3 years, and its safety and efficacy beyond 5 years are unknown.*

Clinical Trials/Outcomes

The optimal management of children with reflux must be determined based on a variety of projected health outcomes subsequent to different treatments.

These outcomes include UTI, hypertension, somatic growth, complications during subsequent pregnancy, the need for further medical testing, VUR resolution, complications from medical and surgical therapy, and renal outcomes like scarring, growth, and function.

To date, only three prospective randomized trials comparing medical management (daily antibiotic prophylaxis for 2 to 5 years) to open surgical treatment in children with VUR and UTI have been performed. Most of the children in these trials had moderate or severe reflux, often with kidney scarring at the outset. Although the incidence of new renal scarring between the surgical and medical arms was similar, children who had undergone surgery and discontinued antibiotic prophylaxis were significantly less likely to develop kidney infection than those who still had reflux and were receiving daily antibiotic therapy. In addition, at the end of 5 years, the majority of children in the antibiotic treatment arm still had VUR. Currently, however, many cases of VUR detected through screening, are low grade.

The role of endoscopic therapy remains unclear. A recent meta-analysis of more than 100 reports of children undergoing subureteral implantation has shown that the VUR resolution rate is high, but other outcomes were not reported in most series. However, the incidence of UTI following endoscopic therapy appears to be significantly lower than following open surgical correction.

Other considerations relevant to VUR clinical practice are ongoing concerns in the medical community regarding the emergence of resistant strains of infectious organisms caused by widespread antibiotic usage, as well as questions as to the long-term safety of daily antibiotic prophylaxis. *Although daily antibiotics are considered standard therapy in children with VUR diagnosed following a UTI, there are no contemporary trials evaluating the relative effectiveness of close clinical monitoring in which antibiotics are withheld until a UTI is suspected ("observation therapy").*

Priorities for Basic Science Research

- Investigate the genetic basis of kidney development and the genetic/developmental aberrations that lead to VUR.
- Create genetically engineered animal models of VUR relevant to human disease.
- Develop noninvasive radiologic or biological methods for detecting and monitoring VUR.
- Elucidate the molecular basis of renal scarring after UTI.
- Identify genetic or other biomarkers that predict reflux or kidney scarring and failure.

Priorities for Translational and Clinical Research

High Priority

- Determine the safety of observation therapy in children with VUR and UTI compared to conventional medical therapy (daily antibiotic prophylaxis), as well as selection criteria for patients suitable for this approach.
- Evaluate the patterns of bacterial resistance in children receiving antibiotic prophylaxis.
- Assess the psychological impact of cystography on children with VUR using contemporary quality of life instruments.
- Apply contemporary outcomes instruments to assess quality of life and health care costs in children with VUR who have been treated in different ways.
- Evaluate the long-term safety and efficacy of currently available injectable materials.
- Determine the effectiveness of immediate endoscopic therapy compared to conventional medical therapy.

Medium Priority

- Determine the role of voiding dysfunction in the development of VUR in newborns and older children and its role as a risk factor for complications of reflux.
- Revise national registry mechanisms to ensure the accurate prospective collection of data. Establish, using registry data, the true incidence of reflux-related renal insufficiency.
- Determine whether VUR should be corrected before adolescence.
- Assess the risk of hypertension in adolescents and young adults with lesser amounts of renal scarring.
- Develop new materials for endoscopic therapy that are safer and more durable.
- Determine if circumcision can eliminate the need for prophylaxis in boys with VUR.
- Determine whether VUR increases the risk of lower urinary tract infection.

Low Priority

- Assess the benefit of sedation or hypnosis during cystography, as well as the benefit of having support personnel present for the procedure.
- Determine if bladder pressure during VUR has prognostic value for predicting spontaneous resolution.
- Develop criteria for reflux screening in newborns on whom a dilated kidney was discovered prenatally.
- Determine which family members of children with reflux should undergo screening and treatment.
- Determine if non-surgical alternatives to prophylactic antibiotics are feasible.
- Devise better methods of diagnosing and treating voiding dysfunction in children with VUR.
- Develop improved techniques of laparoscopic anti-reflux surgery
- Determine risk factors for the most severe complications of reflux occurring during pregnancy.
- Conduct prospective studies of young adults with both corrected and uncorrected reflux to assess clinical risk factors for late complications of reflux.

5. Urinary Tract Infection

Summary

The frequency of urinary tract infections and their potential for causing kidney damage and other related morbidity make them a major challenge for pediatric urology research. The complex mechanisms by which bacteria infect the urinary tract and, in cases of pyelonephritis, cause renal scarring should be topics of investigation. Treatments to interfere with uropathogenetic colonization without prolonged antibiotic use and to prevent renal scarring are needed. Clinical management would benefit greatly from new methods that would permit immediate identification of infectious bacteria in patients, as well as improved technologies for post UTI.

Health Impact

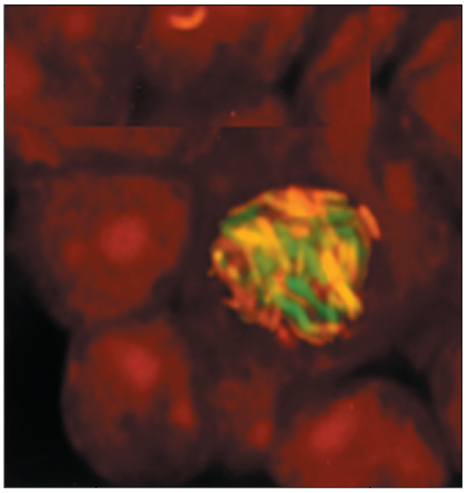
Urinary tract infections (UTIs) are frequent in children of all ages (3 percent of prepubertal girls and 1 percent of prepubertal boys are diagnosed annually), and they cause significant morbidity that can lead to renal failure. Although they are not reportable diseases, and accurate incidence data are not readily available, UTIs have been estimated to

account for 40,000 hospitalizations each year at a cost of $180 million. The impact is much greater when one takes into account that UTIs are generally treated on an outpatient basis; they account for 1.1 million visits to pediatrician's offices and 94,000 visits to emergency departments annually. No evidence is available regarding the cost of medications, hospitalizations, office visits, tests, or the burden posed by long-term care for UTI and complications such as hypertension, complications during pregnancy, and renal scarring.

Clinical Description and Treatment

UTIs in children can be classified according to probable site of disease. Cystitis or infection of the bladder, is the most prevalent; pyelonephritis refers to infection of the kidney. On the basis of clinical symptoms, it may be difficult to determine the site of infection, and furthermore, symptoms of UTI (dysuria, frequency, urgency, fever, and back and abdominal pain) may be non-specific. Routine urinalysis results, although quickly available, are usually unreliable. The diagnosis of UTI is made with a urine culture, the results of which are not available for at least 24 hours.

Bacteria enter the urinary tract from the rectum, and infection depends on attachment to the urinary tract wall by specialized surface structures called pili. Ascent of the bacteria to the kidneys can occur through either the ureter or through spread from lymph or blood flow. Pyelonephritis is the most frequently occurring serious bacterial illness in febrile infants and children, and it results in kidney scars in approximately 20 percent of cases. The reasons why some children develop scars while others do not is currently unknown. At particularly high risk for UTI are neonates, uncircumcised infant boys, girls older than 3 months, children with urinary tract anomalies or voiding problems, children with neurologic abnormalities affecting the bladder, and hospitalized children (UTIs are the most frequent nosocomial infection in children). Evidence suggests a lower incidence of UTI in African Americans. Among infants with UTI, 18 percent will develop recurrences.



During urinary tract infection, quiescent reservoirs of bacteria form in the bladder mucosa, helping to explain the limited effectiveness of antibiotics. Rod-shaped *E. coli* are labeled with green fluorescent protein (Courtesy of Dr. Scott Hultgren, Washington University School of Medicine).

Treatment is generally based on age and severity of clinical presentation. In general, neonates are admitted for intravenous antimicrobials. Children appearing very sick, toxic, or unable to take fluids may require hospitalization as well. In most cases, broad spectrum antibiotics (amoxicillin, cephalosporins, aminoglycosides, sulfonamides and fluoroquinolones) are used for 7 to 14 days. The emergence of bacteria resistant to frequently used antibiotics limits the efficacy of these drugs in treating UTIs.

Children with an initial UTI are generally evaluated with imaging studies for possible upper (kidney) or lower tract (bladder) abnormalities. These studies may include kidney and bladder ultrasound and a voiding cystourethrogram. *The necessity for performing renal ultrasounds following an initial episode of UTI when a prenatal ultrasound was performed close to birth is questionable. The role of kidney scans in the management of young children with UTI has not been evaluated systematically.*

Priorities for Basic Research

- Develop a better understanding of the genetic and molecular basis of bacterial uropathogenicity.
- Establish procedures to prevent uropathogenic microbial shift (resistance).
- Identify host factors that determine the risk, severity, and recurrence of bacterial colonization and infection.
- Elucidate the role of the immune response in the course of UTI.
- Characterize the mechanism of renal scarring as a complication of UTI.
- Identify biomarkers predictive of the complications of UTI.

Priorities for Translational and Clinical Research

- Determine the prevalence of UTI in various ethnic and racial groups.
- Determine the correlation of UTI signs and symptoms with the level of infection in children older than 24 months.
- Describe the natural history of asymptomatic bacteriuria.
- Improve methods to characterize the pathogenicity of clean voided specimens in toilet-trained children (3 to 13 years).
- Develop new technologies for immediate identification of bacteria and sensitivities.
- Optimize methods for post-UTI imaging.
- Determine the utility of prenatal ultrasonography in UTI evaluation.
- Develop improved methods for imaging of inflammation and scarring.
- Develop approaches for prevention of uropathogenic colonization.
- Explore non-antimicrobial interventions and treatments.
- Evaluate existing antibiotics more thoroughly, and develop new antibiotics.
- Develop means of preventing renal scarring using adjunctive therapy.
- Determine the efficacy of antibiotic prophylaxis in preventing recurrences and renal scarring following acute pyelonephritis.

6. Neurogenic Bladder

Summary

Abnormal bladder function can have profound consequences for a child's health such as constant urinary leakage and, ultimately, deterioration of kidney function. An improved understanding of lower urinary tract dysfunction and its management is critical to the physical, social, and psychological well-being of children with neural abnormalities affecting bladder function. The following major recommendations are made for future research:

- ***Investigate, using tools and approaches from developmental genetics, molecular and cell biology, neurophysiology, and biomechanics, the progression of the neurogenic bladder in order to develop novel therapies.***
- ***Conduct multicenter prospective studies of the value of early, aggressive treatment for children with neurogenic bladder.***
- ***Conduct longitudinal studies of the long-term outcomes for children with neurogenic bladder, including assessments of cancer risk, renal function, continence, growth, and quality of life issues.***

The initial stages of bladder function begin in the older fetus as it develops reflex emptying. The complex development of neuronal control of the bladder continues after birth and throughout the next few years of normal child development. The bladder/urethra complex is responsible for the safe storage and efficient expulsion of urine, and when the neural input to this complex is abnormal due to maldevelopment, trauma, or disease, a "neurogenic bladder" results. Neurogenic bladders may exhibit problems with safe, low-pressure storage of urine and/or complete low-pressure expulsion of urine.

Viewed very broadly, the condition has diverse origins. The most common is spina bifida, or myelomeningocele. Other causes include tethered cord, spinal cord injuries, and tumors. Several conditions produce patterns similar to that of a neurogenic bladder and may have similar pathophysiology, including congenital bladder outlet obstruction (i.e., posterior urethral valves), abnormalities of bladder development (exstrophy, ureterocele, ureteral ectopia, and prune belly syndrome), and dysfunctional voiding. Spina bifida, a congenital defect in which part of the spinal column is imperfectly closed, is the most common underlying cause of the "neurogenic bladder," and it affects 3,000 newborns in the United States each year. Ninety-five percent of patients with spina bifida have some degree of bladder dysfunction, with major economic and social impact on the child's well-being. Spina bifida is linked to dietary deficiencies, particularly insufficient folic acid, but regional differences in its incidence not explicable by diet suggest other factors, including genetic predisposition, in certain individuals. Prenatal spine closure has decreased the incidence of hydrocephalus, but not the severity of neurological bladder impairment.

Health Impact

Bladder dysfunction resulting from neurological abnormalities is a common and challenging problem seen by pediatric urologists. Neurogenic bladder dysfunction can lead to upper urinary tract dilatation (hydronephrosis), vesicoureteral reflux, urinary tract infection, urinary tract stones, urinary incontinence, renal deterioration and, ultimately, renal failure requiring dialysis. In addition to causing a dramatic alteration in the quality of life of the child, these clinical problems translate into millions of dollars in annual health care costs for hospitalization, surgery, and imaging evaluation. Additional long-term health care expenditures are associated with followup visits, surgery, urodynamic measurement, chronic medication, diapers, caretakers, lost work for parents, and multidisciplinary health care teams.

Clinical Description and Treatment

Most children with neurogenic bladder present at birth suffer from a recognized neurological disorder. They have long-term problems with bladder control and need clean, intermittent catheterization several times a day in combination with anticholinergic drugs. This regimen is inadequate for many children, who ultimately require multiple surgical interventions to allow adequate urinary storage. *Although studies now suggest that early intervention improves ultimate bladder compliance and results in fewer surgical interventions, there is a treatment burden to families in instituting these programs.* Neuromodulation and bladder stimulation have also been shown to improve bladder function in a few patients.

Surgical intervention may include bladder augmentation or replacement with portions of intestine and bladder neck procedures to improve continence. Since none of these treatments is ideal, many children suffer from the consequences of inadequate and improper urinary storage, including complications such as bacteriuria, stones, continual leakage, and, in the most severe cases, deterioration of renal function related to persistent high bladder pressures. Even those successfully treated with bladder augmentation may suffer long-

term complications of the operation, including urinary tract infection, stone disease, metabolic derangements leading to bone and growth problems, spontaneous bladder perforation, and an increased long-term risk of bladder cancer.

Priorities for Basic Research

- Investigate the development of the normal and neurogenic bladder; one focus should be the role of growth factors and integrin/ECM interactions in the complex signaling networks that mediate normal and abnormal bladder development and innervation.
- Define the intrinsic changes in smooth muscle associated with neurogenic bladder, including the mechanisms that lead to aberrant deposition of connective tissue within muscle bundles and the development of fibrosis.
- Elucidate the roles of various modulators of bladder tone and contractility, including prostaglandins, angiotensin, nitric oxide, and others.

Priorities for Clinical and Translational Research

- Improve surgery and other fetal interventions for neurogenic bladder.
- Identify the basis of regional differences in the incidence of spina bifida.
- Develop minimally invasive urodynamics methodologies for measuring bladder pressure, with one goal being improved patient stratification prior to therapy.
- Conduct clinical trials that establish the usefulness of early aggressive management of neurogenic bladders.
- Evaluate alternative therapies for neurogenic bladder, including neuromodulation and bladder stimulation.
- Continue research in tissue engineering of bladders. Investigate whether tissue from neurogenic bladder patients can be used to regrow normally functioning bladder tissue.
- Conduct long-term studies to define the risk of long-term complications related to bladder augmentation, including metabolic effects and tumor formation.
- Perform long-term quality of life evaluations of children with neurogenic bladder.

Infrastructural Needs

Clinical and translational research in the study of children with neurogenic bladder is hampered by the lack of well-trained, well-funded physician scientists with interest in this area. Training of academic urologists capable of undertaking large prospective clinical trials and translational research is essential.

- Make available training awards for undergraduate and medical student mentorships in established laboratories studying neurogenic bladder, as well as awards for physician scientists with an interest in the field.
- Establish a neurogenic bladder patient registry and national tissue bank.
- Provide funding for multidisciplinary and multicenter collaborative studies relevant to neurogenic bladder disease.

7. Voiding Dysfunction

Summary

Voiding dysfunction is a general term encompassing several syndromes in which the child fails to empty the bladder normally, has abnormal urgency and/or frequency, or incontinence. Although several clinical forms have been identified, a universal classification system for urologic practice is lacking and should be a major priority. Epidemiological research that could help establish causes and long-term consequences is called for. Improved urodynamic techniques, selective therapeutics, and the identification of a valid biomarker for various syndromes could lead to more effective treatment of this common and complex condition.

Infants void frequently—as many as 20 voids per day are normal—largely without being aware of it. By the age of 1 or 2, a child has developed an awareness of bladder fullness and the ability to start and stop voiding. As they grow older, children develop better control, store more urine, and void less frequently. The mean age for achieving toilet training in the daytime is about 2 years old. With continued maturation and growth, this process of increasing bladder capacity and decreasing voiding frequency continues, until by puberty, an adult pattern is achieved: four voids while awake and a bladder capacity of approximately 12 ounces. Development is such that children first achieve bowel control, then daytime urine control, and finally night-time urine control.

As the bladder stores urine, it gradually expands to maintain low pressure. Voiding involves coordinating muscles to relax the bladder neck and sphincter and to contract the bladder (lack of coordination in this process is termed dyssynergy). Voiding dysfunction, the disturbance of normal bladder storage and emptying, has a spectrum of clinical presentations ranging from minor urgency and frequency to severe syndromes that damage bladder and kidney function.

The causes of voiding dysfunction are not clear. Adverse psychosocial support for toileting, inadequate cognitive development, and genetic factors have been suggested. Several clinical forms are recognized: the Hinman syndrome is typified by children whose urinary tracts are severely damaged by dyssynergy. The bladder and sphincter muscles working against each other markedly raise bladder storage pressures, resulting in vesicoureteral reflux, hydronephrosis, UTIs, and even renal failure. Infrequent voiding or "Lazy Bladder" syndrome presents with children who delay voiding habitually by maneuvers such as sitting on the heel of their foot. Constipation, often indicated by encopresis (fecal soiling), is frequently associated with and aggravates many forms of voiding dysfunction. Other forms include the overactive or unstable bladder with urgency and frequency, giggle incontinence, and post-void wetting. Voiding dysfunction significantly affects children with vesicoureteral reflux, nearly half of whom will show some of its symptoms and experience an increased incidence of breakthrough urine infection and ureter reimplantation.

There are reports of familial voiding dysfunction associated with Down's syndrome and the Ochoa syndrome, the gene for which has been tentatively mapped to chromosome 10q23-q24.

Health Impact

The prevalence of voiding dysfunction in children is estimated to be around 20 percent, with girls more frequently affected than boys. However, it should be noted that urinary incontinence encompasses a heterogeneous family of disorders and the economic burden of voiding dysfunction in children is difficult to assess. An estimate of $15 to $20 million in annual costs from voiding dysfunction of all etiologies, primarily stemming from outpatient visits, has been made.

