A Panel Discussion on Gender Assignment

Elizabeth B. Yerkes, M.D., Guest Editor

From the Guest Editor

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This isn’t the 1950s......

John Money’s well-known 1950s case of gender re-assignment of a twin after a traumatic circumcision (the “John-Joan” case) attempted to demonstrate that Nurture could trump Nature in the establishment of gender identity. Although initially it appeared that rearing the child as female resulted in female gender identity, he ultimately chose typical male role behaviors and fatherhood. Appearance of the genitalia, alone, does not define gender identity or sexual identity. Ultimately he took his own life, highlighting the potential psychological ramifications of these decisions. The details of this famous case, along with less-publicized anecdotal accounts of self re-assignment in young adults after early genital reconstruction, suggest that the power of Nature should not be underestimated. (For further information on this case, the reader is referred to John Colapinto’s book, “As Nature Made Him,” Perennial Publishers, 2001.) While rearing is important in developing values and establishing the global identity of an individual, his or her preferences and talents are more likely innate than orchestrated qualities.

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FROM THE EDITOR

Anthony A. Caldamone, M.D.

As one surveys the history of pediatric urology relative to specific entities that have defined the specialty, it is easy to recognize that since its inception there have been many areas within our specialty that have undergone significant changes in our understanding and management. For the most part, these have been slow evolutionary changes relative to both basic science findings as well as clinical observations. However, there has been no area that has undergone such a dramatic change as that of gender assignment for intersex conditions. While the undercurrents have been there for many years, it has only been in the last 10 years that significant clinical observations have been brought to light which have substantiated some of the findings in basic science research. It is quite clear that the impetus for the change in our approach to the intersex patient has been fostered primarily by the courage and conviction of past patients who often had to undergo significant psychosocial stress in order to educate us about the consequences of our decisions.

Dr. Yerkes and her contributors have put together a master issue on gender assignment for congenital abnormalities of the genitalia. They focus on 3 clinical scenarios: (1) congenital adrenal hyperplasia, (2) cloacal exstrophy, and (3) true hermaphroditism. The discussions are focused. Moreover, it becomes clear in these discussions that there are certain areas in which there is information that we can rely on to help make our decisions and other areas where there is a significant lack of evidence based management. It is these areas in which further research needs to be focused.

I would like to congratulate Dr. Yerkes and her contributors for an insightful issue on a very difficult topic.
CASE 1
This child is evaluated in the Neonatal Intensive Care Unit for genital ambiguity. The pregnancy was uncomplicated and the child was delivered at term. There are no other medical concerns.

Upon examination, you note hyperpigmentation and significant fusion of the labioscrotal folds without any palpable gonadal tissue. The anus is normal, and there is one additional perineal orifice at the base of a hooded phallus.

Laboratory and Radiographic Evaluation:
17-OH progesterone: elevated
Karyotype: 46XX
Ultrasound: uterus and ovaries present; adrenal glands serpiginous
Genitogram: urogenital sinus with cervical impression
Gender Assignment

**Dr. Aaronson:** This is a classical case of congenital adrenal hyperplasia with an impressive although not severe degree of virilization of the external genitalia. The gender of rearing here should unquestionably be female. Although in such patients gender role behavior may show masculinized traits, the likelihood of a gender identity problem arising is small.

**Dr. Reiner:** This is a term newborn genetic female with CAH. She is a Prader stage 3-4. She may well identify as female; therefore, I would recommend assignment to female. Her prenatal androgen exposure was likely near that or even higher than that of a typical male, however. She might identify later as male. Parents must be counseled about the likelihood of more male-typical behaviors despite declared sexual identity, as well as the possibility (or likelihood) of sexual orientation towards females.

**Dr. Reiner:** As mentioned, she might identify as male later. Therefore, if any surgical reconstruction is performed before she is able to give realistic consent, I would recommend that nothing be excised. In other words, clitoral recession rather than clitoral resection would be advisable, if the parents so desired after a fully informed consent. A vaginoplasty could be performed, especially if the child develops recurrent urinary infections, but performed without labioscrotal resection. If as female she wished more feminization (for example, at or after puberty), this could then be easily accomplished secondarily. If she desired male assignment, nothing has been lost.

If, on the other hand, she were to be assigned male at birth or declare male identity in childhood, I would not recommend ovariec-tomy until such age that the child could satisfy physicians about his sexual identity, perhaps not until 10 to 13 years of age. Leuprolide acetate could be used to block ovarian maturation until such identity was clear, if necessary.

**Dr. Reiner:** If, on the other hand, she were to be assigned male at birth or declare male identity in childhood, I would not recommend ovariec-tomy until such age that the child could satisfy physicians about his sexual identity, perhaps not until 10 to 13 years of age. Leuprolide acetate could be used to block ovarian maturation until such identity was clear, if necessary.

