

## II. Genital Tract

### 10. Development and Maldevelopment of the Genital Tract

#### Summary

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

#### Sexual Differentiation and Development in the Early Embryo

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

Much of the development of the genital tract is determined by gonadal development. The sexually undifferentiated gonad is first observed histologically at 5 to 6 weeks post-conception as a thickening in the urogenital ridge, with differentiation into an ovary or testis beginning around the 7th week. Ovarian development was thought to be constitutive (i.e., in the absence of a specific genetic signal, an ovary will develop).

Recently, however, genes that may induce ovarian development have been identified. The critical gene for testicular development is the SRY gene, found on the Y chromosome. Although numerous other genes are involved, the presence of SRY will, in nearly all cases, induce testicular development.

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

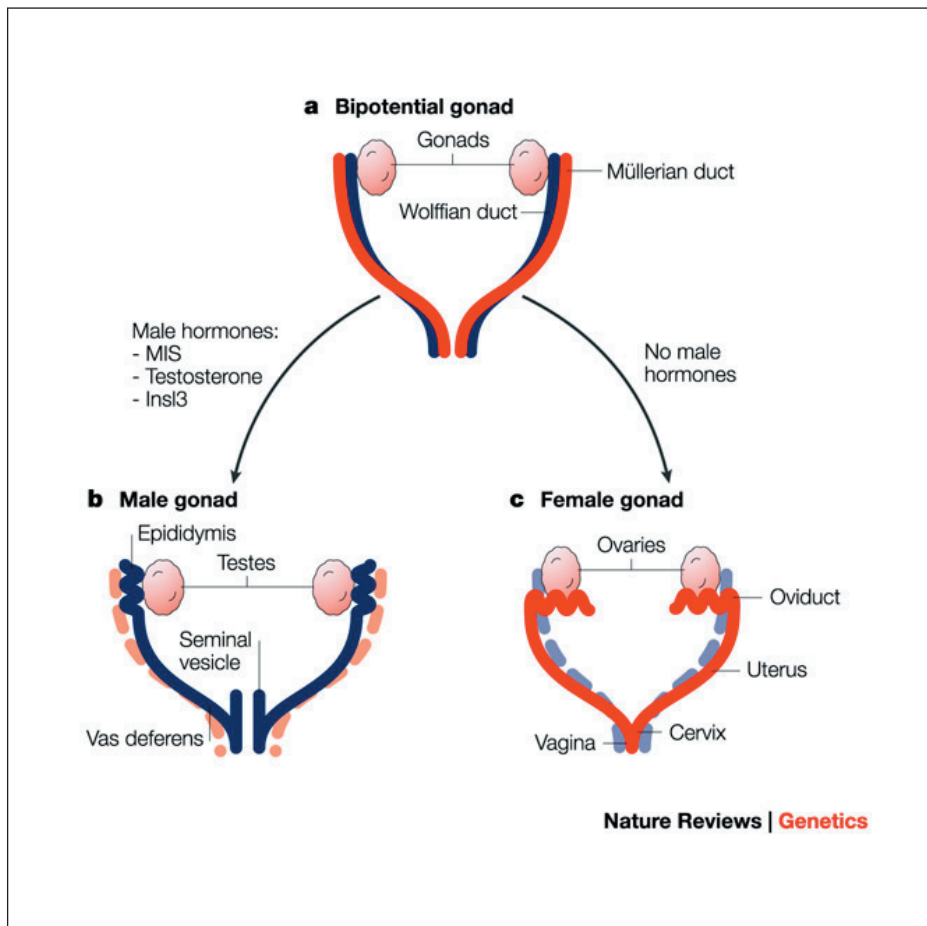
Without the SRY gene, the gonad develops into an ovary; the Müllerian duct system develops into the fallopian tubes, and as it meets and fuses with its contralateral mate, the uterus and most of the vagina are formed. The Wolffian ducts remain rudimentary once their contribution to the developing kidney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

Müllerian ducts and leads to their degeneration by apoptotic mechanisms.

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

larger and forms the penis. The urethral folds fuse to form the male urethra and the genital swellings form the scrotum as opposed to the labia.

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



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

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

## Research Challenges

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

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

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

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

## Development of the External Genitalia: Penis, Clitoris, Testes

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

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

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

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

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

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

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

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

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

## Priorities for Research

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

## 11. Cryptorchidism

### Summary

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

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

## Health Impact

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

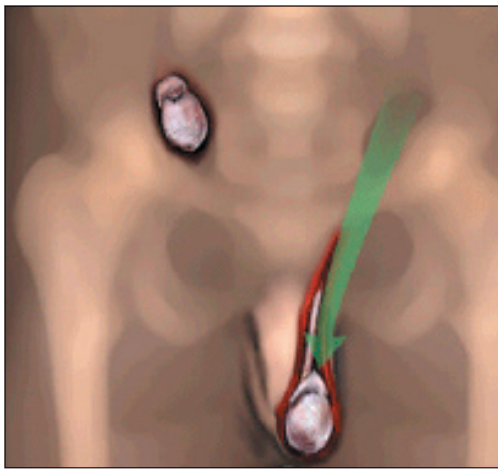
## Clinical Presentation and Treatment

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

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

## Fertility

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



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

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

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

## Cancer

It is recognized that there is an increased incidence of testicular tumors, particularly seminomas within cryptorchid or formerly cryptorchid testes. This incidence may be greater than previously thought and may be different among different populations. It is unclear what factors cause carcinoma *in situ*

cells in the immature testis to become malignant. The general consensus has been that correcting the location of the cryptorchid testis does not alter the risk of malignancy.