Clinical Description and Treatment

Children with voiding dysfunction may present with wetting, UTI, constipation, urgency, frequency, and painful voiding. They appear normal, with no neurologic deficits or urinary anomalies. It is important to elicit an accurate history of toilet habits; a questionnaire of elimination habits is helpful and can quantify severity. Urine is examined to evaluate for infection. Ultrasound can be useful but is not always needed. Plain abdominal films are helpful in assessing constipation and the appearance of the bony spine, and MRI can show spinal cord abnormalities. Urodynamic studies may be done to demonstrate dyssynergy and bladder instability. Cystoscopy is usually not necessary.

Treatment is multimodal and directed by the child's age, symptoms, and needs. Behavioral therapy with biofeedback can correct aberrant toileting, and computer games have been used to conduct and reinforce biofeedback training. However, biofeedback is often not covered by insurance carriers because of a lack of evidence validating its efficacy. "Lazy" bladders can be treated by a scheduled voiding program. Bowel regimens can correct the fecal soiling and constipation, which may be contributing factors. Anticholinergic drugs can dampen bladder spasms, and alpha-blockers are useful to help relax the bladder neck and sphincter. More severe cases may require intravesical instillation or injection of drugs such as botulinum toxin, although these are short-term solutions. Very poor bladder emptying can be managed by clean intermittent catheterization.

Priorities for Basic Research

- Conduct epidemiological research on possible causes of aberrant toilet training, including adverse psychosocial support for toileting, inadequate cognitive development, and genetic factors.
- Investigate potential molecular mechanisms underlying voiding dysfunction and relating to the development of neural control of the bladder.

Priorities for Clinical and Translational Research

- Develop a classification system for voiding dysfunction, including a validated symptom score scale to assess individual cases objectively.
- Develop more sensitive urodynamic testing methods appropriate for children; investigate the use of telemetry technology to permit continuous or "at home" monitoring in a more natural environment.
- Define the effectiveness of biofeedback training and research cost-effective biofeedback programs; promote development of interactive biofeedback computer programs; determine if biofeedback training can reduce the incidence of UTI and severity of VUR in patients with voiding dysfunction.
- Determine the long-term effects of voiding dysfunction, including its association with UTI, hypertension, kidney scarring, renal failure, effects on sexuality and social development, and possible psychological consequences.
- Assess the long-term impact of performing intermittent catheterization on acquisition of urethra stricture, UTI, and psychological health.
- Identify a biomarker for voiding dysfunction among families with multiple affected members.
- Develop more selective agents (e.g., anticholinergics, alpha blockers, calcium channel blockers, botulinum toxin) that act specifically on the bladder. Investigate alternative delivery methods such as intravesical instillation of drugs.
- Encourage development of multidisciplinary programs involving pediatricians, psychologists, psychiatrists, gastroenterologists, neurologists, and neurosurgeons to better treat the condition.

- Improve awareness and understanding of voiding dysfunction among primary care doctors, allied health workers, families, and patients.
- Assess the therapeutic role of complementary medical methods, such as acupuncture for dysfunctional voiding.

8. Enuresis

Summary

The physical basis of many cases of nocturnal enuresis is still difficult to determine. Renal deficiencies, hormonal abnormalities, small bladder, and psychological and social factors have been identified as playing a role in its etiology, but continued research to clarify its neurophysiological basis is needed. Clinical trials can validate and optimize current pharmacological and behavioral treatment modalities.

Nocturnal enuresis (NE) results when the bladder contracts during sleep without the child's control. While wetting the bed at night is considered normal in infants, society expects night dryness by age 5 years. However, NE affects about 15 percent of 5-year-old children; from that age, prevalence tends to diminish steadily so that the rate is only 3 percent in adolescents. NE is a heterogeneous disorder that may be caused by overlapping problems in the kidneys, bladder, and central nervous system. In 50 percent of bedwetters, there is a deficiency of antidiuretic hormone (ADH), and the normal nightly decrease in urine production does not occur. Another renal deficiency that may cause enuresis is a lack of aquaporin, a protein that transports water out of the urinary tract. Some children with NE show a sleep disorder characterized by a reduced perception of bladder filling and the inability to inhibit urination; bedwetting in children with deep sleep is worsened by a small bladder. *Children with NE have a greater tendency to be diagnosed with attention deficit hyperactivity disorder (ADHD), which may need to be addressed as part of the treatment plan.*

Health Impact

Nocturnal enuresis affects about 500,000 children in America and is responsible for about one-third of outpatient visits for wetting; the annual rate of outpatient visits has doubled during a 7-year period, to 200 per 100,000 children. *In America, the yearly medical cost of NE is estimated at $20 million. In Europe, the cost of not treating enuresis was more than treating it.*

Clinical Treatment

Nocturnal enuresis has been viewed as an untreatable condition by the public. In fact, it is a legitimate condition that can be treated with pharmacological and behavioral interventions.

Imipramine addresses both the bladder and central nervous system abnormalities. Initial response rates approximate 50 percent; however, the long-term cure rate is only 25 percent. A serious drawback is that imipramine can be lethal. Oxybutnin helps manage NE associated with bladder overactivity in 20 percent of children. Combination therapy with imipramine and oxybutnin is sometimes prescribed, but it does not provide a lasting cure. DDAVP, an antidiuretic hormone analog, improves the kidney's concentrating ability in about 50 percent of children, but unfortunately about 30 percent of those showing improvement relapse after the medicine is stopped. A small bladder size may reduce the success rate of drug treatment.

The moisture alarm, which is a conditioning device, is the most effective treatment for NE, with up to 90 percent of children who initially respond being cured, and this course of treatment is associated with an

increase in bladder capacity. Many parents resist this approach because it is very labor intensive.

Priorities for Basic Research

- Research should be directed to improved understanding of the physiological basis of nocturnal enuresis, including such topics as water transport by the kidney, control of bladder function by the central nervous system, and bladder control during sleep.
- Identify genetic factors associated with this disorder.

Priorities for Translational and Clinical Research

- Conduct clinical trials to determine the most cost-effective and expedient treatments.
- Improve awareness of NE as a disease entity.

9. Exstrophy-Epispadias Complex and Cloacal Malformation

Summary

The exstrophy-epispadias complex is a set of developmental anomalies involving the urinary, genital, and intestinal tracts, as well as the musculoskeletal system. Cloaca is a malformation in the female wherein the urinary, genital, and gastrointestinal tracts exit the body as a single opening. These rare conditions require extensive surgical intervention to achieve urinary tract function. To properly evaluate treatments, long-term clinical trials assessing outcomes such as bladder and kidney function and quality of life are needed. Establishment of a patient registry is a vital prerequisite for adequate clinical trials.

Exstrophy-epispadias complex is an all-encompassing term for a spectrum of congenital anomalies of the bladder and urethra. As an example, in bladder exstrophy the bladder, bladder outlet, and urethra are exposed as an "open book" on the lower abdominal wall. The cause of exstrophy is not clearly understood, and few surgically created animal models and no natural models of this condition exist. Major goals in the management of exstrophy are preservation of normal kidney function, development of adequate bladder function, including urinary continence, and provision of acceptable cosmesis, and function of the genitalia. To achieve these goals, multiple complex surgeries, lengthy hospitalizations, and intense followup are typically required. Cloaca is a rare and complex malformation in the female wherein the urinary, genital and gastrointestinal tracts exit the body as a single opening (common channel), having serious consequences for bladder and kidney function. Spinal cord abnormalities are present in approximately one-third of these patients

Health Impact

Exstrophy occurs in one in 30,000 live births while epispadias is seen in one in 400,000. Cloaca occurs in approximately one in 50,000 live female births. Although they are rare, the impact of these conditions is enormous. Patients face multiple and often life-long challenges: urinary tract infections that can be complicated by vesicoureteral reflux (backflow of urine from bladder to kidney), urinary incontinence, sexual dysfunction, and problems with fertility. Of grave concern is that some of these patients develop kidney failure. Multiple, complex surgical procedures are typically required, and lifelong evaluation and a dedicated caregiver are requisites. The economic costs to family and society are significant, and the impact of these conditions on childhood and family life is profound.

Clinical Issues

We highlight here some current issues in the clinical treatment of these disorders and the research initiatives needed to resolve them.

Exstrophy

Fetal Diagnosis and Intervention: Prenatal diagnosis of exstrophy has been described. However, evaluation of the sensitivity and specificity of prenatal diagnosis is critical for counseling. *Since there is no available treatment for the fetus, fetal intervention, potentially in the form of coverage or closure of the exstrophy defect, should be explored.*

Initial Surgical Management: Currently, there are two popular methods used to treat exstrophy: the multistage and the single-stage complete primary repair of exstrophy (CPRE) techniques. The only valid way to answer which of these treatment options, if either, provides superior outcome is to form multicenter groups committed to collaborative prospective studies. Similarly, the use of adjunctive surgical procedures such as osteotomy (partial incision of the pelvic bones to facilitate closure) in the newborn with exstrophy is sporadic among institutions and without consensus regarding indications.

Kidney Function: The majority of exstrophy patients begin life with normal kidney number and function. Unfortunately, approximately 20 percent develop renal damage and some kidney failure. The pinnacle of our priorities of care should be maintaining normal kidney function. A prospective evaluation of renal function alone, and with comparison to continence, may identify relationship(s) between these two important outcomes, as well as predictors of loss of renal functional loss.

Bladder Function/Urinary Continence: Following repair, reports of urinary continence rates vary from the 20 percent to 70 percent. *There is no standard definition of continence for this group of patients and standardization of nomenclature is warranted.* As continence is highly dependent upon bladder function, prospective evaluation of bladder function following either CPRE or the multistage repair with standardized urodynamic study would be informative in determining and comparing outcomes. Pelvic anatomical relationships—both skeletal and soft tissue, are abnormal in exstrophy—have implications for the necessity and timing of osteotomy, and significantly impact outcome. *Anatomical study via autopsy and radiologic imaging in the normal and exstrophic newborn would shed light on current surgical approaches and stimulate development of more appropriate and effective techniques for management.*

Long-term Outcome/Quality of Life: Long-term data on outcome in this group of patients is limited. *Basic questions remain unanswered: What is the chance of a newborn being dry and voiding? What is the chance of normal fertility? Can an affected female carry a pregnancy? What is the risk of bladder malignancy? Consequently, long-term outcome studies including documentation of "Quality of Life" issues are vital.* Sexual function in both males and females has been described in small series, but *a more detailed understanding of the sexual and fertility issues in these patients is needed.*

Gender: In some children born with cloacal exstrophy and a 46XY male genotype, the choice of the optimal gender of rearing is still a fiercely debated issue. A thorough, well-constructed and multidisciplinary retrospective evaluation of these patients (whether or not "gender reassigned") is needed.

Cloaca

Epidemiology/Pathophysiology: Currently, there are a number of genetically created animal models with cloaca. This has led to ongoing human genetic studies. Banking of DNA in these patients and their families would improve the chances of identifying genetic components to this problem.

Diagnosis and Management: Prenatal diagnosis has been reported, but the sensitivity and specificity has not been documented. As many families opt for termination once the diagnosis is made, an accurate evaluation of prenatal diagnosis is important. Recently, the role of total urogenital mobilization (TUM) for the management of these girls has been

described. This technique is now widely used, and there is no common alternative method to compare for short common channels. For longer common channels, separation of the vagina and urethra, and tubularization of the channel is still performed. *Standardized terminology (short versus long channel) for appropriate surgical care and valid comparison is needed.*

Kidney function: Kidney function is impaired in a significant number of these children and is associated with congenital kidney anomalies and late renal failure. Early, more aggressive management of the bladder has been described, but the impact of this on the kidneys has not been studied.

Bladder Function/Urinary Continence: Urinary and fecal incontinence is common, occurring in up to 60 percent of patients. The current effect of TUM on both short and long common channels has been described, yet needs further evaluation. *Detailed outcome of bladder function with urodynamic study is needed in these patients.*

Long-term outcome: Complete long-term outcomes of urinary tract, gastrointestinal tract, kidney, and sexual function are important, as are gynecological outcome and fertility rate. *A cohort study is vital to understanding the impact of this condition on patients. "Quality of life" studies would add greatly to the current literature.*

Priorities for Research

Our knowledge of basic, fundamental cause and effect relationships in exstrophy and cloaca are extremely limited. Therefore, studies that evaluate both environmental and genetic risk factors are needed. In addition, the development of animal models that clarify our understanding of the defect and its impact on bladder development and function at the basic level and provide further insight into optimal management would be valuable. The genetic construction of animal models with cloaca has led to ongoing genetic studies in humans. The rarity of exstrophy and cloaca makes scientifically valid clinical studies difficult as most centers see few patients.

- Continue to develop relevant animal models to further fundamental understanding.

Exstrophy

- Conduct a collaborative, prospective evaluation of kidney and bladder function for single and multistage approaches to management.
- Investigate long-term quality of life issues including sexual function and fertility.
- Fetal intervention, potentially in the form of coverage or closure of the exstrophy defect, should be explored.
- Conduct a prospective evaluation of renal function and continence in exstrophy patients and clarify the relationship between these two outcomes, as well as predictors of renal functional loss.
- Perform detailed anatomical characterization via autopsy and radiologic imaging in the normal and exstrophic newborn to shed light on current surgical approaches, and stimulate development of more appropriate and effective techniques for management.
- Investigate the developmental consequences of exstrophy on the bladder and pelvic floor on a molecular basis to enhance ultimate function potential.

Cloaca

- Document the sensitivity and specificity of prenatal diagnosis.
- Develop a standardized terminology (short versus long channel) for appropriate surgical care and valid comparisons.
- Perform detailed outcome studies with urodynamic measurements to assess bladder function in patients after reconstruction.

- Conduct a cohort study to assess quality of life and long-term outcomes such as kidney function, sexual function, fertility, and other relevant parameters.

Infrastructural Needs

Develop a national or international registry that would facilitate communication and collaboration between centers, and potentiate the prospective, randomized trials that are an absolute necessity if new treatments for patients with these rare conditions are to be developed.

II. Genital Tract

10. Development and Maldevelopment of the Genital Tract

Summary

Formation of the genitalia is a complex developmental process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. Understanding the molecular mechanisms of normal development is critical if we are to be successful in elucidating the causes of abnormalities of both the internal and external genitalia. Basic research in this area will be vital for prevention and alleviation of diseases such as hypospadias, epispadias, undescended testes, and uterine abnormalities.

Sexual Differentiation and Development in the Early Embryo

The early embryo is sexually "indifferent"—structurally the same in genetic males and females and bipotential; subsequent development into male and female genital tracts is determined by a complex set of interactions based on genetic, molecular, and ultimately, physiological processes.

Much of the development of the genital tract is determined by gonadal development. The sexually undifferentiated gonad is first observed histologically at 5 to 6 weeks post-conception as a thickening in the urogenital ridge, with differentiation into an ovary or testis beginning around the 7th week. Ovarian development was thought to be constitutive (i.e., in the absence of a specific genetic signal, an ovary will develop). Recently, however, genes that may induce ovarian development have been identified. The critical gene for testicular development is the SRY gene, found on the Y chromosome. Although numerous other genes are involved, the presence of SRY will, in nearly all cases, induce testicular development.

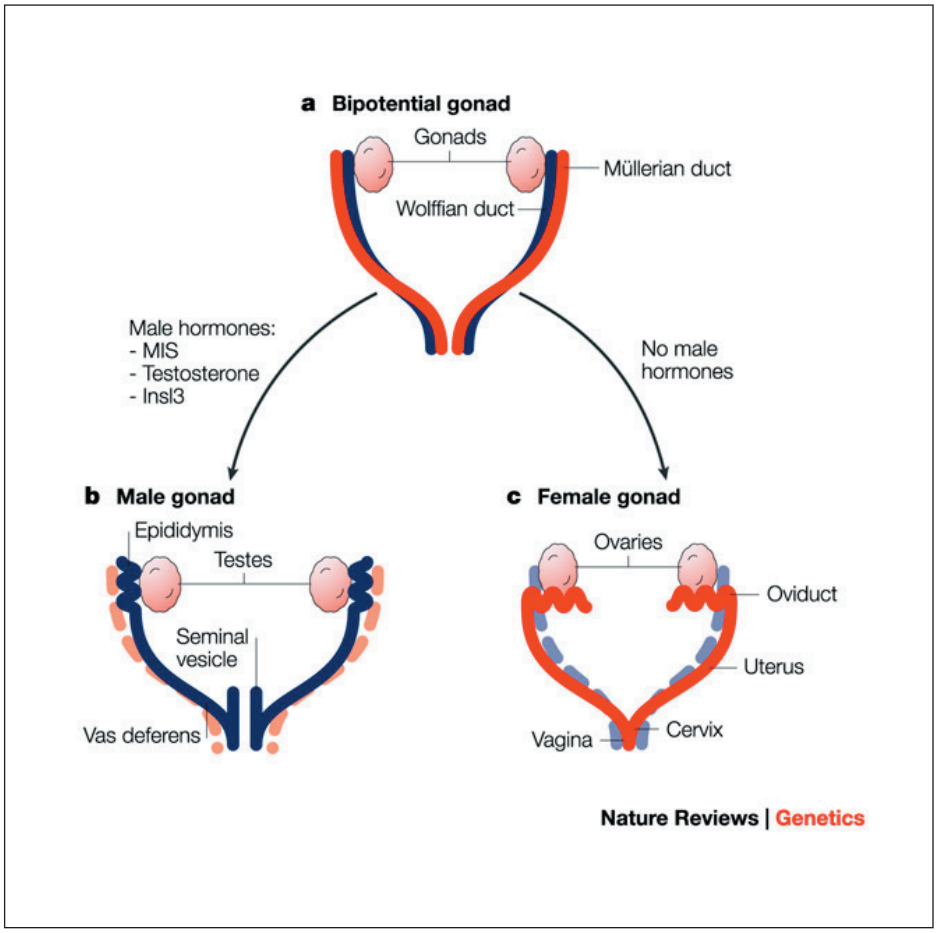
Alongside the indifferent gonads are two closely related ductal systems, the Wolffian and the Müllerian ducts. The Wolffian duct is originally the nephric duct and only later develops into a genital duct in the male fetus. Indeed, the Wolffian duct very early in development joins the cloaca, and the lower end of this duct gives rise to the ureteral bud, a critical element in the formation of the kidney. The Müllerian duct, in contrast, is purely a genital duct, developing somewhat later and not reaching the urogenital sinus until about the 9th week.