**Dr. Schober:** This case proposes a diagnosis of Congenital Adrenal Hyperplasia (21-OH or 11B-OH) in a female child with considerable masculinization. The labia are highly pigmented and ruffled though not completely fused. They join above the clitoris, which is considerably hypertrophied. There is a sizable vagina with low confluence. Female gender assignment in this case would be difficult to dispute considering straightforward chromosomal data, known long-term gender identity studies to date and fertility potential in this condition.

**Dr. Wilcox:** This is a child with Congenital Adrenal Hyperplasia (CAH) with 46 XX chromosomes. In children who I see early in life, I would recommend female gender assignment. Occasionally, children with 46 XX CAH present later in life who have more severe virilization and who have been brought up male. In this situation, where possible, I counsel the family to change the sex of rearing to female. My rationale for this is: 1) their future sex hormone production will be female, 2) the only chance of fertility is through the female sex of rearing, 3) “masculiniza-tion” of the brain to some degree has been observed in females with CAH, but most appear happy in their female sex of rearing, and 4) some form of surgical reconstruction is required in either case.

Type and Timing of Reconstruction

**Dr. Aaronson:** Although the genital virilization may show some regression with good replacement therapy, a two centimeter phallic is likely to remain very prominent. I would counsel the family that surgery is available to reduce the size of the clitoris and to tuck it back using a technique designed to preserve erogenous sensation and erectile function. Presently, however, there is little follow up data to reassure us that we are always successful in this regard.

Leaving the phallus alone would optimize the function, but this consideration should be offset against the potential for psychological problems were the child to grow up with very unusual looking genitalia. I would, therefore, recommend feminizing genitoplasty, although I would defer to the parents should they want to withhold surgery. Should they wish to go ahead, I would also lay open the horizontal portion of the urethra and excise clearly redundant labioscrotal skin at the same time.

With regard to vaginoplasty, which will ultimately be required, the genitogram suggests that the confluence with the urogenital sinus may be sufficiently high to require a challenging procedure. In order to clarify the situation I would carry out an endoscopy, as the images are sometimes deceptive. In the event of a high insertion, I would recommend deferring surgery until puberty. If low enough to allow a straightforward flap vaginoplasty, I would carry this out at the same time. I would explain to the family, however, that an examination under anesthesia prior to puberty will be required, and often some revision of the introitus will be needed.

**Dr. Reiner:** At the time of clitoral surgery I would perform Total Urogenital Mobilization (TUM) to create a vaginal orifice on the perineum. The genitogram suggests that this is a low confluence. Even with high confluences, however, I perform TUM and commence with the child prone and use a posterior sagittal incision.

Since I have recommended clitoral surgery in this child, I would perform a cystoscopy within the first 3 months of life to help plan the procedure and then complete the reconstruction within the first year. If no clitoral surgery is necessary, then I am happy to wait on the vaginal surgery until peri-puberty.
Gender Assignment

Dr. Aaronson: Gender assignment in this male infant with cloacal exstrophy is a very difficult decision. There is no doubt that as a fetus he had been exposed to normal physiological doses of testosterone, which may result in a conflicted male gender identity among such (46 XY) infants raised as girls. We are urgently in need of more follow-up studies to determine just how frequently this occurs. The data available suggests the incidence is certainly worrisome, but it is by no means certain that this will affect the majority of such children.

On physiological grounds, therefore, the default gender of rearing should ideally be male. Reconstructing the external genitalia along male lines, however, is fraught with difficulty, particularly for those surgeons who see very few such cases.

Dr. Reiner: Genetic males with cloacal exstrophy are boys. If reared as boys, they will have normal hormonal exposures throughout life and will be potentially fertile with technological assistance. They will likely require psychosexual and psychosocial developmental counseling along with later specific sexual counseling.

If we assign them to female sex-of-rearing at birth, then we have added a level of confusion to their psychosexual development with the possibility that they will transition to male anyway. They will also require life-long exogenous hormone administration (estrogen or testosterone).

Dr. Schober: Though I would suggest a male gender assignment in this child, I have some very serious reservations. A male child born with cloacal exstrophy (CE) may be one of the most difficult decisions for gender assignment. Normal male chromosomal complement and normal but undescended testes might bias one to think that brain masculinization would/could only lead to comfortable male gender identity. Evidence-based judgment suggests that some XY female-assigned CE patients, from a variety of studies by different authors, have changed gender to male. There are no reports of XY male CE patients that have reassigned to the female gender. However, there are no long-term quality-of-life or sexual function studies that give us any information of the adult lives of either male or female CE patients.

The child’s neurological status may be crucial. There are a very high percentage of myelomeningocele and lipomeningocele defects which confer genital insensitivity and lack of erectile ability. Even if there was the possibility of tissue engineering for corporal replacement, sexual outcomes are dim without underlying neurologic erectile normality. With the abdominal wall and pubic symphysis abnormalities, forearm phalloplasty also seems an unlikely possibility. There is no known fertility in boys with CE.