## Priorities for Research

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

## 12. Hypospadias

### Summary

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

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

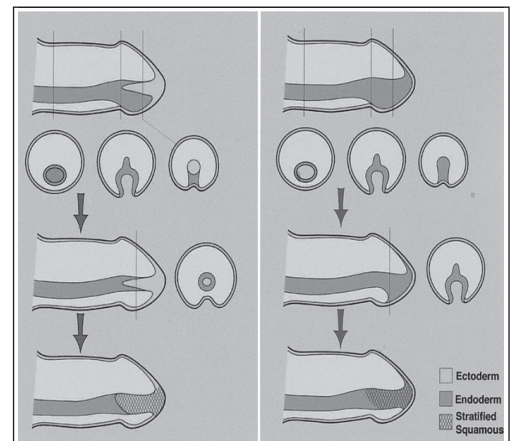
### Health Impact

Hypospadias is one of the most common congenital anomalies in the United States, occurring in approximately one in 250 newborns or roughly one in 125 live male births. There is significant morbidity associated with some surgical procedures to correct severe forms of hypospadias, as well as potential psychosocial consequences of having an abnormal penis. In addition to the difficulty

of surgery, the emotional and physical stress for the parents of patients with abnormal appearing genitalia must be considered.

### Development of the Male External Urogenital System

Formation of the external male genitalia is a complex developmental process involving genetic programming, cell differentiation, hormonal signaling, enzyme activity, and tissue remodeling. Up until 7 weeks gestation, the male and female genitalia are essentially indistinguishable. Then, under the influence of testosterone in response to a surge of luteinizing hormone from the pituitary, masculinization of the external genitalia gland occurs. The penile urethra forms as a result of fusion of the medial edges of the endodermal urethral folds, and ectodermal edges of the urethral groove fuse to form the median raphe. By 12 weeks,



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

the coronal sulcus separates the glans from the shaft of the penis, and the urethral folds have completely fused in the midline on the ventrum of the penile shaft. During the 16th week of gestation, the glanular urethral appears; evidence suggests two possible means by which it could form: endodermal cellular differentiation or primary intrusion of the

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

## Etiology of Hypospadias

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

### Genetic Impairment

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

### Environmental Factors

The reported increase in cases of hypospadias during the last 30 years and the fact that known genetic defects explain only a small percentage of cases has raised concerns about environmental

causation. Environmental factors under consideration as causative agents for hypospadias include parental occupation, obesity, exposure to chemicals, including endocrine disruptors (e.g., gestational exposure to progestins and estrogen-like compounds), and smoking.

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

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

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



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

## Clinical Treatment

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

## Research Priorities

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

## Basic Research

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

## Translational Research

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

## 13. Hernia and Hydrocele

### Summary

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

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

## Health Impact

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

## Clinical Treatment

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

## Priorities for Research

- Investigate molecular and hormonal factors that may predispose to the development of hernias and hydroceles.

- Identify and validate novel, noninvasive, or minimally invasive perioperative methods to detect silent hernias.
- Improve awareness of hydrocele and hernia in children of the parents of at-risk groups to decrease time elapsed until diagnosis.

## 14. Congenital Anomalies of Sexual Differentiation

### Summary

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

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

## Health Impact

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

## Clinical Management and Treatment

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

### Sex assignment

Until the mid-1950s, medical management of individuals with disorders of sexual differentiation was guided by the belief that an individual's "true sex" could be determined by examination of internal anatomy. Then, based on reports suggesting that this assumption was incorrect, guidelines were changed; sex assignment decisions were based on the principle of "optimal gender," which considered multiple aspects of outcome, most prominently, the potential for complete sexual functioning, with particular emphasis on phallic size and reproductive potential. This approach, largely uncontested until recently, is predicated on two assumptions: (1) "gender identity" (i.e., identification of self as either girl/woman or boy/man) is not firmly established at birth, but rather is the

outcome of the sex of rearing; (2) stable gender identity and positive psychological adaptation require that genital appearance match assigned sex, which often calls for reconstructive genital surgery. Clinical outcomes have demonstrated that there is a window of time until the second year of life, during which gender identity is malleable. Therefore, this clinical management strategy suggests that early surgical correction of genitalia is critical.

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

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

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

## Surgical Intervention

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

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

## Priorities for Research

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

(7) limited measurement tools; and (8) limited normative data on relevant outcomes.

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

## Infrastructural Needs

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