

STRATEGIC PLAN FOR PEDIATRIC UROLOGY

NIDDK — RESEARCH PROGRESS REPORT

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.