My experience is a cohort of both XY and XX CE patients, raised female with gender appropriate appearance, who exhibit a stable female gender identity. None have asked for reassignment. But, all available literature must be considered objectively. The outcomes of CE patients through a period of adult challenge will be vitally important information, for physicians and parents alike, before making this difficult decision.

Dr. Wilcox: In this unfortunate child, gender assignment is a more difficult problem. Recently Ransley and colleagues have shown satisfactory outcome in 46XY cloacal exstrophy children raised female, when the gonads were removed early in infancy. This contradicted earlier work by Reiner and colleagues.

In this child I would consider recommending male sex of rearing because: 1) at 33 weeks the gonads may well descend and function normally and, consequently, hormone supplementation should not be necessary and 2) it is the child’s best chance of future fertility. The phallus will be very small and require significant surgical reconstruction (as would rearing the child female), but in the future phalloplasty may be performed leaving the original penis intact. If successful, this may leave a more cosmically appealing penis that has some sexual sensitivity preserved.
CASE 3:

This is a term newborn with genital ambiguity. There was no known maternal androgen exposure.

On the birth exam the labioscrotal folds are rugated but not fused, and there is no palpable gonadal tissue. The hooded phallus is 2.0 cm with significant ventral chordee. The anus is patent and in a normal position, and there is a single anterior perineal opening between the labioscrotal folds.

Laboratory and Radiographic Evaluation:
- CAH panel: negative
- HCG stimulation test initiated while karyotype still pending: positive
- Karyotype: 46 XX, SRY negative
- Ultrasound: uterus present
- Genitogram: short UG sinus (< 1 cm) with apparent cervical impression

Evaluation and multispecialty counseling was performed at outside institution and female gender assigned. The child is referred to your care at age 2 months.

Laparotomy for gonad biopsy confirms a small uterus. The right gonad has an ovoid shape, fallopian tube and possible partial epididymis. The left gonad is flat with the appearance of a streak gonad and has an associated fallopian tube. Frozen and permanent sections identify an ovotestis on the right and only ovarian tissue with follicles on the left. Seminiferous tubules and ovarian stroma and follicles were intermingled rather than polar. The right gonad is removed and the left gonad is preserved. The karyotype of the gonadal tissue is also 46 XX, SRY negative bilaterally.
**Gender Assignment**

**Dr. Aaronson:** There is no compelling reason in this particular infant with true hermaphroditism to be raised either as a boy or girl, for each choice has advantages and disadvantages.

The remaining gonad here is presumably a histologically normal ovary with fertility potential, albeit requiring assisted reproductive techniques. Reassurance can be obtained that it does not harbor any foci of functioning testicular tissue by repeating the hCG stimulation test and, in addition, carrying out a Müller inhibiting substance assay. The uterus, however, is unlikely to be of any use, and the vagina will require potentially challenging reconstruction. Furthermore, erogenous and erectile clitoral function may possibly be compromised by a feminizing genitoplasty.

On the other hand, the external genitalia show impressive masculinization, and reconstructing the phallus along male lines should not pose a major technical problem. There has also presumably been a concomitant masculinizing effect on the developing brain as a result of testosterone production in utero, which may have a bearing on the child’s eventual gender role behavior and gender identity. In true hermaphroditism hard data in this area is lacking. Lifelong testosterone replacement will, of course, be necessary, commencing at puberty. Nonetheless, on balance, I would favor male as the gender of rearing in this case.

**Dr. Reiner:** This child has a Wnt-4 deficiency or other unusual genetic presentation leading to abnormal gonadal development with subsequent prenatal androgen exposure. Such prenatal exposure may alter GnRH-LH-estrogen relationships and feedback inhibition, along with the more obvious genital and brain effects. This child may identify as male in childhood.

The remaining left gonadal tissue may have the risk of neoplastic transformation, and one must suggest the possibility of total gonadectomy. Any remaining gonadal tissue would likely respond to (extended) HCG stimulation, measurable by subsequent testosterone levels. Adrenal rest cells, possibly also present, would not respond to HCG.

This child must be followed throughout childhood for declared or preferred sexual identity. Additionally, parents must be counseled about the likelihood of more male-typical behaviors despite declared sexual identity, as well as the possibility (or likelihood) of sexual orientation towards females.

**Dr. Schober:** This case fulfills the criteria for diagnosis of true hermaphroditism. With all factors considered, I would suggest that female gender assignment be continued. Studies have noted uterine presence, bilateral fallopian structures and ovarian tissue left in place. Though this ovarian tissue did not have an altogether normal appearance, there exists the possibility of natural pregnancy. Assisted fertility possibilities are present even if adequate ovarian production fails.