Without the SRY gene, the gonad develops into an ovary; the Müllerian duct system develops into the fallopian tubes, and as it meets and fuses with its contralateral mate, the uterus and most of the vagina are formed. The Wolffian ducts remain rudimentary once their contribution to the developing kidney is completed. In males, the endocrine contributions of the cells within the developing testis have a strong influence on male ductal development. Local testosterone, produced by developing Leydig cells under the influence of maternal human chorionic gonadotrophin, is thought to be the primary element in the growth and development of the Wolffian ducts into the collecting ducts for the testis, including the rete testis, epididymis, *vas deferens*, seminal vesicles and ejaculatory ducts, as well as the developing prostate. Equally important, the Sertoli cells in the developing testis secrete Müllerian inhibitory factor, a hormone that prevents development of the

Müllerian ducts and leads to their degeneration by apoptotic mechanisms.

The external genitalia are also indifferent and bipotential early in development—not until about 3 months post-conception can male/female differences be determined. Again, female development is constitutive, with the clitoris, urethra, vaginal vestibule and labia developing unless other factors intervene. In the male, under the influence of androgens— primarily dihydrotestosterone, derived locally from systemic testosterone—the genital tubercle grows much larger and forms the penis. The urethral folds fuse to form the male urethra and the genital swellings form the scrotum as opposed to the labia.

Although most research has focused on the effects of hormonal stimulation on the development of the genital tracts, it is now recognized that the genetic factors and hormonal effects that influence genital development may play roles in the development of other systems. SRY is expressed in the brain, and testosterone has been shown to affect many other organs including the testis, prostate and brain. Hence, the development of the genital tract appears



Schematic of normal process of sexual differentation. The anatomy of the internal reproductive structures and external genitalia of genetic males and females are initially bipotential ("We all start out the same"). Differentation is the consequence of a cascade of events from determination of the gonad, to secretions of the fetal testis, to differentiation of reproductive structures. (From Kobayashi, A. and Behringer, R. Developmental genetics of the female reproductive tract in mammals. *Nature Reviews Genetics* 4 2003 969-9800)

to have wide-ranging effects on other systems and clearly may affect behavior independently of any psychological effects of abnormal external genitalia.

Research Challenges

Clearly, a better understanding of the development of the genital tract from the perspectives of anatomy, embryology, physiology, and genetics must inform treatment of patients with congenital anomalies in this area. In spite of the fact that the GU tract has one of the highest rates of congenital malformation (upwards of 2 percent), surprisingly little is known in genetic terms; a survey of the literature indicates that fewer than 20 articles examining gene function during GU development have been published between 2002-2004. In the few instances when a developmental approach has been adopted, important insights into the mechanisms underlying specific defects of the genitourinary tract have been achieved.

Initially, the major determinants of gender-specific development were thought to be genes whose products are required for androgen signaling. However, recent investigations of developmental genes suggest there are equally important factors controlling the formation of these tissues independently of androgen signals. *To explain how sexual differentiation is ultimately regulated, it will be necessary to elucidate how hormonal and non-hormonal determinants are integrated, particularly at the level of transcription.*

Because transcription factors interact with DNA in a tissue-specific context, investigations focused on discerning the tissue-specific DNA binding sites will provide a mechanistic link between the transcription factors, their target genes, and tissues affected by loss of transcription factors or target gene expression. The identification of the DNA sequence elements bound by GU transcription factors also will permit translational collaborations between clinicians and basic scientists, because patient DNA samples can be re-evaluated for mutations in the cis-regulatory sequences necessary for normal gene expression.

Genetically engineered mice, bearing loss of function mutations (knockouts, conditional knockouts, and gene fusions permitting fluorescence-based localization) will permit investigators to correlate gene function with specific congenital defects. While the mouse is the essential genetic model, it is important to note that significant morphological and physiological differences exist between the human and mouse GU tract. Other model sytems (including zebrafish, chicken, frog, and some yet to be identified) may be needed to address particular developmental questions.

Development of the External Genitalia: Penis, Clitoris, Testes

Development of mammalian external genitalia requires tight coordination of proximodistal outgrowth, three-dimensional patterning, and tubular morphogenesis. The developmental program can be divided operationally into two distinct phases. The first involves initial outgrowth and patterning of a bud of cells known as the genital tubercle, which is the embryonic precursor to the penis and clitoris. The second phase is hormonally controlled and involves either (a) continued growth and differentiation of the penis, or (b) arrest of outgrowth and differentiation of the clitoris. During the first phase, there are no discernable morphological differences between male and female external genitalia. In the embryo, external genital development is initiated when paired cellular outgrowths emerge on either side of the cloaca and then merge medially to form a single genital tubercle. An extension of (*epithelial*) tissue from the lining of the cloaca moves between these swellings to form the urethral plate, a two-layered sheet of cells that later cavitates to form the *urethral tube*. The urethral plate extends to the distal tip of the genital tubercle where, in the clitoris, it persists as an epithelial cord; or, in the penis, it canalizes to form a urethral tube.

Surprisingly, *even at the tissue and cellular levels, the embryology of external genital structures remains*

unclear. For example, most medical embryology texts indicate that the opening of the penile urethra forms by in-growth of cells at the distal tip of the penis, although recent experimental work has failed to find evidence for this process. Therefore, we still do not know which cells give rise to the distal urethra, the region most frequently affected in hypospadias.

While malformations of the external genital system occur at a frequency second only to that of cardiac defects, the molecular mechanisms that regulate early development of the external genitalia, and which are presumably deregulated in congenital abnormalities, remain largely unknown.

To date, fewer than 10 genes have been identified with roles in external genital development, most playing roles in development of other organs systems. Given the high number of children that present with isolated malformations of the external genitalia, it seems unlikely that mutations in such developmental control genes are a major causal factor. Instead, localized genitourinary defects may result from altered regulation of gene expression in the genitalia, either by exposure to environmental factors that influence gene activity, or by mutation of DNA sequences are critical to transcriptional control.

Interactions between the genetic pathways that act during phase one and the hormonal cues that act in phase two remain to be explored. Local and systemic signals must be integrated for normal genital development to occur, yet how these signaling pathways intersect and influence one another is largely unknown. This question is particularly germane to understanding how environmental factors contribute to abnormal genital development.

Development of the Internal Genitals: Ovary, Uterus, Fallopian Tube, and Testes

Formation of normal internal genitalia is a complex process that remains incompletely understood. By the 8th week, a testis will develop male hormone-producing cells, while an ovary will develop female hormone producing cells. Hormone production by the fetal testis is active, while the ovaries are nearly silent. Several key testicular male hormones act to masculinize the two sets of embryonic paired tubes and induce testicular descent into the scrotum. These male hormones are not made by the ovary, so the two sets of embryonic paired tubes feminize. Adjacent to the developing gonads, the Müllerian ducts and the Wolffian ducts develop extending from the midback to the external genitals. In males, testosterone causes the Wolffian ducts to differentiate into the several parts of the male reproductive tract—the tubing needed to carry the sperm from the testis to the penis. Other testis hormones cause the Müllerian ducts to regress and the testes to descend into the scrotum. In females, the absence of male hormones causes the Wolffian ducts to regress, while the Müllerian ducts differentiate into the female reproductive tract. Approximately one in 2,000 women in the United States are affected by an abnormally formed uterus or vagina, which can lead to infertility and repeat miscarriage.

Formation of normal internal genitalia is a complex process that remains incompletely understood. We are beginning to identify the key genes and proteins that are crucial for this development as well as the important timing of their appearance. *Clearly, research needs to continue to understand how these molecular processes work together and how their alteration results in birth defects.*

Priorities for Research

- Identify the genes and signaling pathways necessary for the development of the genitalia. Which genes are under hormonal control; what are the patterns of tissue-specific gene regulation, and how are they determined?
- Elucidate the cell lineage of the genitalia.
- Define the molecular mechanisms by which environmental factors disrupt genital development.
- Produce, characterize, and validate animal models for normal and abnormal genital development. Mouse knockout strains, conditional knockouts and GFP strains should be freely available within the research community.
- Develop novel molecular tools to treat and prevent genital abnormalities and improve reproductive potential.
- Investigate the effect of sexual differentiation and genital development on other organs systems, including the brain.

11. Cryptorchidism

Summary

Cryptorchidism requiring surgery occurs in approximately 1 percent of male births. The research challenge is to determine the genetic and endocrinological basis of this anomaly and to develop strategies to prevent the loss of fertility associated with the bilateral condition.

Cryptorchidism, the absence of a testicle from the scrotum, is the most common anomaly of male sexual differentiation, affecting 1 percent of 1-year-old boys.

Health Impact

The economic impact of surgical care for this disease is significant. In 2002, 4.022 million births occurred in the United States. Given that cryptorchidism requires surgery in 0.8-1 percent of all male births, a conservative estimate of the annual cost of its surgical care in the United States is $189 million. The bilateral form of the condition impacts fertility, and crytorchidism also is associated with an increased risk of testicular malignancy.

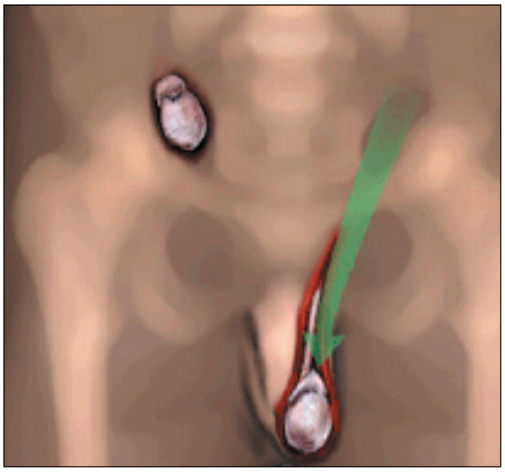
Clinical Presentation and Treatment

When a testis is not found in the scrotum, the testis may be undescended (halted in the normal path of descent) or ectopic (strayed off of the normal path of descent). In other cases, cryptorchid males will have either no testis or a shriveled remnant of a testicle ("testicular nubbin"), likely representing the end result of testicular torsion. In one-third of cases, cryptorchidism is associated with abnormal development of the male ductal system (epididymis), and this can contribute to maldescent and infertility. Cryptorchidism also can be associated with ambiguous genitalia and intersex conditions.

The mainstay of treatment is early orchiopexy, surgical placement of the testicle into the scrotum. Currently, this procedure is recommended between 6 and 12 months after birth, since after that point spontaneous descent is unlikely to occur. In testes remaining cryptorchid beyond 12 months, histological deterioration of the germ cells has been observed. Alternative therapy may include drugs to stimulate testosterone production, but unfortunately these rarely cause testicular descent.

Fertility

Recent reports indicate that only 65 percent of men who had bilateral cryptorchidism achieve paternity, compared with 93 percent of controls. The endocrine profiles, which may be normal or



Abdominal cryptorchidism, the path of normal descent is shown in green (Image provided courtesy of Dr. Sam Gambhir).

abnormal, are not necessarily predictive of fertility. Fertility in unilateral cryptorchidism was not appreciably different from controls in recent studies.

To combat infertility, some centers are investigating the use of medications such as gonadotropin-releasing hormone agonists to preserve the germ cells of the testis (future sperm) in prepubertal children. However, the value of this therapy remains to be determined.

Cancer

It is recognized that there is an increased incidence of testicular tumors, particularly seminomas within cryptorchid or formerly cryptorchid testes. This incidence may be greater than previously thought and may be different among different populations. It is unclear what factors cause carcinoma *in situ* cells in the immature testis to become malignant. The general consensus has been that correcting the location of the cryptorchid testis does not alter the risk of malignancy.

Priorities for Research

- Characterize the genetic basis of familial cryptorchidism.
- Identify and characterize the endocrinopathy of cryptorchidism, in infancy and prior to or after treatment, and assess its role in fertility.
- Define the predisposing factors for infertility (genetic factors, environmental factors, and any potential biomarkers) in the bilateral cryptorchid population.
- Identify novel medical strategies to treat maldescent, the loss of germ cells, or associated infertility and associated risks. (Gonadotropin releasing hormone GnRH research strategies should focus upon identifying patient groups at greatest risk for infertility and upon treatments to enhance fertility.)
- Assess whether subgroups are susceptible to malignancy and identify risk factors for intervention.
- Perform studies to assess whether endocrine disruptors induce human cryptorchidism.
- Investigate the frequency and endocrinopathy of testicular ascent, and perform a longitudinal study to assess the long-term outcomes.
- Determine the incidence of epididymal anomalies in cryptorchidism and their significance.

12. Hypospadias

Summary

Hypospadias is the second most common birth defect, and its incidence is increasing according to the Centers for Disease Control and Prevention. Although there is increasing evidence that environmental factors such as maternal exposure during pregnancy may explain the increased incidence, the etiology of hypospadias remains unknown in the majority of cases. A program of developmental genetic research leading to a better understanding of urethral development will provide insights into the causes of this congenital disorder and explanations for its increased incidence.

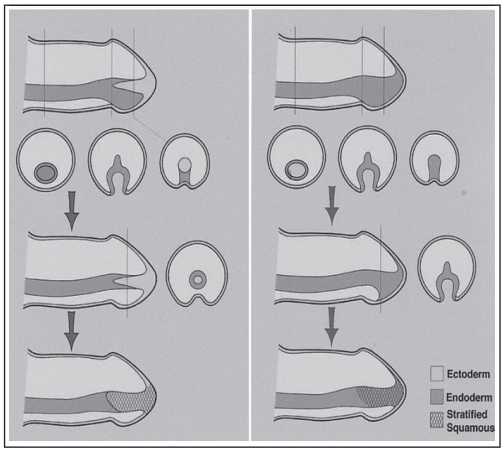
Hypospadias can be defined as an arrest in normal development of the urethra, foreskin, and ventral aspect of the penis. This results in a wide range of abnormalities with the urethral opening being anywhere along the bottom of the shaft of the penis, within the scrotum, or even in the perineum. The more severe forms of hypospadias are associated with penile curvature. Left uncorrected, patients with severe hypospadias may need to sit down to void and tend to shun intimate relationships due to anxiety related to abnormal sexuality. Babies born with severe hypospadias and penile curvature may have "ambiguous genitalia" in the newborn period.

Health Impact

Hypospadias is one of the most common congenital anomalies in the United States, occurring in approximately one in 250 newborns or roughly one in 125 live male births. There is significant morbidity associated with some surgical procedures to correct severe forms of hypospadias, as well as potential psychosocial consequences of having an abnormal penis. In addition to the difficulty of surgery, the emotional and physical stress for the parents of patients with abnormal appearing genitalia must be considered.

Development of the Male External Urogenital System

Formation of the external male genitalia is a complex developmental process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. Up until 7 weeks gestation, the male and female genitalia are essentially indistinguishable. Then, under the influence of testosterone in response to a surge of luteinizing hormone from the pituitary, masculinization of the external genitalia gland occurs. The penile urethra forms as a result of fusion of the medial edges of the endodermal urethral folds, and ectodermal edges of the urethral groove fuse to form the median raphe. By 12 weeks, the coronal sulcus separates the glans from the shaft of the penis, and the urethral folds have completely fused in the midline on the ventrum of the penile shaft. During the 16th week of gestation, the glanular urethral appears; evidence suggests two possible means by which it could form: endodermal cellular differentiation or primary intrusion of the



Two theories of urethral development. Ectodermal intrusion theory is older, and endodermal differentiation is more recent (from LS Baskin, Hypospadias and urethral development, *Journal Of Urology* 163 (3): 951-956 © 2000).

ectodermal tissue from the glans. Recent studies support a theory of endodermal differentiation indicating that the epithelium of the entire urethra is of urogenital sinus origin.

Etiology of Hypospadias

Reports of increasing incidences of hypospadias have raised questions concerning etiology, treatment, and prevention. *To date, there is no sound understanding of the etiology of hypospadias that can inform primary prevention efforts and improve therapeutics.*

Genetic Impairment

Adequate virilization of the urogenital sinus and external genitalia during embryogenesis is dependent on the conversion of testosterone to DHT by 5α-reductase, and it has been demonstrated that defects in the androgen receptor gene are associated with isolated hypospadias. However, the frequency of these genetic defects accounts for an extremely small subset of cases. Furthermore, no significant differences in the androgen precursors as measured by defects in three major enzymes in the biosynthetic pathway of testosterone—3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, and 17,20-lyase—were found between the controls and the individuals with hypospadias. Increasingly, researchers are examining the role of cellular signals other than testosterone and DHT in the morphogenesis of the phallus and the etiology of hypospadias. Normal embryogenesis of the urogenital system depends on cell-cell signaling, and it has been hypothesized that aberrant signaling between cell layers (epithelium and mesenchyme) could lead to hypospadias.

Environmental Factors

The reported increase in cases of hypospadias during the last 30 years and the fact that known genetic defects explain only a small percentage of cases has raised concerns about environmental causation. Environmental factors under consideration as causative agents for hypospadias include parental occupation, obesity, exposure to chemicals, including endocrine disruptors (e.g., gestational exposure to progestins and estrogen-like compounds), and smoking.

The case for chemical exposure as a causative factor is supported by animal models, which demonstrate that *in utero* exposure to a variety of environmental chemicals—pesticides, plasticizers, and pharmaceuticals—can cause hypospadias. Some of these have been shown to act as estrogens, antiandrogens, and inhibitors of fetal testis. Furthermore, some researchers have noted that a variety of other endpoints related to male reproductive health and dependent on hormonal action—testicular cancer, cryptorchidism, and impaired semen quality—may have increased in parallel with levels of these environmental pollutants.

Attempts to determine risk for hypospadias have yielded a number of maternal and paternal factors. In traditional studies of maternal risk factors for congenital anomalies, maternal age and primiparity were found to be significantly associated with hypospadias, although some studies have contested the maternal age effect. Paternal risk factors include abnormalities of the father's scrotum or testes, low sperm motility, and abnormal sperm morphology. (It has been suggested that the recent increase in hypospadias reflects the improvement in fertility treatment, contributing to more sub-fertile men fathering children.) There is strong consensus in the literature that boys with hypospadias have lower birth weight, and it has been reported that they also have a lower placental weight than controls.

While these risk factors do not reveal direct information about the causes of hypospadias, they provide additional information that may reveal a common developmental pathway and can inform future research. For example, there is growing evidence that androgens play a central role in the lower birth weight of girls compared to boys.

Androgens are also crucial to the development of the male reproductive tract. Perhaps exposure to an agent that compromises the weight-gaining advantage of androgen during gestation could play a role in the development of hypospadias and lowered birth weight.

