

# A Newborn Infant With a Disorder of Sexual Differentiation\*

## CASE

Following an uncomplicated 38-weeks pregnancy, a normal labor, and delivery with Apgar scores 8 and 9 at 1 and 5 minutes, respectively, a newborn was delivered with a birth weight of 6 pounds 5 ounces. The physical examination was unremarkable except for complete absence of the penis. The scrotum appeared normal with bilateral palpable gonads of normal size. A voiding cystourethrogram demonstrated a normal bladder without uretero-vesical reflux; the contrast study revealed that urine partially emptied into the rectum and colon. The urethral meatus was positioned at the anterior anal verge. Karyotype was 46,XY. This is the third child for this couple. They have a 4-year-old boy and a 6-year-old girl.

To which sex should this infant be assigned? Accompanying decisions concern disclosure of information to patient and family (what should be disclosed about the condition and its treatment and when?); surgery to have the genitalia match the sex assignment, or alternatively, female genital anatomy (what should be done and when?); psychological support of the patient and family (who should provide it, and what model of care should be followed?); and involvement of other family members and friends (should they be told, and if so, what should they be told and when?).

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INDEX TERMS. *ambiguous genitalia, sex differentiation, intersex, biomedical ethics, penile agenesis.*

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### Dr Martin T. Stein

This Challenging Case is a rare condition that will not be encountered by most pediatricians. However, it represents a dramatic example of other more common conditions discovered in the newborn period associated with ambiguous genitalia. Primary care pediatricians are often the first to recognize the structural abnormalities in the external genitalia and the first to speak to the parents about the condition. A knowledge of genetic and endocrinologic principles that modulate fetal sex differentiation is essential but insufficient to provide comprehensive information to the parents. The influence of fetal sex hormones on gender identity and the incorporation of principles of patient rights and patient autonomy are additional areas of knowledge required to guide therapeutic decision-making.

A variety of new concepts about newborns with intersex conditions have surfaced in the medical and bioethical literature. They reflect recent knowledge

about the complexity of gender identity and gender role, bioethical considerations, and the influence of patient-advocacy groups. These recent considerations are of interest to developmental-behavioral pediatricians in that they focus on critical aspects of subsequent developmental outcomes.

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Don't be fooled—this rare case has more to teach than you might think! The infant is born with the extremely rare condition of penile agenesis (also known as aphallia). Mortality is high because of associated urinary and gastrointestinal tract problems; however, complex forms of these associations are absent in this particular infant. Although rare, the case illustrates common challenges in the clinical care of patients with disorders of sexual differentiation ("intersex"), in whom there is discordance among sex chromosomes, gonads, sex hormones, and phenotypic sex (internal reproductive structure and external genital appearance).<sup>1</sup> These conditions include true hermaphroditism (in which both ovarian and testicular tissue are present in the same or opposite gonads); 46,XX individuals with congenital adrenal hyperplasia, particularly those born with marked or complete masculinization of the external genitalia; 46,XY individuals with partial androgen insensitivity; 46,XY individuals with 5- $\alpha$ -reductase deficiency; 46,XY individuals with a very small but normally formed penis (micropenis) or malformed penis (microphallus); and 46,XY individuals with

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cloacal exstrophy. The prevalence rate for these conditions combined may be as high as 1 of 3000.<sup>2</sup>

Until the mid-1950s, medical management of individuals with intersex conditions was guided by the belief that an individual's "true sex" could be revealed through examination of internal anatomy. It was assumed that a person's identification as male or female would naturally conform to "true sex." Based on reports suggesting that this assumption was incorrect, guidelines were changed, and sex-assignment decisions were based on the principle of "optimal gender," which considered multiple aspects of outcome, most prominently potential for complete sexual functioning.<sup>3</sup> This approach, which stood largely uncontested until recently, is predicated on 2 assumptions<sup>4</sup>: (a) "gender identity" (ie, identification of self as either girl/woman or boy/man) is not firmly established at birth but rather is the outcome of rearing sex; and (b) stable gender identity and positive psychological adaptation require that genital appearance match assigned sex, which often calls for reconstructive genital surgery. It is essential to distinguish between gender identity and other aspects of gender-related behavior, which may be influenced by prenatal hormones. This includes "gender role," which refers to behaviors that differ in frequency or level between males and females in this culture and time (such as toy play or maternal interest), and "sexual orientation," which refers to sexual arousal to individuals of the same sex (homosexual), opposite sex (heterosexual), or both sexes (bisexual).