In this case there is no indication of SRY in any specimen taken thus far. But a low level mosaicism may still exist, so vigilant observation of any gonadal tissue left in situ is prudent. The use of new immunohistochemical markers for diagnosis of gonadal tumors, OCT3/4 and TSPY, may help in screening.

**Type and Timing of Reconstruction**

**Dr. Aaronson:** I would carry out a one-stage hypospadias repair at six months of age. I would also remove both the uterus and the remaining gonad at the same time.

**Dr. Schober:** I would suggest genitoplasty in the first year of life, with repositioning of the glans clitoris immediately beneath the highest point of joining of the labia. I would leave at least a 1 cm crescent of inner prepuce attached to the glans clitoris dorsally, using it as a hood. I would split the residual shaft skin, bringing it laterally and posteriorly for labia minora. The vaginal introitus already looks well formed. I would not reduce the size of the glans, but might make incisions into the corpora and remove a small amount of erectile tissue, depending on the length of the shaft once repositioned. I would use estrogen cream (Premarin) prior to surgery and for at least two days postoperatively to promote vascularity and neural branching and to limit scarring.

**Dr. Wilcox:** In this situation, evaluation of the internal anatomy and gonads is vital; consequently, I would recommend cystoscopy and laparoscopy within the first 3 months of life. In my experience, the appearance of gonads at laparoscopy can be misleading, and I favor biopsy. Often, on inspection, the two different types of gonadal tissue are easily seen; but, as in this case, the tissue can be intermingled. In those cases, because of the high risk of leaving testicular tissue within the abdomen, I would suggest gonadectomy.

Surgical reconstruction would be similar to that described in case 1.
Summary Points and Pearls

Dr. Schober

- Even though there is no set guideline for gender assignment in many cases, we all realize that some modification or adaptation for a child born with intersexual attributes will be necessary. Our goal in choosing a gender is to help convey confidence to that child in an outward way.

- Parental and physician encouragement are needed to endorse concepts that feature: achievement (knowledge of assets and strengths), autonomy, harm avoidance, self-esteem, impulsivity (risking social rejection), play, and comfort with one’s self as a sexual being. There could not be a better time in history to experiment with being different. Gender-bending fashions, hairstyles, lifestyles and partnering are all exhibited in mainline culture in our westernized environment. Maybe some things should not be seen as quite so pathologic.

- Acceptance of emerging sexual identification in an intersexual adolescent will probably follow some patterns of the typical adolescent and young adult in most aspects. This would include the regulation of stable dating patterns, experimentation with different dating models and longer-term dating models, experimentation with sexual relationships, increased incidence of sexual intercourse as part of a relationship, and practiced sex, with a similar experience of insecurity and anxiety to the typical non-intersexual adolescent.

- Unusual approaches learned by those with this imposed condition may lead to original observations and capabilities, for both educational and professional occupations, in the said individual. I, for one, embrace new visions.

Dr. Wilcox

- Establishing the assignment of gender can be an extremely complex issue for the multidisciplinary team and a very difficult and anxious time for the family. The factors that I believe are important, but in no particular order, are: the chance of future fertility, the requirement of supplementary hormones, the psychological impact on the child’s development, and the internal and external sexual organs.

- As surgical reassignment either from female-to-male or male-to-female ultimately results in less than satisfactory genitalia, I tend to allocate this area the least weight or importance. Historically the ability to “make” a penis was sacrosanct in the decision making process. Consequently, I use the functional ability of the gonads as the most important in guiding the decision process. The psychological development of the child is, correctly, gaining status. To understand and evaluate this area, an interested clinical psychologist is an invaluable member of a multidisciplinary team.

- With regards to reconstruction, where possible I think this decision can be delayed until the child is able to take part in the decision. However, there are situations where the severity of the abnormality and the social environment require a decision. On these occasions, I still believe that early surgical reconstruction is in the best interest of the child.

Concluding Remarks from the Guest Editor

I would like to thank the panelists for their insightful comments regarding the clinical challenges in gender assignment and the tremendous weight of the decisions facing both parent and child. There remains no absolute consensus or algorithm for the management, social or surgical, of many of these patients.

Mindfulness of the past, present and future was a universal feature in the recommendations of our panelists. Comprehension of the long-term impact of our initial medical and surgical decisions upon the psychosocial and psychosexual development of these children and young adults is crucial. Through collective anecdotal experience, maturing cohorts and the desire to do no harm, our knowledge has increased; but much of the controversy remains unresolved. As pediatric urologists we have a responsibility to work together to continue to find answers for these children. We have many miles to travel before we will have exhausted our ability to learn from and about these patients.

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GENDER ASSIGNMENT

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A panel discussion on the rationale for gender assignment, recommendations for surgical reconstruction, and the timing for reconstruction.