Clinical Treatment

The only treatment for hypospadias is surgical repair of the anatomical defect. Reconstruction, if performed by an experienced pediatric urologist, generally involves a single outpatient procedure. Occasionally, however, more extensive surgery is required, or patients may face multiple surgeries to improve results.

Research Priorities

The origin of most hypospadias is unknown, and real insight will depend on a more fundamental understanding of the process of normal genital development. The incidence of hypospadias appears to have increased in the last generation. The hypothesis that this is explained by environmental pollutants is supported by experiments in animal models of hyposapdias and should be investigated further.

Basic Research

- Identify the genes that regulate normal urethral development and establish the cell lineage of the developing genitals.
- Elucidate at the molecular level cell-cell interactions and intercellular signaling critical to external genital development.
- Determine, at a molecular level, etiologies of hypospadias.

Translational Research

- Characterize the impact of environmental factors on genital development and their mechanism of action, and develop guidelines to limit harmful exposure.
- Develop reliable outcome measures, and perform outcome studies with respect to quality of life, sexual function, and psychosocial well-being for the surgical repair of hypospadias.

13. Hernia and Hydrocele

Summary

Occurring in approximately 1 percent of males, inguinal hernia and hydrocele can be successfully treated surgically. A key priority for clinical research is to validate non-invasive methods of detecting silent hernias, thereby eliminating unnecessary surgery.

The processus vaginalis develops during the 3rd month of gestation as a natural pocket of the lining of the abdominal cavity. It extends through the muscle layers of the groin (inguinal canal) to reach the scrotum during the 7th month. This pocket usually seals itself off prior to birth, but remains open in some children, and is termed a patent processus vaginalis (PPV). The precise timing and the factors controlling closure of the processus are unknown, although new research has implicated insulin-3, a testis hormone. When the PPV produces a groin swelling accentuated by crying or grunting, it is termed an inguinal hernia (IH). When fluid collects in the PPV beside the testicle, it is called a hydrocele.

Health Impact

Approximately 1 to 5 percent of children are affected by IH, with a significant male and right-sided predominance. IH is highest in the first year of life, and premature infants have a higher incidence (16 to 25 percent). A variety of other disorders, including undescended testis, exstrophy, intersex, ascites, ventriculo-peritoneal shunts incidence, peritoneal dialysis, and cystic fibrosis, are associated with higher incidence. *Although the costs of surgical repair of the bulging PPV are justified, surgery for the silent hernia is controversial and adds unnecessary hospital and anesthesia costs for all the negative explorations.*

Clinical Treatment

An IH will not resolve spontaneously and should be repaired within several weeks of diagnosis. In fact, if intestines travel into the PPV and become trapped, the intestines can become gangrenous and emergency surgery is needed. Surgical complications are fortunately uncommon. Most hydroceles resolve by 24 months of age without surgery. In children with a one-sided hernia, a silent hernia without symptoms may be present on the other side. This silent hernia will become symptomatic in 10 to 15 percent of patients. *Controversy exists in its management—although many surgeons perform exploration on the side with the possible silent hernia, it is usually unnecessary since no hernia is found in 80 to 90 percent of cases.* Some studies have suggested that ultrasound detects silent hernia with up to 92 to 95 percent accuracy, but it is not used routinely. Inguinal laparoscopy is used to detect the presence of a contralateral PPV, yet controversy exists as to its overall clinical value.

Priorities for Research

- Investigate molecular and hormonal factors that may predispose to the development of hernias and hydroceles.
- Identify and validate novel, noninvasive, or minimally invasive perioperative methods to detect silent hernias.
- Improve awareness of hydrocele and hernia in children of the parents of at-risk groups to decrease time elapsed until diagnosis.

14. Congenital Anomalies of Sexual Differentiation

Summary

Congenital anomalies of the sex organs can confront clinicians with the need to assign sex and perform appropriate surgical reconstruction. Sex assignment decisions in which optimal gender was based on factors like potential for sexual functioning and reproductive potential have been highly contested; affected individuals may object to the gender assigned, and they may resent the effects of genital surgery and feel a sense of stigmatization. Prospective studies of gender identity and reproductive function and quality of life are needed in this group of patients to guide clinicians and families in making decisions about gender assignment and surgical reconstruction.

Patients with congenital anomalies of the sex organs present major challenges to the clinician. These conditions include anomalies of the gonads, internal reproductive ducts, and external genitalia, including malformations like cloacal exstrophy and penile agenesis. The primary focus here is on that subset of conditions in which there are issues of sex assignment and surgical reconstruction of the genitalia to match assigned sex.

Health Impact

The use of screening procedures, prenatally and in newborns, has increased the early diagnosis of many anomalies of sexual differentiation. State-mandated screening for congenital adrenal hyperplasia indicates that its incidence is in the range of one in 10,000 to one in 15,000 live births. Abnormalities of sexual differentiation force many families and clinicians to make difficult decisions regarding sex assignment with insufficient outcome data. Individuals who are unhappy with their sex assignment may have profound psychological disturbance.

Clinical Management and Treatment

There is currently a crisis in clinical management of children with disorders of sexual differentiation, and it has received considerable public attention. It stems from two issues. First, for some of these disorders, there are *insufficient data to guide the clinician and family in sex assignment. Second, the optimal application of surgery and its timing remain unclear.*

Sex assignment

Until the mid-1950s, medical management of individuals with disorders of sexual differentiation was guided by the belief that an individual's "true sex" could be determined by examination of internal anatomy. Then, based on reports suggesting that this assumption was incorrect, guidelines were changed; sex assignment decisions were based on the principle of "optimal gender," which considered multiple aspects of outcome, most prominently, the potential for complete sexual functioning, with particular emphasis on phallic size and reproductive potential. This approach, largely uncontested until recently, is predicated on two assumptions: (1) "gender identity" (i.e., identification of self as either girl/woman or boy/man) is not firmly established at birth, but rather is the outcome of the sex of rearing; (2) stable gender identity and positive psychological adaptation require that genital appearance match assigned sex, which often calls for reconstructive genital surgery. Clinical outcomes have demonstrated that there is a window of time until the second year of life, during which gender identity is malleable. Therefore, this clinical management strategy suggests that early surgical correction of genitalia is critical.

This clinical approach to disorders of sexual differentiation has recently been criticized from several perspectives. First, the notion of gender "neutrality" at birth has been challenged by several highly publicized cases of unsuccessful gender reassignment in which the patient ultimately initiated a return to their original gender. Some have interpreted these outcomes in terms of the effect of genes and/or androgens on the brain, and this is supported further by increasing experimental evidence.

A second challenge to the "optimal gender" policy comes from affected individuals who are angry about their treatment. They object to the fact that they were either not informed or were misinformed about their condition and had difficulty obtaining accurate information about their condition and treatment. They feel stigmatized and shamed by the secrecy surrounding their condition and its management. Many also attribute poor adult sexual function to damaging genital surgery and repeated and insensitive genital examinations, both performed without their consent.

As a result of these concerns, *there exist no clear guidelines to direct the current practice of gender assignment*. Indeed, *there is evidence that clinicians have altered their management strategies with limited outcome data to support these changes*. In conditions in which psychosocial factors are paramount, there are few mental health specialists with the specific expertise to participate in interdisciplinary care and clinical research for these conditions.

Surgical Intervention

The "optimal gender" policy mandated early surgical reconstruction to normalize the appearance of the genitalia in accordance with the assigned gender. Although this approach was thought to be successful in most cases, only limited long-term outcome data are available. Because of concerns regarding irreversibility and possible sensory damage to the genitalia after early surgery, this policy has been questioned, and some have gone so far as to suggest a total moratorium on surgery of the genitalia in children.

Although current techniques used by skilled surgeons may produce better cosmetic and functional outcomes than in the past, confirming evidence is essential. Unfortunately, systematic outcome data about sexual function in individuals with disorders of sexual differentiation and the data pertaining to the association of sexual function with genital appearance and types of genital surgery is lacking. There are either retrospective or anecdotal reports with incomplete measures and limited comparison groups. These suffer from sampling bias and the insensitivity of measures of sexual function. *Even the best studies show poor correspondence between objective and subjective indicators, and wide variation in subjects' responses. Indeed it is unclear whether gender identity requires gender-consistent genital appearance.*

Priorities for Research

Research on disorders of sexual differentiation has been difficult for a number of reasons: (1) the relatively low incidence of some of these disorders; (2) difficulties in obtaining representative samples—individuals with poor outcome may be more likely to speak out; (3) continuing improvements in surgical techniques; (4) the complexity of outcome; (5) the likelihood that outcomes are influenced by complex psychosocial factors; (6) some important outcomes are not readily apparent until adulthood; (7) limited measurement tools; and (8) limited normative data on relevant outcomes.

- Develop appropriate animal models for gender identity and surgical reconstruction.
- Identify intermediate markers/predictors of adult endpoints (for example, childhood indicators of adult gender identity and sexual and reproductive function).
- Determine for these conditions the optimal timing and type of genital reconstructive surgery with regard to anatomic, reproductive, and psychosexual outcomes.
- Examine patient and family adaptation following the diagnosis of children with these conditions when mental health specialists have been integrated into the care of the child.
- Elucidate the process of decisionmaking regarding sex assignment and genital surgery by physicians and families.
- Conduct long-term prospective and retrospective studies of gender identity, sexual and reproductive function, and quality of life in relation to early medical, surgical, and psychosocial factors.
- Determine the importance, for gender identity and quality of life, of concordance of the genitalia and physical appearance with sex of rearing.
- Identify new molecular markers for the rapid diagnosis of disorders of sexual differentiation.

Infrastructural Needs

- Workshops that facilitate the skills development of qualified mental health professionals.
- A patient registry to facilitate recruitment of representative samples of patients with rare conditions for outcome studies.

III. Other Pediatric Urinary Conditions

15. Pediatric Genitourinary Tumors

Summary

Treatment of renal, bladder/prostate, and testicular tumors in children may entail significant short- and long-term morbidity, as well as the threat of death from metastatic disease or complications of treatment. The large multicenter groups under the umbrella of the Children's Oncology Group (COG) have defined the standard management of these tumors in the United States, and COG continues to develop large prospective studies. We suggest research priorities—studies of the cytogenetic changes underlying tumorigenesis, the evaluation of organ-sparing approaches, and longitudinal study of late effects of treatment on organ function and secondary malignancy risk—which are not currently a focus of COG.

Current Clinical Management

Kidney

The initial treatment for children with kidney cancer (Wilms' tumor is the most common kidney and genitourinary tumor in children) is removal of the affected kidney. Based on the type of kidney cancer and extent of the disease, children receive multiagent chemotherapy with or without radiation therapy. The cure rate for most patients following these protocols is approximately 90 percent.

Bladder

Current therapy for bladder and prostate cancers, which account for 3 percent of pediatric genitourinary tumors, emphasizes bladder salvage. Most tumors are biopsied and then treated with chemotherapy in the hope of gaining enough tumor shrinkage to allow for bladder preservation. Many children receive pre- and postoperative radiotherapy as well. Survival is approximately 85 percent with this approach, although 40 percent will have lost bladder function after 4 years.

Testis

Yolk sac tumor of the testis is highly curable; prospective multicenter trials in Europe and the United States have shown that a nearly 100 percent survival can be achieved for prepubertal children. However, this cure rate requires removal of the affected testicle and, for patients with metastatic disease, multiagent chemotherapy. Adolescents with mixed germ cell tumors have been managed largely as adults with some combination of removal of the testicle, removal of abdominal lymph nodes, and chemotherapy depending on the stage and histology of the tumor.

Health Impact

Wilms' tumor, cancer of the bladder and prostate (rhabdomyosarcoma), and testicular tumors (yolk sac and mixed germ cell tumors) account for a significant fra ction of all solid pediatric tumors. While the outcome for children with genitourinary cancers has improved in the last century, many children still die from these tumors. The children who survive are subject to the long-term complications of chemotherapy, radiation, and surgical removal of some or all of the affected organ.

Research Priorities

Many clinical questions regarding the standard management of pediatric genitourinary tumors are

being addressed by COG. However, these studies are inherently conservative and can answer only a limited number of questions with each protocol. There are many important questions that need to be addressed by additional studies.

Since children treated for genitourinary cancer have a known increased risk for other cancers later in life, clinical studies are needed to identify the specific risk of late secondary malignancies and the implications for initial treatment and long-term surveillance. These should take into account both treatment effect and genetic predisposition to help understand the pathogenesis of the secondary tumors. Other functional endpoints must be evaluated for a variety of pediatric genitourinary tumors: long-term gonadal function in adults treated for testicular tumors in childhood, long-term kidney function in those treated for Wilms' tumor with chemotherapy and radiation, and long-term bladder function after radiation treatment of rhabdomyosarcoma.

Organ-sparing approaches for pediatric genitourinary tumors need to be assessed in terms of safety and effectiveness. For example, in the treatment of Wilms' tumor, partial removal of the kidney has proven effective in special cases; investigation of the wider use of kidney-sparing surgery could significantly reduce the long-term risk to kidney function in these children.

Basic Research

- Elucidate the role of the fetal tissue lesion nephrogenic rests in development of cancer in Wilms tumor patients.
- Apply cytogenetic approaches that identify the genetic and mechanistic basis of genitourinary tumorigenesis as a prelude to intelligent stratification of patients for treatment.

Translational and Clinical Research

- Conduct multicenter studies of organ-sparing approaches for pediatric genitourinary cancers, particularly partial kidney removal for Wilms' tumor.
- Conduct prospective studies of treatment options for adolescents with testicular cancer.
- Evaluate with epidemiologic and outcome studies whether the adult protocols for surgery and chemotherapy used to treat adolescents with testicular cancer including mixed germ cell tumors are appropriate.
- Conduct longitudinal studies of long-term outcomes including renal, bladder, and gonadal function, and the risk of secondary malignancies.
- Conduct phase I/II trials needed to develop new therapies, particularly for patients with high-risk disease.

Infrastructural Needs

- Training of academic urologists capable of undertaking large, prospective clinical trials assessing the evaluation and management of children with pediatric genitourinary cancer.
- Establishment of a pediatric genitourinary cancer patient registry.
- Expansion of the COG tissue banks, with access to non-COG scientists for appropriate studies.
- Administrative mechanisms to encourage multidisciplinary and multicenter collaborative studies.
- Establishment of research awards for the investigation of genitourinary cancers in children.

16. Pediatric Genitourinary Trauma

Summary

The treatment of pediatric genitourinary trauma would greatly benefit from the re-establishment of a national database to track trends in causes and management. Two important questions to be addressed would be the long-term sequelae of major kidney injuries and the value of prompt expert intervention in pediatric genitourinary trauma. Continued research into the basis of graft survival and approaches to combating infection in reconstructive surgery is called for if the results of reconstructive surgery are to be improved.

While trauma centers have increased survival and decreased morbidity, trauma remains the leading cause of death and injury for people between the ages of 1 and 44 years. Both upper urinary tract and genital trauma often occur with other injuries—sports and recreational injuries comprise the largest single reason for primary care office visits outside of routine checkups, and pose unique concerns about future maturation and fertility. Representing 8 to 10 percent of all trauma cases, renal trauma is the most common urological trauma. Most genital trauma is blunt trauma resulting from accidents and falls, and infrequently can have profound psychosocial consequences including incontinence, loss of sexual and reproductive function, and altered body image. Except for a few differences, the evaluation and treatment of pediatric genital trauma parallels that of adults. In general, management is improved by prompt expert intervention. Below, we list some categories of trauma and make recommendations for future research.

Kidney and Ureteral Trauma

Motor vehicle accidents and falls cause most pediatric renal and ureteral trauma. Children are especially at risk because the rib cage and abdominal musculature is less rigid and well developed than in adults. Most kidneys can be saved, and advances in imaging and resuscitation and support make conservative therapy effective in 85 to 90 percent of cases.

Bladder and Urethral Trauma

These are usually due to falls and accidents; often the pelvis may have been broken. When trauma is suspected, careful, thorough imaging is called for. Management is usually conservative with diversion of the urine and secondary repair after the other injuries have been stabilized.

Penile Trauma

Minor penile injuries usually heal well with little consequence. More serious injuries result from amputation, bites, and surgical mishaps. Bites, especially human ones, pose a high risk of infection and require aggressive treatment with antibiotics and debridement. In circumcision, the glans, if not carefully protected, can be cut or amputated. Current practice is to preserve as much tissue as possible and attempt primary repair. Partial or complete amputations can be reattached. When the amputated segment is unusable, later reconstruction is possible using a penile prosthesis and grafts.

Scrotal and Testicle Trauma

Blunt scrotal and testicle trauma, typically presenting with bruising, swelling, and pain, is common in boys. Severe testicular injuries are rare, comprising fewer than 5 percent of recreation- and sports-related pediatric injuries. Most severe are testicular rupture and traumatic torsion.

Genital Skin Avulsion

Rapid deceleration injury can result in genital avulsion; the loose genital skin can become snagged while the rest of the body continues moving rapidly.

The scrotum, labia, and penile shaft are well vascularized, and unless there is massive infection or tissue loss, primary repair can yield good results.

Perineal Laceration

The perineum can become torn apart as the result of a crush or rollover injury: the pelvic bone splinters, the floor of the pelvis tears, and the urethra and genitalia become disrupted. Management is complex and requires immediate control of bleeding, colostomy to divert the fecal stream, and bony fixation.

Burns

Thermal and electrical burns to the genitalia in children are managed like those in adults. Radiation burns can occur as a side effect of radiotherapy. Treatment requires complete excision of the affected skin and graft reconstruction.

Sex Abuse

Sexual abuse occurs in both boys and girls. It is often underreported because of fear and embarrassment by the child, and overlooked by health care and child care providers.

Research

Pediatric trauma occurs sporadically and it is difficult to make any significant observations without a larger pool of data. Therefore, it needs to be tracked nationally. The National Pediatric Trauma Registry (NPTR) served this purpose for many years. For example, it gave firm evidence on the safety of sports participation for boys with only one testicle or kidney. Unfortunately, it is no longer funded and became inactive in 2003.

Many of the posttraumatic reconstructive surgical techniques require mobilization of healthy tissues for graft coverage and reconstruction. Critical to the improvement of these is a better characterization of the fine vascular and neurological anatomy of the genitalia, as well as improved means of combating infection, which remains the primary complication that jeopardizes reconstruction efforts. For patients with insufficient local skin, research should be directed to better understanding of the use of other tissues, such as the buccal mucosa, and to developing practical engineered tissues grown from donor cells taken from the patient's own genitalia.

