

# 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

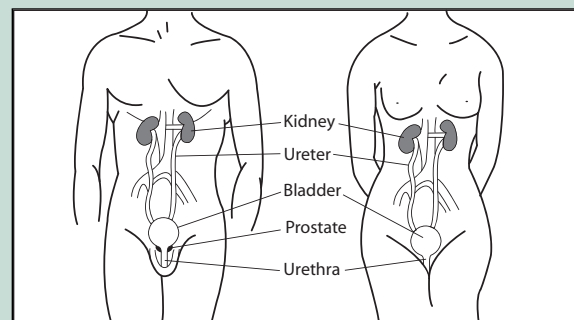
by the kidneys into the bladder at low pressure without causing the holdup, or stasis, that might permit infections. The renal pelvis and the ureter pump urine in a similar manner, with an automatic pacemaker that controls the rate and force of contraction. The urine then passes into the bladder through 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 supravescical 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 TGF $\beta$ 1, 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

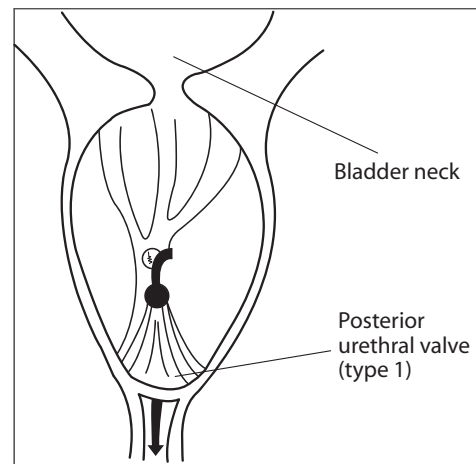
Prenatal diagnosis of bladder outlet obstruction confers a poor prognosis with a large number of fetuses succumbing before birth. Among the one in 5,000 to 8,000 males born with the most common cause of bladder outlet obstruction in children—posterior urethral valves (PUV)—25 percent will experience 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

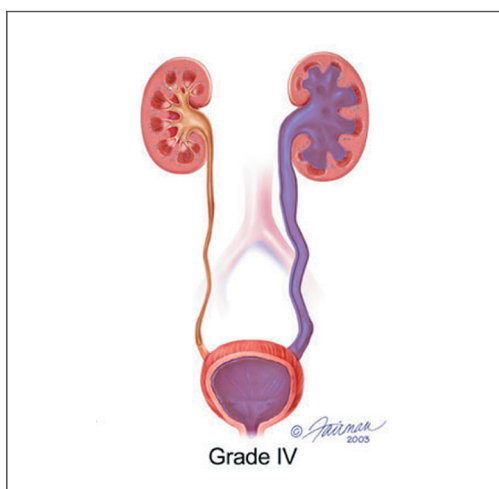
## 4. Vesicoureteral Reflux

### 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

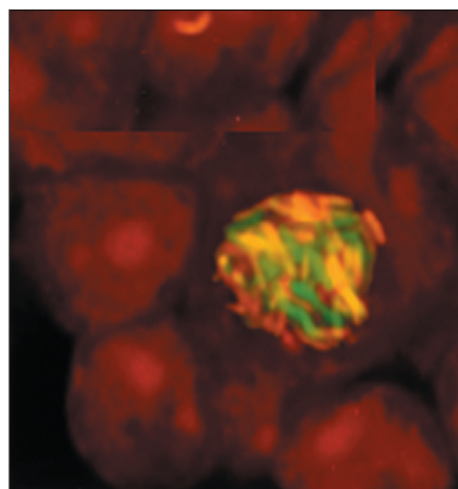
Urinary tract infections (UTIs) are frequent in children of all ages (3 percent of prepubertal girls and 1 percent of prepubertal boys are diagnosed annually), and they cause significant morbidity that can lead to renal failure. Although they are not reportable diseases, and accurate incidence data are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



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).

African Americans. Among infants with UTI, 18 percent will develop recurrences.

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.