Priorities

- Develop new techniques to prolong graft survival and improve functional and cosmetic results.
- Develop improved methods of combating infection as a complication of reconstructive surgery—in ways that deter development of antibiotic resistance.
- Investigate the fine vascular and neurological anatomy of the genitalia.
- Explore the use of other tissues, such as the buccal mucosa, in genital reconstructive surgery and develop practical engineered tissues grown from donor cells taken from the patient's own genitalia.
- Evaluate the effect of prompt intervention at specialty centers.

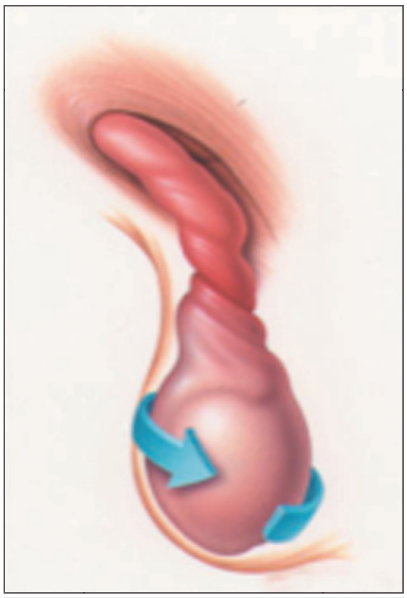
Infrastructural Needs

A national patient registry and database should be restarted to track trends in the causes and management of pediatric urinary genital trauma.

17. Testicular Torsion

Summary

A delay in the diagnosis and treatment of testicular torsion (spontaneous rotation of the testicle) can result in significant morbidity, including loss of the testicle. While early diagnosis and rapid surgical detorsion is imperative, it is currently difficult to distinguish testicular torsion from other diseases of the scrotum, and new diagnostic approaches are needed. If new therapeutic approaches are to be developed, investigation, at the cellular level, of the consequences of torsion and accompanying ischemia will be essential. New assays are needed to determine testicular viability at the time of surgery.



Testicular torsion (torsion of the spermatic cord) © Todd Buck, Illustration Inc.

Testicular torsion is the spontaneous rotation of the testicle, resulting in its compromise or death due to the twisting of the arteries and veins that vascularize it. In humans, the long-term effects of testicular torsion are not well characterized; in animal models, severely reduced testicular blood flow for one hour can lead to permanent testicular atrophy. The degree of hormonal dysfunction in the torsed testis has been variably reported, but there is a consensus that the endocrine function of the testis is significantly reduced acutely after torsion repair.

Health Impact

Affecting one in 4,000 males under the age of 25, testicular torsion is a significant source of emergency room and emergency surgery costs. Delay of diagnosis can result in significant morbidity, including loss of the testicle and medical-legal costs. Fortunately rare, bilateral testicular torsion, which typically presents at birth, results in loss of the testes, sterility, and the inablility to produce testosterone.

Clinical Presentation and Management

Testicular torsion is the most common cause of acute pain with scrotal swelling in children. It is primarily seen in the newborn or in the peripubertal male, and while it is a sporadic disease, several reports of familial torsion, both neonatal and peripubertal, exist in the literature, suggesting a genetic predisposition in some cases. Abnormal attachments between the testis, *vas deferens*, epididymis, vessels and the scrotum, called the "bell-clapper deformity," have been noted in affected children (autopsy series found 12 percent of testes with this deformity), but currently the molecular and developmental basis of these anomalies is unknown. Occurrence of torsion on one side is associated with increased risk of torsion of the opposite testis. Although testis growth during puberty and trauma have been suggested to trigger the torsion event, this hypothesis has not been proven and should be researched further. Some families and children affected by testicular torsion suffer from worries about future fertility and the absence of one testicle, and occasionally they opt for the placement of a testicular prosthesis.

Diagnosis

Because of the high morbidity associated with this condition, early recognition and rapid surgical detorsion are imperative. However, the clinical and radiological evaluation can be quite challenging, since many other nonsurgical diseases of the scrotum can masquerade as testicular torsion. The diagnosis is made currently by history, physical examination, urinalysis, and ultrasound or nuclear scan. None are perfect, and research addressing alternative strategies for diagnosis is greatly needed.

Therapy

If the diagnosis can be made within 6 hours of the onset of testicular pain, there is a chance that the testis can be salvaged if the torsion is released. However, testicular torsion is of variable severity—dependent upon the duration and degree of twist and therefore the duration and degree of vascular compromise—and there is variability in the severity of symptoms. At the time of surgery, it can be an equivocal and rather subjective decision as to whether the testis is viable, and methods to objectively assess the viability need to be developed. If treated rapidly, the testis can be untwisted, and permanent immobilizing stitches are then placed in both the untorted testis (orchiopexy or septopexy).

Unfortunately, treatment is often delayed and the necrotic testis must be removed (orchiectomy). The opposite testicle is also at risk of torsion, therefore, a simultaneous orchiopexy is performed on the opposite testicle. The worst scenario is that of bilateral testicular torsion, which typically presents at birth. In these fortunately rare cases, virtually none of the testes are salvaged, leaving the child unable to produce testosterone and without reproductive potential.

Priorities for Research

It is important to understand the cellular pathophysiology of testicular torsion so that new therapies can be developed to deactivate the degenerative cascade initiated by the torsion event. Animal models of testicular torsion have been particularly helpful in understanding the mechanism of torsion-induced damage. There are experimental data to suggest that anti-sperm antibodies might develop after testicular torsion and impair fertility. This has not been definitely proven in humans and should be studied further.

- Characterize at the molecular and cellular level ischemia/reperfusion injury, including subsequent germ cell apoptosis in the torsed testes.
- Improve and validate novel, noninvasive means to detect torsion, such as biomarkers or imaging techniques.
- Identify assays to determine testicular viability at the time of surgery.
- Create medical therapies to diminish ischemia-reperfusion damage to the torsed testis.
- Identify risk factors for torsion; improve its anatomical characterization.
- Define and validate the diagnosis of intermittent torsion by novel biomarkers.
- Assess long-term endocrine function and fertility in patients with past torsion.

18. Phimosis and Circumcision Practice

Summary

The benefits of routine circumcision remain controversial. We suggest that the effect of neonatal circumcision on UTI frequency be evaluated prospectively using cohort-matched groups in a statistically sound longitudinal study.

The foreskin covers the glans or head of the penis. At birth, it is not retractable, but in most children it becomes so by age 5. In some children, formation of a tight ring of scar (phimosis) due to repeat infection, irritation, or tearing prevents retraction; this causes spraying of the urine and traps urine beneath the foreskin, fostering infection in the urine or in the penis. Other health effects of circumcision are somewhat controversial. The tougher and easier to clean exposed glans may increase resistance to STDs, including HIV, and prevents penile cancer as this rare malignancy occurs almost exclusively in uncircumcised men. Human papilloma, which can hide under the foreskin, is associated with cervical cancer—women diagnosed with it are more likely to have an uncircumcised sexual partner.

Health Impact

Removal of the foreskin which toughens the skin of the glans, has been theorized to have many additional beneficial effects. In addition to possibly preventing the cervical cancer caused by sexual contact, it appears to prevent penile cancer, a rare malignancy affecting about 1,000 men in the United States—patients are almost exclusively uncircumcised men. Furthermore, in uncircumcised infants, UTIs have been shown to be more common, perhaps because the moist environment under the foreskin can harbor UTI bacteria. In those particularly vulnerable (e.g., boys with congenital urinary anomalies, such as posterior urethral valves, prune belly syndrome, vesicoureteral reflux, and hydronephrosis), circumcision might be a way to decrease the risk of UTI.

Current Clinical Practice

Phimosis can be treated in three major ways. First, the foreskin can be removed by circumcision. Serious complications are rare and may include bleeding, infection, or damage to penis. Second, the dorsal foreskin can be slit to retract it more easily. Some families prefer this because the patient is technically uncircumcised. Finally, topical corticosteroid cream (0.05-0.1 percent betamethasone) applied to the penis can loosen the scarring in mild and moderate cases. Circumcision rates have changed with time and reflect population and socioeconomic shifts; in the United States, there are regional differences, with the Northeast and Midwest having the highest circumcision rates of newborns.

Given the potential benefits of circumcision, some researchers call for a change in the official American Academy of Pediatrics policy, which currently does not go so far as to recommend it as routine practice. However, opponents of routine circumcision point out that STDs occur in circumcised men and that STD prevention depends more on promoting safe sex practices. Furthermore, other factors are associated with penile cancer besides circumcision, and penile cancer incidence in societies with low circumcision rates and high levels of hygiene is comparable to that in societies with high circumcision rates. The UTI risk studies were nearly all retrospective and may have been skewed by other risk factors such as vesicoureteral reflux. Another factor that must be weighed in the balance is complications from circumcision; while the complication rate is very low, disastrous outcomes such as total loss of the penis are possible. Routine circumcision in the population would mean that thousands of children would be placed at risk to prevent just one case of cancer.

Priorities for Research

- Prospectively study the effect of neonatal circumcision on UTI frequency using cohort matched groups in a statistically sound longitudinal study. Two arms of investigation could be males with no genitourinary anomalies and males at increased risk from genitourinary anomalies.
- Investigate the efficacy of surgical alternatives to complete circumcision such as the dorsal slit and corticosteroid creams.

- Study the effect of education of pediatricians and parents on the proper care of the uncircumcised penis, with the goal of preventing pathological phimosis.
- Investigate on an epidemiological basis the role of cultural influences and U.S. regional migration on decision making for or against circumcision.

19. Varicocele

Summary

Treating varicocele in adolescents to improve prospects for fertility in adulthood remains controversial. A prospective clinical trial to assess long-term outcomes (semen parameters, testicular growth, and fertility) of watchful waiting versus surgery is needed to permit rational therapy. Such a study could provide specimens, including serum and fractionated semen for identification of novel biomarkers, to predict fertility problems.

Varicocele, the abnormal dilation of the veins of the testis, occurs in approximately 15 percent of teenage and adult males. The major long-term concerns are impaired testicular growth and infertility. The pathophysiology of varicocele remains unclear. Some patients have compression of venous drainage associated with absent or poorly functioning valves of the testicular veins. This can result in increased testicular temperature bilaterally and be associated with increased bilateral testicular blood flow, a decline in intratesticular testosterone, and a decline in spermatogenesis, likely through increased germ cell apoptosis.

The future fertility status of the adolescent children with varicocele is not known. Thus, there is a need to determine which adolescents are at risk and in need of intervention. Varicocele surgery successfully restores fertility in only 40 to 50 percent of infertile men who undergo repair. The possible advantage of earlier surgery should be investigated.

Health Impact

Affecting as many as 40 percent of infertile adult men, varicocele represents the most common clinical finding associated with reversible male factor infertility. The incidence in adolescents approximates that in adults (15 percent), and the long-term followup of these children entails enormous costs. Furthermore, tens of thousands of surgeries in adolescents with varicocele are performed annually, despite controversy as to whether they prevent infertility.

Clinical Description and Management

Varicocele most commonly occurs on the left side, but it can occur bilaterally and affect the function of both testes. The condition varies in severity, described by grades 1-3. Impaired growth of the affected testis can be seen in many boys with varicocele and may result in impaired sperm production. Fewer than 5 percent of patients experience testicular pain, and this can be relieved by surgery. Some families and children affected by varicocele suffer from worries about future fertility.

Varicoceles can be managed surgically and observationally; there is controversy as to whether surgery impacts future fertility. Impaired growth of the involved testis has been the most widely accepted criterion for surgical intervention. While size difference would appear to represent an objective and logical sign on which to base a surgical management decision, the reality is more complicated. After hypotrophy, a commonly used criterion for surgical correction has been a large varicocele. The adult data correlating varicocele size with fertility status would suggest that large grade III varicoceles correspond to lower

sperm counts and improved response to surgical correction of the varicocele.

It is rational to manage most adolescent patients with a varicocele by observation and regular followup examinations. Those who would clearly fall into this category would be boys with equal testicular volume and no symptoms, independent of varicocele size. In fully developed adolescent males, it is desirable to obtain semen analysis data when they are willing to comply.

Priorities for Research

Perform well-designed clinical study(s) to assess long-term outcomes of watchful waiting versus surgery for varicocele. Ideally, the study would:

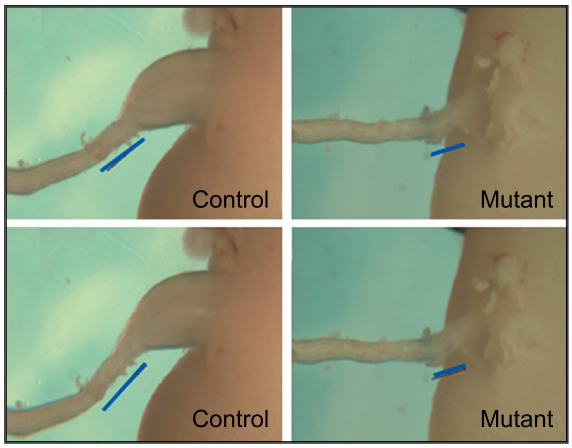
- Determine whether early repair improves semen parameters, testicular growth, and fertility.
- Develop reference data of normative semen parameters in the fully developed male adolescent.
- Identify possible clinical and hormonal indicators that allow identification of adolescents at risk for infertility.
- Define clear indications for intervention to correct varicocoele.
- Provide specimens, including serum and fractionated semen, for identification of novel biomarkers.
- Identify the molecular basis of testicular damage in varicocele by assaying for novel biomarkers from banked specimens, including testicular vein blood and fractionated semen.
- Exploit the use of animal models of varicocele to study factors that control testicular growth and the mechanisms by which varicocelectomy restores fertility.
- Assess the outcomes of testicular artery-sparing surgery versus other methods.
- Study the health benefit of educating primary caregivers and teens on varicocele to increase early detection.

IV. Research Methodologies

20. Animal Models

Summary

At present, our understanding of cellular and molecular mechanisms of normal and abnormal development of the genitourinary system lags behind that of other organ systems. A broad program of research using model organisms is essential if this situation is to be remedied. While the mouse remains indispensable, non-mammalian models such as the zebrafish hold great promise; rat, chicken, frog, and other models will continue to have unique applications. Essential to progress will be collaborations; between clinician and basic researcher, between those working **in vivo** *and* **in vitro**, *and among those with expertise in different animal systems.*



Deletion of a calcium signaling protein, calcineurin, causes defects in pyeloureteral peristalsis, obstruction, and nephropathy in the developing mouse. Blue bars indicate length change in the most proximal segment of the ureter (from CP Chang et al. Calcineurin is required in urinary tract mesenchyme for the development of the pyeloureteral peristaltic machinery. *Journal Clinical Investigation* 113: 1051-1058 © 2004).

Basic understanding of development and maldevelopment of the GU tract will derive largely from work in model organisms. The mouse is the most widely used system for a number of good reasons: available resources and infrastructure include a sequenced genome, cDNA and genomic microarrays, tissue- and stage-specific cDNA libraries, and a multitude of mutant lines. Morphology and physiology is sufficiently similar to that of humans so that translational research can be accomplished. Among mammals, the mouse is uniquely amenable to intensive genetic and experimental manipulation. *In vitro* mammalian studies often use cells from rats as well as mice, and the rat is the primary model for physiology studies. Models for obstruction include sheep as well as rats, and bladder dysfunction has been studied mainly in cats and sheep.

Non-mammalian models have been underutilized but hold great promise for progress in this area. Zebrafish and medakafish have the advantage of being genetically tractable model systems with rapidly expanding genomic and proteomic resources and extremely short generation times. The power of the frog (*Xenopus*) system derives from the ease with which embryos can be manipulated. It is now possible to generate transgenic frogs, carry out genetic crosses, overexpress genes by electroporation and microinjection, and prevent gene function using antisense oligonucleotides or morpholinos. The

chick embryo has been a powerful system for developmental studies of numerous organs and, while not amenable to genetics, it offers a number of advantages over the mouse. Chick eggs are inexpensive, easy to obtain, and well suited to ***in ovo/vivo*** experimental manipulations, including tissue recombinations, surgeries, overexpression and knockdown of genes, and analysis of cell lineage by microinjection of lineage tracers and heterospecific transplantation. We suggest that a highly collaborative research effort continue across multiple experimental systems, profiting from the unique advantages and potentials of each.

Research Priorities

Multifaceted, collaborative approaches need to be strongly encouraged.

- Combine *in vitro* and *in vivo*/genetic approaches within the same animal model.
- Encourage collaborative efforts involving two or more investigators with expertise in different systems (e.g., *in vivo* versus *in vitro*, or in different animal models).
- Clinicians and basic researchers should work jointly to develop new *in vivo* and *in vitro* systems using model organisms.
- Use multiple animal models for the purpose of tissue engineering; this research will require interactions between cell and developmental biologists, clinicians, and physiologists.
- Investigate patterns of genitourinary malformations and disease in natural animal populations exposed to environmental contaminants.

Infrastructural Needs

All mutant mouse strains, particularly those produced in large centers, should be included in a database and be freely available for use as animal models or for *in vitro* studies of genitourinary disease.

21. Biomechanics

Summary

While biomechanics is a discipline essential to a functional understanding (from the cellular to the organ level) of organs of the genitourinary tract and to such goals as reengineering of the bladder wall, its application to urologic research has been limited. We list some important research goals in this area and underline the need to bring together selected specialists in biomechanical science and urologists with interests in the role of mechanical properties in urological disease.

Overview of Biomechanical Science as Related to the Bladder

Biomechanics, the study of mechanical forces in living cells and tissues, pertains to the bladder as a smooth muscle organ with dynamic prerequisites: urine storage at low pressure, and efficient and complete evacuation of urine through active muscle contraction. A comprehensive biomechanical description of the bladder would encompass the following topics, among others:

- fluid dynamics in non-rigid conduits including the bladder outlet, sphincter mechanisms, and urethra
- the mechanics of the individual cells (e.g., the effect of mechanical forces on the bladder smooth muscle cells, urothelial cells, and other cells in bladder)
- cell forces that may influence the extracellular matrix
- the assembly of connective proteins and other molecules that underlie the bladder's viscoelastic properties
- modification of intrinsic cell biomechanical behavior (e.g., muscle cell contractility and

blood vessel mechanics) by neurotransmitters and hormones

- the effect of mechanical bladder smooth muscle cell (BSMC) properties on cell phenotype and the surrounding microenvironment

Multiple cellular and molecular effects of mechanical stimuli have been described in whole animal bladder models, urothelium, BSMC cells subjected to strain, stretch, and compression, as well as the whole bladder in tissue culture. However, no systematic approaches have been established for such studies. Therefore, a more robust utilization of the principles of biomechanics, which can provide a conceptual framework to integrate mechanical force information from the molecular to the organ level, is clearly needed.

Biomechanics and Clinical Needs

If clinical practice is to be successful in maintaining the low-pressure storage and event-free evacuation critical to protecting the upper urinary tract, it must be informed by an understanding of the biomechanical properties of the bladder and its cellular and extracellular matrix components. It should be noted that biomechanical properties may also impact non-storage and emptying conditions, such as infection and tumor growth, in so far as microorganisms and tumor cells may respond to transient or permanent changes in cell biomechanics.

Biomechanics is of course fundamental to the long-term engineering goal of duplication of native bladder wall; here there is a need to establish minimal functional prerequisites necessary to guide design of functional bladder replacements. Also critical to the success of the bioengineering enterprise are models of long-term remodeling and engineered tissue survival that minimize the need for costly animal trials; because of the complexity of the remodeling process, *in vitro* model development should be undertaken first to avoid costly *in vivo* testing and development.

Research Obstacles

Our knowledge of bladder structure and shape—thought to be closely associated with the development and spatial distribution of wall tension—is very incomplete. Areas of contact with other pelvic structures still need to identified, quantified, and mapped out over a reconstructed, three-dimensional surface. We also know little or nothing about how the bladder layers are connected, to say nothing of the mechanical properties of these connections or how the bladder can accommodate large volume variations. Furthermore, a systematic approach to the *biomechanical* properties of cells with respect to their impact on bladder function and development is lacking.

Progress in these areas is greatly hindered by insufficient communication between clinical urologists and urologic investigators on the one hand, and biomechanical scientists on the other: clinical urologists and urologic investigators often possess only *ad hoc* knowledge of biomechanical science and do not appreciate its complexity; basic biomechanical scientists are largely unaware of bladder research goals and have not shown interest in developing clinically relevant models of bladder function.

Research Priorities

- Create new biomechanical models for the bladder with potential application to other systems (particularly the cardiovascular system). These should include organ culture models, and mechanical models describing tissue and cell behavior. Mechanical models of bladder wall function and wall stress should take into account the influence of adjoining pelvic cavity structures.

- Characterize the bladder's shape; areas of contact with other pelvic structures should be identified and quantified.
- Investigate the mechanical role of individual tissue components.
- Characterize the three-dimensional tissue structure of the bladder and other urologic organs from the cellular to the tissue level (1 – 1,000 μm)[1]

Infrastructural Needs

- Create a database of transgenic animals to collect unappreciated, non-utilized bladder tissues from *existing* transgenic animal models. This issue potentially cuts across all areas of bladder research.
- Convene a meeting/roundtable of selected specialists in biomechanical science and urologists with interest in the role of mechanical properties in bladder disease. The overall goal should be better communication of bladder biomechanical/biological requirements and questions to basic physical science, engineering, and biomechanics scientists.

[1] This will require high-throughput approaches to streamline integration of diverse imaging data into a three-dimensional structure. The structural information should be converted into databases suitable for immediate use in bioinformatic and computational biomechanics applications.

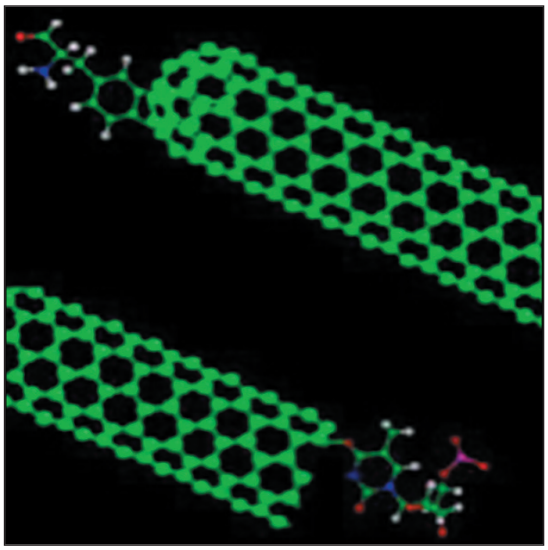
23. Nanotechnology

Summary

Nanotechnology is a new cross-disciplinary field emerging from technological advances that permit the manipulation of individual atoms and molecules. It promises to have manifold applications in disease detection, medical imaging, construction of complex biomaterials, and drug delivery and targeting. We propose steps to foster the active collaboration and communication between diverse scientific, engineering, and medical research communities necessary to develop the technologies that could revolutionize medical practice.

Nanotechnology has the potential to revolutionize biology and medicine by offering the ability to control and manipulate matter at a resolution that is at the molecular and atomic scale, in the 1 to 100 nanometer range. This means that scientists in this field are able work with individual atoms and molecules—a nanometer, or a billionth of a meter, is, about one eighty-thousandth of the diameter of a human hair, and only 10 times the diameter of the smallest atom. This technology does not derive from a single scientific discipline. Rather, it is a multidisciplinary combination of physics, chemistry, biomechanics, material science, and biology. Broadly speaking, nanotechnology incorporates:

- Research and technology in the length scale of approximately 1 to 100 nanometers
- Creation and utilization of structures, devices, and systems that have novel properties and functions because of their small and/or intermediate size
- Creation and utilization of materials, devices, and systems by building from the level of atoms and molecules



The electric properties of derivatized carbon nanotubes could make them invaluable as biosensors.

Two approaches to nanotechnology development are used: "top-down" and "bottom-up." In the top-down approach, development is driven mainly from the traditional disciplines of engineering and physics, and it makes use of current technologies like lithography used in making computer chips. This approach has the advantage of large-scale fabrication and more rapid integration of existing technologies. The bottom-up approach, starting from single atoms and molecules and exploiting the novel physical properties of the nanostructures, has more in common with chemistry and molecular biology. It uses the self-assembly of atoms or molecules to form nanometer-sized structures and is generally more difficult to control and characterize. However, in this field, both these approaches are often required concurrently. For example, in developing an antigen-specific sensor, the supporting circuitry would be fabricated from the top-down approach on traditional substrates, while the actual sensing element, consisting of biological molecules or nanoparticles, would be self-assembled.

Nanotechnology promises to allow us to communicate chemical information at a cellular and subcellular level, to place artificial components and assemblies inside cells, and to fabricate materials using self-assembly methods. New materials for use in pediatric urology could be created to act as templates for cell growth, structural components in tissue engineering, and antimicrobial surfaces. Nanostructured materials will facilitate early detection of diseases such as cancer and enable unprecedented advances in drug delivery technology.

As with any new field, applying breakthroughs in basic research in nanoscience to medicine presents obstacles to be overcome. Often it is difficult to fully characterize the structure or morphology of nanomaterials, particularly when they are functionalized or encapsulated. Typically, several advanced microscopy and analytical techniques such as NMR, EPR, and optical spectroscopy are required. Nanoparticles easily form aggregates, reducing their effectiveness as therapeutic agents, and toxicity studies have not kept pace with development and will lag for some time due to the proliferation of new nanomaterials.

Research Goals and Opportunities

It is difficult to encapsulate the research program of this new and diverse field in terms of priorities; we highlight some general directions for research that are likely to impact pediatric urology.

- **Develop biocompatible exogenous nanomaterials to control infection** and mitigate biofilm formation on the surface of long-term indwelling catheters, dressings, and engineered urological implants. Nanoparticles have been shown to be effective antimicrobials against bacteria and have shown the ability to penetrate biofilms.
- **Incorporate nanomaterials in tissue engineering.** Prosthetic bladders and urethra may benefit by the use of nanomaterials in the scaffolding to promote cell growth, quantify remodeling rates, and allow localized drug delivery. Nanomaterials might also be used

as templates for neuron growth when treating urologic diseases caused by spinal cord injuries.

- **Develop nanotechnology to improve drug targeting and specificity and allow timed, local release of drugs.** Tumor-restricted surface antigens may be targeted by adding specific nanoreceptors on the surface of nanoparticles. Drugs may be incorporated into nanoscale particles with coatings several nanometers in thickness, permitting controlled, local release of a drug through biodegradation of the encapsulant or stimulated release by radiation.
- **Create specific and rapid nanosensors for early detection of urological diseases using the properties of nanotubes and other technology.**
- **Enhance imaging systems for contrast at the cellular level using nanotechnology.** Nano-iron, and gadolinium particles can be used to enhance contrast in magnetic resonance imaging (MRI). Quantum dots allow visible and infrared imaging enhancement of tumors and cellular processes, and monitoring of tissue scaffolds during remodeling.

Infrastructural Needs

One of the most significant hurdles the new field presents is in education. Although the number of institutions offering programs in nanotechnology is growing, programs are primarily at the undergraduate level. Instruction needs to be developed for medical graduate and postgraduate students in pediatric urology to help them integrate the new technology. Since nanotechnology cuts across traditional disciplines such as biology, chemistry, engineering, physics, and material science, a new paradigm will be needed to train basic and clinical researchers.

Nanoscientists have materials and technologies in need of applications, and clinicians have problems in need of materials. A dialogue must be fostered between the two groups through seminars and workshops. Industrial, as well as academic, participation should be encouraged for effective cross-fertilization of ideas.

- Arrange joint mentoring of researchers by mentors with extensive experience in pediatric urology and nanotechnology.
- Fund new investigators taking a multidisciplinary approach to urology and nanotechnology.
- Encourage multidisciplinary research efforts between nanoscientists, urologists, and industry.
- Establish regional technical centers for nanotechnology and pediatric urology to assist with fabrication of new materials and their characterization.
- Develop educational programs to acquaint the next generation of urological researchers with nanotechnology.
- Convene workshops to foster interaction between clinicians and nanoscientists.

24. Stem Cell Biology

Summary

If the promise of stem cell research is to be realized in terms of beneficial treatments for patients, some major hurdles must be overcome. Methods for identifying, isolating, and enriching human stem cells—including those of the GU tract—at different stages of differentiation will need to be developed, and scientists need better means of tracking the location and fate of stem cells in the body. Much remains to be learned about the molecular signaling mechanisms that would mediate functional integration into human tissue.

Stem cells are undifferentiated, self-renewing cells that have the unique potential to produce many kinds of cells in the body. Various types of these cells are thought to be actively maintained in diverse adult tissues, including the intestinal lining, the hematopoietic system, and muscle. Their normal role in human disease is currently unclear. When grown in culture, stem cells can be induced to differentiate into many specialized cell types that form muscle, nerves, cartilage, blood, and other tissue. This property could revolutionize medicine, enabling doctors to repair specific tissues or to grow organs. A vast research effort has been directed to transplantation of these cells into animals with damaged or diseased organs—some improved function has been reported, but how enhanced function occurs and whether it derives from the function of differentiated stem cells remain unclear.

Major Research Obstacles

Significant challenges have to be overcome before any type of stem cell can be harnessed and translated to meaningful treatments for patients. These include identifying the optimal type of stem cell for specific assays and therapies for individual disorders, harvesting and growing sufficient quantities of the appropriate cell type, deciding the best therapeutic strategy for each condition to be treated, and assessing the potential side effects that may arise when such pluripotent cells are introduced into a patient. While methods exist to follow how some stem cells differentiate in animal models, there are no well-defined, non-invasive methods with which to study the survival, migration, fate, and function of stem cells in the living animal or human, and there are currently few markers, antibodies, or probes with which to distinguish specific classes of stem cell. Currently, little is known about the host environments that facilitate regeneration of tissue or the molecular signals that are responsible for tissue organization.

Research Priorities

- Isolate and characterize in molecular terms the stem cells from the GU tract.
- Investigate the effect of urological diseases on the fate of stem cells from the GU tract.
- Define *in vitro* culture conditions for maintenance and differentiation of GU tract stem cells.
- Use existing *in vitro* systems for complex morphogenesis to study cell biology, differentiation, and morphogenetic behavior of stem cells in three-dimensional environments.
- Utilize stem cells for drug discovery studies.
- Develop methods for identifying, isolating, and enriching human stem cell populations at different stages of differentiation.
- Develop reliable protocols for expansion, maintenance, verification, preservation, storage, and shipment of stem cells.
- Develop non-invasive methods and agents with which to visualize or track stem cells in the body.
- Develop therapies based on stem cells to treat urological diseases.

Infrastructural Needs

Advancing stem cell research will require dissemination of technical knowledge and skills in cell culture techniques across a variety of disciplines and disease research areas. There are few investigators who have sufficient experience with this research tool.

- Educational courses focused on the cell culture techniques for human embryonic stem cells; designated workshops for the dissemination of technical knowledge pertaining to isolation, characterization, maintenance, *in vitro* assessment, and *in vivo* application of stem cells.
- Standardized laboratory practices for use of human stem cells including proper exposure precautions, safe methods of disposal, and recordkeeping.
- Centers that will bring together basic stem cell biologists, researchers skilled in novel modes of cell delivery, urologists with disease-specific expertise, and investigators experienced in developing and assessing animal models of human diseases to create new research teams.
- A national stem cell repository and stem cell technology and bioinformatics core. This clearinghouse could receive, process, store, and distribute information on stem cells.

25. Clinical and Developmental Imaging

Summary

Imaging technology is central to both basic and clinical research in pediatric urology. In the area of basic research, understanding the genetic basis of genitourinary tract development depends on precise images of the developing urinary tract as researchers assess the consequences of a specific mutation or use gene fusions to localize specific proteins. On the clinical side, the key impact of imaging technologies is to provide a noninvasive means for researching the onset and extent of pediatric urology disorders, as well as to provide the means to evaluate effectiveness of treatment. The use of imaging technologies, such as prenatal MRI to examine genitourinary tract development in real-time, will provide, for the first time, the capability to assess the cellular and molecular processes affected during urologic malformation. This will facilitate the accurate diagnosis and treatment of common pediatric urologic disorders.

Research Priorities

Imaging innovations have progressed rapidly, but a rigorous and systematic assessment of the emergent technologies has not been performed. Formal assessments are required to determine whether they will actually result in improvements in GU-specific health outcomes and be cost effective.

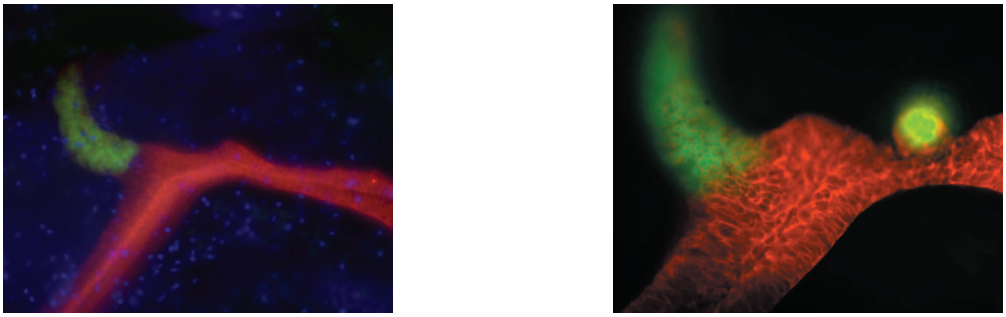
- Develop non-invasive imaging technologies:
  - to target GU abnormalities
  - to facilitate the analysis of prenatal GU tissues and improve the understanding of how congenital urologic malformations occur

  - to eliminate or reduce the radiation exposure to children during the diagnosis and management of common pediatric urologic disorders
- Develop imaging technologies to examine newly identified GU genes for their specific patterns of expression and function in tissues commonly affected by urologic malformations.
- Support the production of novel mouse lines bearing gene fusions and other constructs to facilitate the imaging analysis of gene function during prenatal GU development.
- Develop non-invasive imaging technologies for large animal models to identify processes and mechanisms involved in the diagnosis and therapy of pediatric urologic disorders.
- Examine whether the fusion of functional and anatomic images can replace invasive imaging procedures.
- Expand the use of low-radiation dose fluoroscopy and nuclear medicine technologies to facilitate the analysis of urologic disorders.

Infrastructural Needs

Pediatric urology requires a focused funding initiative to help insure that both the clinical and developmental imaging sciences are integral to the training and practice of pediatric urologists. Programs that provide enhanced research opportunities for pediatric urologists to understand imaging technology assessment and gene function in a developmental context will augment their clinical pediatric urology training and their effectiveness as caregivers.

- Establish programs in which education in imaging science is integral to the training of urologists.
- A platform for the sharing of imaging information on the developing urinary tract by clinicians and researchers



A mouse strain expressing a Hoxb7-Gfp transgene which is localized in the ureter and Wolffian ducts has been-stained with E-cadherin, a general epithelial marker that also labels the urogenital sinus, the primordium of the bladder, and urethra. The ureter and the Wolffian duct (both in green) are initially fused (left panel). During days 13-14 the ureter separates from the Wolffian duct, inserts in the urogenital sinus and is transposed to a new position at the base of the developing bladder (right panel). Disruption of this process underlies a number of developmental anomalies in humans including VUR, thought to affect 1 to 2 percent of the population (courtesy of Dr. Catherine Mendelsohn, Columbia University).

26. Systems Biology

Summary

Technological advances in the separation and characterization of biomolecules, coupled with the emerging field of bioinformatics, have allowed for the acquisition and organization of enormous amounts of data describing an organism in terms of gene and protein expression, metabolism, DNA modification, and other parameters. The possibilities for identifying relevant biomarkers to assist the clinician in the diagnosis and treatment of specific diseases are enormous. We propose some specific steps to ensure that clinical investigators in urology can take advantage of this new field.

"Systems Biology" is a new term for the discipline forming in response to the assembly of enormous data sets of biological information, data sets made possible by advances in biotechnology—automated DNA sequencers, chip-based methods of transcriptome and genome scanning, mass spectrometry-based methods for sequencing proteins, and many others. These data sets are quite diverse; they might include the sequences of entire genomes of related organisms, tables specifying the relative expression of all the genes in an organism in a particular tissue under specific conditions, or the relative amounts of all different proteins in a particular cell.

The organization and analysis of the data to address meaningful questions in biology and medicine depend on powerful computational tools and the emerging discipline of bioinformatics. The transfer of data between laboratories, across technical platforms, and between investigators with divergent expertise presents complex problems whose solutions are now in their infancy, and are a focus of active research.

The categories below give some idea of the breadth of investigations in systems biology:

Genomics

The systematic study of the genetic information of an organism (genome) offers researchers the prospect of developing new insights into the genetic basis of disease. Based on assays for single nucleotide polymorphisms (SNPs) in populations, scientists can identify individuals who are at genetic risk for particular diseases or particular adverse outcomes in the clinic. Studies often extend beyond one generation and require tracking of ancestral groups and migration/immigration patterns, and the number of specimens and the genetic loci to be analyzed in these studies is enormous. Additional challenges occur at the level of computation and data analysis. Several high-throughput platforms are becoming available for rapidly assessing SNPs, permitting us to envision a genetics-based urologic practice.

Transcriptomics

With the advent of high-density oligonucleotide or cDNA arrays, the transcription of thousands of genes in a particular biological sample can be studied simultaneously. After a decade of efforts toward standardization of array platforms, attaining accurate annotation of thousands of genes, and development of data-mining software, global gene profiling has becoming a common experimental tool. If its application in pediatric urology is still limited, the conceptual and technical foundations now exist for: (1) comprehensive description of transcriptomes (the set of all RNAs in an organism) and deeper insight into the program of transcriptional regulation; (2) identification of novel molecular pathways for the discernment of new disease mechanisms; (3) discovery of gene clusters whose expression are altered in a pre-disease state (biomarkers) or are associated with subsets of patients (patient-stratification tools), and; (4) identification of molecular targets of

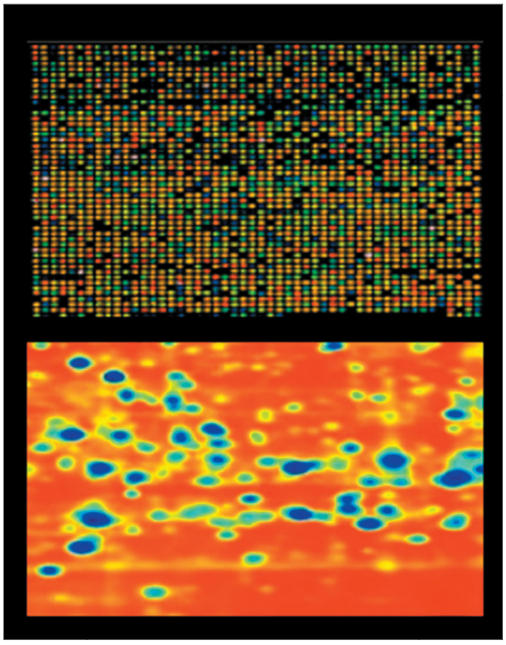
value to intervention and classification of patients' responses. When combined with appropriate animal models or well-designed clinical trials, this technology may become one of the most powerful tools for pediatric urologic investigations.

Epigenomics

Epigenetic mechanisms mediate heritable changes in gene expression that do not involve a change in DNA sequence *per se*. They can involve either chemical modifications of the DNA itself or modifications of proteins that are closely associated with DNA. Epigenetic regulation controls important biological processes such as imprinting, X chromosome inactivation, and transcriptional control of gene expression; its disruption contributes significantly to the etiology of many human diseases. In the past decade, "epigenomics," or the study of whole-genome epigenetic changes, has gained momentum with the advent of modern investigative tools: methylation-sensitive fingerprinting, restriction landmark genome scanning, and methylation-specific oligonucleotide arrays that allow identification of aberrant hypo- or hyper-methylation sequences and simultaneous assessment of methylation status of multiple CpG islands. Like the SNP- based approaches for the systematic analysis of sequence, determining the methylation patterns of a large enough number of genes has the potential to yield highly discriminating signatures for specific diseases.

Proteomics

The field of proteomics began with efforts to determine the structure, expression, localization, activity, and cellular roles of the ensemble of proteins (proteome) in the body. Great progress has been made in this field of research owing to novel instrumentation, experimental strategies, and bioinformatics methods. A more contemporary goal of proteomics research is to obtain a comprehensive, quantitative description of expression of hundreds, if not thousands,



Two methodologies that permit a systems biology approach. In gene expression arrays (top), the immobilization of defined DNA sequences at particular points in a grid allows for simultaneous measurement of the abundance (reflected by pixel color) of all RNAs in a biological sample. In the lower panel, the electrophoretic separation of a complex mixture of proteins allows the amount of each protein component to be quantified. In both approaches, sophisticated methods of data acquistion and analysis allow clinicians to identify patterns of abundance that are markers for diseases.

of proteins/peptides, and changes in their interrelationship under the influence of biological perturbations such as disease or drug treatment. The complex information that proteomics provides has the same potential for providing biomarkers and other predictive information as the gene-based approaches outlined above. Current state-of-the-art methodologies of proteomics permit (1) pattern recognition (without identification of specific proteins/peptides) via protein profiling by sophisticated separation methods; (2) identification of proteins/peptides using a multidimensional protein identification technology (MudPIT); (3) relative and absolute protein quantification using techniques such as isotope-coded affinity tag (ICAT) labeling, iTRAQ, and metabolic labeling-

MS; and (4) construction of two-dimensional ion density maps of proteins directly from the surface of tissue sections using MALDI imaging.

Metabolomics

Metabolomics is the systematic study of the metabolites of a cell or organism. Traditionally, characterization of abnormal metabolites in blood, urine, or tissue biopsies has been used to detect diseases such as inborn errors of metabolism. However, the concept of parallel analyses of all the metabolites in a biological sample has been made possible only because of rapid advances in technologies such as gas chromatography mass spectroscopy. With these technologies, all the metabolites in the sample set are taken into statistical consideration to derive the algorithms permitting disease or disease-stage identification and prediction of patient response.

A major goal of systems biologists is the creation of "networks" of various kinds. These include signal transduction, protein-protein, DNA-protein, and three-dimensional mapping types of networks. For example, one extension of traditional proteomic approaches would be to characterize, using yeast two-hybrid methods, the set of protein-protein interactions that characterize the state of a living cell.

Relation to Clinical Needs

The value of the systematic approaches briefly described above might be illustrated by recalling traditional approaches. Urinary markers of VUR, for example, have been identified using educated guesses as to what markers might be important, and testing them with relatively crude detection technologies such as Western blotting. In the systemic approach, all of the proteins that appeared in the urine during the course of VUR (and during its spontaneous resolution, and in uninfected patients) can be systematically identified and, using computer-based analytical techniques, patterns that are specific to VUR can be ascertained. With the advent of proteomics, genomics, and epigenomics, we are able to identify many more potential biomarkers or highly discriminative marker-clusters that may serve as diagnostic, prognostic, and therapeutic tools. Significant challenges remain in identifying sufficient numbers of these markers or marker-signatures, testing them through case-control studies and prospective trials, and developing the statistical and computational tools necessary to analyze and model complex data sets.

Research Opportunities

Most major teaching centers include facilities and expertise for genomics research. Proteomics capabilities also are becoming more common, and within a few years will be ubiquitous at major centers. The proximity of these technologies and specialists trained in their use means that it will be possible for clinical and basic scientists conducting urologic disease research to use these approaches in their own studies. Some specific research opportunities are:

- Establishment of databases of gene and protein expression patterns in the genitourinary tract, at various stages of development in health and disease.
- Application of urine proteomic information to developing biomarkers of diagnostic and predictive value, including markers that predict response to certain clinical interventions.
- Identification of at-risk populations based on systems biology approaches.
- Identification of markers for cell types destined to become components of the upper or lower collecting system.
- Creation of cross-platform approaches that incorporate relevant animal models.
- Use of pharmacogenomics to discover new drugs and treatment protocols.

- Identification of maternal factors that contribute to pediatric disease.
- Decoding gene function and complex biological pathways that govern diseases through the identification of unique transcriptomes and their master switches.

Infrastructural Needs

There is a significant technical, cultural, and conceptual chasm between most clinical and basic researchers in urology and those doing genomics, proteomics, and other systems biology studies. Most systems biology experts have little familiarity with urology as a discipline, and often little or no familiarity with medical fields in general. A common misconception of basic researchers in "leading edge" fields is that urology-focused questions are either trivial, derivative, or otherwise uninteresting. Because it is more likely that long-term interest in an area will be spawned when one "grows up" in it, pediatric urology needs new mechanisms for attracting gifted and promising graduate students and junior scientists with an interest in basic research. Research training programs specifically focused on pediatric urology, and in urologic disease in general, need to be developed and implemented.

Systems biology is a technology-driven area. Consequently, infrastructure needs are great and require an extremely large amount of financial capital and other resources. Leaders of urology research programs need to be positioned within their own institutions in a manner that will allow them to maximize their colleagues' access to and participation in the newly forming infrastructure elements (e.g., genomics programs and proteomics core facilities) that are relevant to systems biology studies.

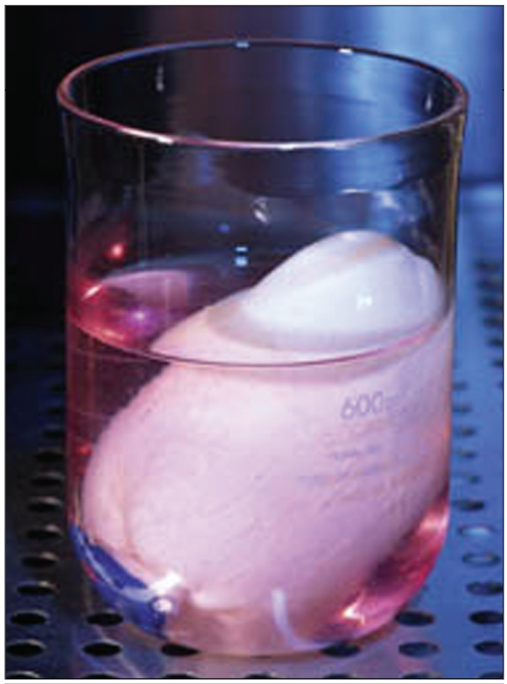
- New NIH pre- and postdoctoral training programs integrating systems biology with urological disease research.
- Better participation of national medical organizations (the American Urological Association in particular) in maintenance and development of academic training programs that promote state-of-the-art research involving clinicians.
- Systems biology requires high levels of dedication and willingness to acquire new expertise. Integration of systems biology research with urology will require clinicians to focus less on high-volume patient care and make more of a commitment to research.
- Development of financial instruments within academic urology practices that will allow research-oriented urologists to pursue academic research careers without being overwhelmed with clinical demands.
- Establishment of accessible tissue banks linked to comprehensive clinical databases.

27. Tissue Engineering

Summary

Millions of American children suffer from congenital and acquired urologic diseases. Dysfunctional organs from these diseases interfere with the normal development of the child and have a large economic impact on our health care system. In the future, tissue engineering will play an important role in the treatment of pediatric urologic disease. Recommendations for future research on tissue engineering include:

- *Conduct tissue engineering research of the bladder, urethra, kidney, and pelvic floor with the following goals:*
  - *Increased understanding of normal and abnormal cells and developmental biology*
  - *Development of cell therapy*
  - *Development of tissue and organ replacement*
- *Enhance training and education of physician/scientists in tissue engineering.*
- *Enhance interdisciplinary collaboration and education.*
- *Establish appropriate infrastructure, training, and core facilities for research.*



Engineered Bladder Prior to Implantation. A small piece of tissue is obtained from the bladder in need of replacement or repair. The progenitor muscle and urothelial cells are expanded and seeded separately on each side of a three dimensional bladder shaped scaffold. The construct is placed in a bioreactor where the tissue is allowed to grow. One week later, the engineered bladder is ready for implantation (courtesy of Dr. Anthony Atala, Wake Forest University).

Diseased pediatric urologic tissues have traditionally been replaced or repaired with autologous tissues harvested from other sites of the body or by heterologous transplantation. However, these approaches rarely replace the entire function of the original tissue. For example, many congenital and acquired pediatric urologic conditions render the child's bladder dysfunctional. When these dysfunctional bladders require reconstruction, a surgical procedure called bladder augmentation is required. This complicated surgical procedure, which uses tissue from the patient's own gastrointestinal tract, is associated with significant complications, including infection, intestinal obstruction, mucus production, electrolyte abnormalities, perforation, and cancer. Other pediatric urologic disease states—hypospadias, exstrophy, and epispadias, posterior urethral valves, prune belly syndrome, intersex, urinary incontinence vesicoureteral reflux, renal failure, and hormone-deficient states—require replacement of organs or organ systems, and the need for advances in tissue engineering to meet this need is critical. Tissue regeneration may or may not require cells. If cells are needed, several sources might be available, including mature stem progenitor stem cells and

other cell types occurring naturally in a person's body (autologous) or derived from another source (heterologous). Stem cell populations associated with the urinary tract recently have been identified, although their characterization is incomplete.

Current tissue engineering techniques using cell-scaffold composite grafts to induce regeneration have utilized cultured cells from the *normal* animal organs. However, future clinical application of this technology in patients with abnormal organs will involve the use of cells derived from the pathologic abnormal organs. For normal organ regeneration process to occur successfully in humans, cultured cells from the *abnormal* organs must not be terminally differentiated and must possess normal proliferative and functional characteristics, and differentiate normally. Unfortunately, little knowledge exists as to whether cells from an abnormal organ retain normal growth patterns and functional characteristics in an *in vitro* culture environment.

Priorities for Basic Research

During the past 2 decades, it has been established that the bladder, urethra, penis, vagina, ureter, pelvic floor, and kidney have the potential to regenerate. From this work, it is now clear that interactions between the epithelium and mesenchyme are essential for the formation of normal tissues and organs. These discoveries may be exploited soon to generate sizable quantities of tissue suitable for study and transplantation, provided that strategies can be developed to isolate, expand, and differentiate native, autologous cells *in vitro* and *in vivo*. This will require that cellular signaling or growth factors that mediate the development of normal functional tissues be identified.

- Elucidate the cell signaling that occurs between the epithelium and smooth muscle of pediatric urologic organs and the role of extrinsic growth factors and their receptors.
- Define further the immunobiology of biomaterials used for tissue engineering.
- Define the effects of biomaterials on surrounding normal tissue.
- Determine how the mechanism of tissue regeneration differs from normal wound healing.

Priorities for Translational Research

It is a reasonable prospect that advances in cell biology and cell research may enable scientists to grow tissues and organs in the laboratory—a small population of cells given the appropriate molecular cues would proliferate and differentiate into functional organs. This would eliminate many of the current obstacles to organ replacement, such as donor-recipient mismatches and limited organ availability.

- Develop models of long-term remodeling and engineered tissue survival to minimize costly animal trials.
- Explore the effect of the pediatric urologic organ biomechanical properties on early regeneration.
- Develop methods to manipulate the local environment (through the scaffold material, extracellular matrix, or appropriate growth factors) to induce the controlled regeneration of tissues or organs starting from these cells.
- Define and standardize biomaterials in terms of such properties as elasticity, induction of cellular proliferations, and stability.
- Explore the use of biomaterials with bioactive functional groups to increase revascularization and other processes critical to normal regeneration.
- Establish biomaterial preparation and scaffold production and standardization laboratories.
- Develop cell production capabilities and cellular function tools.

Infrastructural Needs

The development of tissue engineering technologies is currently hampered by a lack of appropriately trained investigators. The new technologies that would most likely yield the greatest impact are not taught well, and few training programs provide students with in-depth skills to perform tissue engineering research.

- Institute training awards that allow outstanding health scientists to develop expertise in tissue engineering and materials science under the guidance of outstanding investigators in this field.
- Establish Centers of Excellence dedicated to tissue engineering.
- Establish a kidney, bladder, urethral, and pelvic floor primary and stem cell bank that would include a depository and central distribution center for sharing cells, reagents, and model systems.
- Establish a patient registry to assist in obtaining needed samples from a large population.

Public interest and educational efforts

As the sciences of tissue engineering continue to be developed, scientists should not overlook particular experimental therapies that could raise ethical concerns among some members of the public. Forums that discuss the ethical, legal, and social issues in biomedical research should guide policy decisions in these areas. These forums include the NIH Office of Biotechnology Activities, the NIH Office of Human Research Protections, and the President's National Bioethics Advisory Committee

Ongoing communication among scientists, physicians, educators, ethicists, theologians, elected officials and the public is essential to guide the future of this research, and to ensure that America continues to invest judiciously and responsibly in biomedical research.

28. Clinical Trials and Epidemiology

Summary

Pediatric urologic practice should be guided by the kinds of objective criteria that can be only obtained through sound clinical trials and valid and comprehensive epidemiological studies. Top priorities are:

- ***Establishment of standard definitions of pediatric urologic conditions for use in clinical practice and research***
- ***Development of a set of standardized objective and patient-centered outcomes for use in clinical research of various pediatric urologic conditions***
- ***Organization of clinical research networks to undertake randomized clinical trials***
- ***Creation of pediatric urology disease registries for use in clinical research and improvement of quality of care***

Pediatric urology is a focused subspecialty of general urology that deals with relatively uncommon congenital disorders. Consequently, *clinical research is hampered by difficulty in assembling adequate samples from which to draw meaningful conclusions. The research enterprise also is hindered by a lack of a standard nomenclature and validated outcomes for various conditions, and the absence of a centralized support structure and inadequate funding.*

Current Needs in Clinical Research in Pediatric Urology

Standard definitions

There are no established standard classification systems or nomenclature for many pediatric urologic conditions (e.g., hydronephrosis, hypospadias). This is a significant hindrance to clinical research, as existing studies often focus on disparate populations

of affected children with the same condition, limiting the generalizability and validity of the results. *A series of NIH-sponsored multidisciplinary workshops should be convened with the explicit goal of developing these definitions and classification systems*. Each workshop would address a specific pediatric urologic condition. Patient advocacy groups and professional societies would be included in the planning process and the workshop itself.

Training in clinical research methodologies

There are few investigators in pediatric urology formally trained in clinical research methodologies such as clinical trial design, epidemiology, or health services research. Targeted NIH funding for new clinical researchers in pediatric urology is recommended. Included in this initiative should be health care professionals from other disciplines—behavioral specialists, social scientists, and others—to promote an interdisciplinary model of care for patients with urological conditions and an associated research agenda. Workshops on topics ranging from study design to grant writing should be held to encourage the development of advanced research skills and promote new collaborations among investigators.

A central coordinating center

Pediatric urology clinical researchers do not have adequate support services to generate pilot data with which to support initial grant applications. *We suggest the establishment of a central clinical research and epidemiology coordinating center with expertise in biostatistics and study design to support novel studies in the field*. This shared resource would then be available to support new investigators and assist in generating pilot data for future grant applications.

Widely accessible, standardized databases to support clinical research

Currently, there is no agreement on the required data elements for databases of pediatric urologic conditions, and there are significant differences in the information technology platforms of existing databases that prevent data sharing. *Shared databases with common data elements should be developed, with the software for these databases available to all investigators*. Software should be constructed in such a manner that participating centers have the option of uploading data (stripped of personally identifying information) to the World Wide Web for analysis in the aggregate. As new data platforms are developed, they should be vetted by NIDDK staff, representatives of the various professional societies, and patient advocacy groups to ensure both the clinical utility and research applicability of the software. If feasible, a standing board should be created to facilitate this process.

Clinical Research Networks

There are no established clinical research networks in pediatric urology and few adequately sized randomized clinical trials have been completed. Collaborative networks will be needed for the conduct of large, randomized clinical trials. These networks should include a mix of academic and community medical centers, and they should utilize an interdisciplinary approach.

Disease registries

Patient registries, essentially databases containing information about clinical characteristics (e.g., gender, classification of condition, description of treatment), treatment interventions, and outcomes of a patient population with a particular condition, are vital tools in clinical research. Particularly useful in conditions that are relatively rare, registries can merge a geographically diverse patient population and thereby aid the development of randomized clinical trials and observational studies. There are few adequate disease registries available to address scientific questions in pediatric urology. Those that do exist tend to be from single institutions and are either not generalizable or of inadequate size. *We propose the funding of patient registries in pediatric urology that share the following*

features: (1) standardized collection of patient demographic information (including socioeconomic status, race/ethnicity and other sociodemographic factors); (2) standardized nomenclature of disease and descriptions of treatments, procedures, and outcomes; (3) inclusion of health-related quality of life (HRQOL) measures; (4) methods to ensure the generalizability of the collected data; and (5) collection of serum and tissue for deposit into existing NIDDK repositories.

Standardized objective and patient-centered outcomes

There is great debate regarding which objective endpoints should be used to define a successful outcome after treatment for many conditions in pediatric urology and, at the same time, there are few patient-centered tools for assessing outcomes in these diseases. **We suggest** *that standardized objective outcomes (short- and long-term) must be developed for use in clinical research in pediatric urology*. Included in these should be functional status and patient-reported symptom severity and HRQOL. The opinions of patient advocacy groups should be solicited in the development of these measures. Disease-specific HRQOL instruments should capture the distinct perspectives of the patient, his/her parents, and the health care provider. New instruments should provide a unique and much-needed perspective on patients' physical and psychosocial outcomes that are less focused on "pathology" (e.g., clinical depression) and more focused on adjustment to daily living. Finally, these instruments should be culturally sensitive and should be validated in Spanish and well as English, in an effort to capture the unique impact of pediatric urologic disease in minority and underserved populations.

Inclusion of minority and underserved populations

Many clinical studies do not enroll adequate numbers of minority or underserved subjects, limiting the generalizability of the results. Recent evidence suggests that careful preparation and planning of clinical studies can significantly increase minority and underserved subject recruitment and retention. Two models have been developed to guide the investigator: the Interactional Model for Recruiting Ethnically Diverse Research Participants and the Recruitment Triangle. These models essentially tailor the study personnel and recruitment strategies to the target populations, identifying key barriers to recruitment of minority and underserved individuals, and developing successful strategies based on incentives, outreach to parents and health care providers, improved communication, and other elements. They should be used in pediatric urology clinical research.

Identification of risk factors

Few genetic, environmental, and behavioral risk factors for the development of pediatric urologic conditions have been identified. Standard epidemiologic research methodologies, such as case-control and observational cohort designs, should be employed to identify genetic, environmental, and behavioral risk factors for pediatric urologic disease. Birth certificate registries, like the one in the State of Washington, should be utilized to help identify cohorts as well as *in utero* exposures that put children at risk for development of pediatric urologic disease.

Top Priorties

- Establish standard definitions of pediatric urologic conditions for use in clinical practice and research.
- Develop a set of standardized objective and patient-centered outcomes for use in clinical research of various pediatric urologic conditions.
- Establish clinical research networks to undertake randomized clinical trials.
- Create pediatric urology disease registries for

use in clinical research and improvement of quality of care.

Additional Priorities

- Foster the development of clinical research within pediatric urology by establishing a central clinical research and epidemiology coordinating center to support novel studies in the field.
- Increase the number of pediatric urology investigators formally trained in clinical research methodologies.
- Develop bioinformatic software for use in pediatric urology and make it available in the public domain for use by all interested investigators.
- Encourage the enrollment of minority and underserved populations into pediatric urologic studies.
- Identify risk factors for the development of and/or severity of pediatric urologic diseases.

29. Therapies and Diagnostics

Summary

Research that seeks to rigorously assess the usefulness of new technologies in pediatric urology, with the ultimate emphasis on child health outcomes, as well as cost-effectiveness, is strongly encouraged. Collaboration between industry and academia is essential for the development of new diagnostic and therapeutic technologies; professional societies can play a vital role in developing evidence-based guidelines for their use, and modern methods of communication by the National Institutes of Health and other organizations can ensure that the public and health care professionals have the information they need to guide them.

Many new technologies (e.g., endoscopic correction of vesicoureteral reflux) come into common clinical practice before a complete evaluation of their societal value or cost-effectiveness has been documented. In some instances, the efficacy of these new technologies can be questioned based on the inadequacy of the original clinical study design. However, once these technologies become commonplace and widely used, it is difficult to re-evaluate their role and change clinical practice patterns. *This mandates that a more careful assessment of new technologies be performed prior to widespread implementation.*

Assessment, Validation, and Diffusion of New Technologies

The critical assessment of a new pediatric urologic technology should be based on a well-validated conceptual framework. Thornbury and Fryback's "hierarchy of levels of efficacy" guides the logical evaluation of a new technology from the laboratory to clinical practice. Specifically, the framework directs the performance of studies in a defined order, and provides data on the technical feasibility (level 1), diagnostic accuracy (level 2), impact on diagnosis (level 3), changes in clinical management (level 4), improvement in child health outcomes (level 5), and societal value/cost-effectiveness (level 6). Special emphasis, especially in those diseases having long-term ramifications, should be placed on the last two levels, which are generally neglected in childhood diseases. Without long-term assessment with perpetual databases and ongoing statistical efficacy and cost analysis, the cost-benefit analysis that should be the basis of health care policy cannot be performed.

Workshops and forums to discuss ethical, legal, and social issues related to the new technology, and best practice adoption through evidence-based guideline formation by professional organizations, also are needed. Modern information and communication technologies are effective tools to help in the

collection, processing, and targeted distribution of information from which clinicians, researchers, administrators, policymakers in health, and the public can benefit.

Corporations have the financial resources and the incentives to develop new technologies; academic medical centers provide the medical expertise and the infrastructure to evaluate and implement these new technologies. In spite of the mutual need, complex legal and financial issues have sometimes stymied corporate collaboration with academic research. This is particularly true in pediatrics, where pharmaceuticals and medical devices are not often developed or tested and where there are few incentives to include children when evaluating new technologies.

Priorities

- Support research proposals that incorporate rigorous technology assessment with emphasis on health outcomes and cost-effectiveness.
- Encourage development and testing of new technologies in children.
- Establish grants targeted at collaborative research in pediatric urology between industry and academic medical centers.
- Disseminate evidence-based information to the lay public and health care professionals.
- Partner with professional organizations to develop evidence-based guidelines.
- Encourage forums to examine ethical, legal, social issues related to new technology in children.

V. Training And Manpower

30. M.D. Training

Summary

A variety of institutional pressures make life exceedingly difficult for pediatric urologists contemplating a research career. We recommend new training mechanisms that would allow those with a strong commitment to immerse themselves in research under the mentorship of scientific leaders in the field.

A Scarcity of Research Opportunities

During the last decade, funds for supporting urology training have progressively dwindled—while reimbursements to hospitals have been greatly decreased and managed care has reduced clinical revenues to academic departments, departmental administrative costs to support residency and fellowship training programs have greatly increased. Historically, many urology training programs offered 1 year of basic research training during residency training. This often was funded by the hospital or, in rare cases, endowments within urology departments. However, during the last decade, the overwhelming majority of urology training programs have been transformed from 6- to 5-year training programs in which the maximum amount of time that can be allocated to basic research is only 6 months. As a result, many program directors, considering a 6-month exposure to the laboratory too short, even as it limits needed clinical experience, have decided to abandon a research experience altogether. While most would agree that a research experience is important for trainees, it might not represent the optimal resource allocation in the present environment, where the overwhelming majority of urology trainees seek private practice opportunities and may not be motivated to take full advantage of the research experience.

Medical School Research Training

Since the overwhelming majority of individuals who ultimately pursue academic careers are from the minority who complete subspecialty training, the focus of a program to foster research should be on this group, beginning at the medical school level. Pediatric urologists at academic institutions need to actively seek out students interested in a summer research experience or an additional year in a pediatric urology laboratory that would provide a sound foundation and exposure to their field. Funds that would facilitate this research training would be well justified, as a superb mentoring experience with scientific leaders in pediatric urology will attract individuals with a true interest in basic research to enter the field. It is envisaged that these individuals then will seek urology programs with a research year, further enhancing their interest in basic science.

Fellowship Training

At present, the entire burden for supporting fellowship trainees falls on the department or fellowship program. While the return on investment in clinical training is readily apparent, there are no revenues derived from a research experience to defray costs. Further complicating matters is the fact that, with their pressing clinical responsibilities, pediatric urology fellows are at a decided disadvantage in competing for the funds to support a research program. Although a small subset of urology fellows does successfully compete for AFUD scholarships, the number of

these awards is inadequate[1]. Currently, the NIH does fund pediatric urology fellows with 2- or 3-year training grants, but only a limited number of pediatric urology programs currently have these. (The new NIH guidelines that reduce to 50 percent the required time commitment for the K08 and R21 grants will be very helpful.)

Incentives

During the past decade, manpower in pediatric urology has changed in response to the ever-changing health care environment. There has been an increase in pediatric urologic positions, but at the same time, a decrease in some years in those seeking pediatric urology fellowships. The decline is related in part to the emergence of new lucrative subspecialties attracting the best and the brightest trainees. We suggest that program directors or affiliate hospitals might consider financial incentives for individuals entering pediatric urology, especially since, in the academic setting, these individuals often serve the underprivileged and the poorly insured, while at the same time trying to build clinical practices and establish themselves as basic science investigators.

Recommendations

- Pediatric urologists at academic institutions should focus on attracting medical students interested in a summer research experience or an additional year in a pediatric urology laboratory committed to providing a sound foundation in research, while exposing students to the field. Allocated funds for these medical students could be provided.
- One- or 2-year research funding should be widely offered for pediatric urology fellowship training programs. This should be a mentored experience with the goal of providing a strong foundation in the scientific method and exposure to competitive, high-level research.
- The timetable for grant applications should be synchronized with the match for pediatric urology fellowships.
- To ensure a pool of high-quality individuals to meet the needs of pediatric urology, new strategies are needed to attract individuals in medical school as residents to pediatric urology.

[1] One of the reasons fellows do not apply for the AFUD scholarship is that the notification of some of the matching fellowship training program is after deadline for submission of an AFUD grant—the timetable for grant applications needs to be adjusted to meet the match for pediatric urology fellowships.

31. Ph.D. Training

Summary

The participation of Ph.D. investigators in research with direct applications to pediatric urology is inadequate. We discuss some cultural barriers to this participation and advocate training programs to support graduate students studying research problems centered on urologic disease with urologists participating as advisors. Postdoctoral programs in urology research also are recommended.

The Ph.D. degrees relevant to biomedical research usually are obtained after the successful completion of an undergraduate science major, followed by course work and extensive independent research in a specialized area as a graduate student. Following the defense of a thesis before a panel of senior faculty, graduates typically go on to postdoctoral positions of varied intellectual independence prior to obtaining positions as scientists in academia or industry. Postdoctoral training is a critical element of the Ph.D. career path. The most promising Ph.D. graduates typically seek out postgraduate training in leading laboratories, ones that routinely publish papers in high-impact journals such as *Cell*, *Nature*, and *Science*. With their technical knowledge, and scientific training, Ph.D.s are an essential component of any biomedical research program that aspires to national competitiveness and research productivity. Without their participation at the postdoctoral, staff scientist, and faculty levels, it is unlikely that most urologists would be able to assemble research teams of sufficient quality to conduct research at the highest level. Partly because of the emergence of industry as an attractive career option for young Ph.D.s, the percentage of Ph.D.s with faculty career potential willing to commit to a career path in academics may be declining.

Opportunities and Obstacles in Pediatric Urology

Although historically underfunded, pediatric urology presents some very favorable opportunities to those in research: urological diseases are rich with unexplored territory and clinical urology programs at major teaching centers reside within a "scientist-rich" environment; programs in large cities are generally located near some of the finest laboratories in the world. Furthermore, NIH is actively seeking meritorious applications in areas in urology where it has recognized specific needs. This might offer major advantages to those contemplating urology research compared to those in fields such as cardiovascular research and neuroscience, where competition for grants can be fierce and award decisions arbitrary.

Training and Recruitment

Unfortunately, for cultural reasons, urology is at present poorly positioned to compete for the best scientists. Senior academic leaders in urology frequently have little understanding of the modern research process or the unique aspects of the Ph.D. career path in comparison to that of the academic surgeon. In marked contrast to the situation in medicine, the field does not reward urologists who concentrate on research. Research-focused urologists frequently are criticized by their peers for not generating "their share" of clinical dollars. The field does not host a single basic science journal of sufficient impact factor to attract quality, cutting-edge research papers. For these reasons, Ph.D. scientists who encounter an academic urologist with whom they might consider collaborating on scientific grounds, might be put off or otherwise conclude that such a collaboration would not be a productive or enlightening endeavor.

Most Ph.D. training programs do not produce scientists who are prepared for research in urology. Their expertise generally is highly focused to certain model systems and methods of analysis. Their ability or tendency to read outside of their

own discipline may also be limited. Most are not familiar with problems inherent to clinical research.

Infrastructural Recommendations

To retain excellent scientists in urology at all levels, urology research needs to be structured along the lines of mature research programs in areas with historically strong research (e.g., neurology, endocrinology, and pathology). Although the questions addressed in a urology department's research labs should be restricted to those with some relevance to important questions in the field, this should be approached with a broad-minded view of what is in fact topical. The "culture" of the research lab in urology needs to be one of openness, fun, egalitarianism, and a willingness to try out new ideas. The laboratory should not be organized according to a hierarchical or dogmatic structure; this has no resemblance to the environment in which most Ph.D.s were trained. It is in an atmosphere where new approaches and research questions are encouraged, and ideas flow freely that conceptual breakthroughs are likely to occur. Familiarity and intimacy with one or more research areas, combined with appropriate mentoring and attention to career path from superiors, will foster professional commitment and will grow the field.

- Active participation of urologists in Ph.D. training programs, either as collaborators on projects or as "clinical-partner" mentors, would increase the familiarity of young scientists with urological problems and make them aware of potential research opportunities in urology.
- We propose training programs for graduate students studying basic research problems centered on urologic disease. Urologists could participate in these programs and could help in the recruitment of students.
- NIH should sponsor training programs for M.D.s to do urology-focused research before or during their urology residency (preferably for 2-year duration).
- Urologists and urology researchers should be poised to attract Ph.D.s fresh out of their graduate training into their research programs.
- Postdoctoral programs in urology research are needed. These might entail a mechanism to recruit graduate students prior to their completion of their Ph.D.

32. Collaborative Programs

Summary

We underscore the importance of collaboration between basic scientists and clinicians in pediatric urology research. If the number of collaborative projects is to grow, novel funding mechanisms may be needed to address the unique demands of the clinician scientist struggling to fulfill dual roles as well as those of the basic scientist as she or he attempts to maintain funding within, or in collaboration with, a clinical department.

The nature of modern productive research is such that there is little role for the individual scientist. While this may be unfortunate, it is obvious that real progress in understanding diseases relevant to pediatric urology, and in developing novel diagnostic and therapeutic methods, will come from the concerted application of conceptual frameworks and methodologies from molecular biology, genetics, and cellular physiology, coupled with clinical insight. Collaboration by those with diverse expertise is essential; each team member brings a unique and critically important perspective, and intellectual insights beyond the initial grasp of any one individual may be attained. The role of the clinician in this collaboration is becoming increasingly strained: as basic science advances, it requires specialized knowledge and training, making it more difficult for clinicians to participate,

even as their participation becomes essential as translational possibilities emerge.

Support of Collaborative Research Involving the Clinician and Basic Scientist

Training

A basic exposure to research experience and methods should remain an essential part of urological training, and this can be extended into the fellowship years of pediatric urology. Conversely, exposure of basic researchers to those who have clinical training and interests is also vital. Research support from NIH should therefore encourage and foster the development of collaborative efforts in pediatric urology related research through support of both Ph.D. as well as M.D. training tracks, with situationally appropriate mechanisms. The duration and constraints of the support should recognize the different needs, time demands, and roles of members of the team.

Establishing and maintaining laboratories

In relatively young fields of research such as pediatric urology, there is a strong need to support the initiation of viable research programs at more institutions than currently include them in their portfolios. The development of new laboratories should be in the context of a collaborative effort, perhaps as off-shoots of established laboratories. NIH-sponsored initiatives that support the early work of a young clinician scientist or basic scientist in pediatric urology departments with mentorship from an established investigator might foster these new programs. Novel mechanisms of funding that encourage developing collaborative projects between basic scientists and clinician scientists would serve to assist in such new programs, as well as fostering the maintenance of such laboratories.

An ongoing challenge to pediatric urological research has been how to perpetuate productive research efforts as both clinician scientists and basic scientists strive to ensure grant funding in an environment of shrinking clinical support. NIH should consider as a priority the need to develop funding mechanisms that recognize the unique demands of the clinician scientist as she or he struggles to fulfill dual roles as well as those of the basic scientist as she or he attempts to maintain funding within, or in collaboration with, a clinical department. Funding mechanisms that permit less commitment of research time to participate in collaborative research should be considered. Mechanisms that permit research training of physicians also are advised. Recognition of the value of basic scientists in translational fields is equally important.

Priorities

The development of collaborative efforts in pediatric urology-related research should be fostered through support of Ph.D. and M.D. training tracks with situationally appropriate mechanisms.

- Novel mechanisms of funding that encourage collaborative projects between basic scientists should be considered: the clinician-scientist should be supported in such ways as to facilitate protecting time from clinical demands without placing unrealistic financial demands on the clinician or the clinical department.
- The basic scientist collaborating in pediatric urology research should have funding to support development of his or her laboratory, particularly through graduate and postdoctoral students, collaboration with other basic scientists, and involvement with the basic science community.

Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases

NIH Publication No. 06-5879
February 2006