The clinical approach to disorders of sexual differentiation ("optimal gender policy") has recently been criticized from several perspectives. First, the notion of gender "neutrality" at birth has been challenged as a result of a widely publicized case.<sup>5</sup> The individual in this case has a 46,XY karyotype and was born with normally formed male genitalia. After a circumcision accident at the age of 7 months left him without a penis, the child's gender was reassigned but not until 17 months, and the child was subsequently reared as a girl. This individual (referred to as "John/Joan") has been studied extensively as an adult.<sup>6</sup> He reports having been uncomfortable as a girl ("gender dysphoric") and, starting at age 14 years, began to live as a male. He received a mastectomy and began testosterone replacement therapy in adolescence followed shortly after by phallic reconstruction. At age 25, he married and adopted the woman's children. The gender dysphoria and ultimate sex reassignment of this individual is believed by some to have been predictable from experimental studies in animals in which exposure to androgens during sensitive periods of early brain development is associated with male-typical brain and behavioral development.<sup>7</sup> Although animal experimental research has shown a relation between prenatal androgen exposure and sex-dimorphic behavior, such studies have not examined "gender identity" per se.<sup>8</sup> The impact of the John/Joan case for clinical practice is also tempered by the report of another child with a traumatic amputation of the penis with considerably different outcome.<sup>9</sup> As an adult, the individual maintains a female gender identity, although she exhibits mascu-

line occupational and recreational interests and a bisexual orientation.

A second challenge to the "optimal gender" policy comes from intersex individuals themselves, who are angry about their treatment.<sup>10</sup> They object to the fact that they were either not informed or misinformed about their condition, they are still unable to obtain accurate information about their condition and treatment, and they feel stigmatized and shamed by the secrecy surrounding their condition and its management. Many also attribute poor sexual function to damaging genital surgery and repeated and insensitive genital examinations, both of which were performed without their consent.

Finally, social constructionists have challenged the entire enterprise of medical management of intersex cases by arguing that medical practices are rooted in history, language, politics, and culture and therefore are not universal scientific facts.<sup>10</sup> Thus, the "correction" of an intersexed infant's genitals is less a medical emergency than it is the adoption of medical technology to support a cultural imperative to view the sexes as dichotomous. Supporters of this point of view contend that such beliefs result in unnecessary and damaging surgery.

How should a decision regarding sex assignment be reached in the present case? Until recently, most children with aphallia would receive a female sex assignment. Accordingly, the testicles would be removed and genital surgery performed to create the outward appearance of female genitalia, that is, labia and clitoris. Surgical construction of a vagina might be performed at this time or be postponed until adolescence. A feminizing puberty (development of breasts and feminine body) would be achieved through the administration of estrogen therapy beginning in the early teenage years. It has been thought that this approach would maximize the individual's psychological adaptation, including gender identity, body image, and sexual function. Conversely, delaying or avoiding surgical construction of female external genitalia would potentially jeopardize the formation of an unambiguous gender identity because of the incongruence between gender rearing and genital appearance. An alternative decision might be to rear this infant as a male (consistent with his gonadal sex) because prenatal testosterone has presumably "organized" the brain, foreclosing identification as a female. Phalloplasty might then be considered, although the challenges of this option are daunting and it has only rarely been attempted. The option of not attempting to provide the child with a phallic structure would potentially jeopardize stable gender-identity formation.

Given the dearth of systematic information on long-term outcome in individuals with aphallia and other forms of intersexuality, how should this clinical problem be resolved? How are the parents to be involved in the decision? What information do they need to make informed decisions on behalf of their child? Rare as this case is, it has much to teach us. Questions emerge regardless of whether the infant is assigned a gender and reared as a boy or as a girl.

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## Dr Erica Eugster

This case represents one of the most difficult situations faced by parents and health care professionals involved in the care of infants born with an intersex condition. Unlike many other conditions that result in undervirilization of a genetic male, the 46,XY infant with isolated aphallia was presumably exposed to normal levels of male testosterone during intra-uterine life. A major concern revolves around the effect of prenatal androgen exposure on "masculinization" of the brain and ultimate gender identity.

What can we learn from the literature regarding sex assignment and outcomes in similar cases? Congenital absence of the penis is extremely rare, with fewer than 100 cases reported. Although female sex reassignment and early bilateral orchiectomy historically have been considered the standard of care for these patients, follow-up studies focus primarily on success of surgical procedures rather than psychosexual development and function.<sup>1</sup> In the few case reports of aphallia in which a male gender was assigned,<sup>2</sup> limited information is available regarding psychological adaptation and long-term satisfaction. Another strategy is to attempt to extrapolate from similar populations of 46,XY patients with apparently normal early prenatal testicular function, such as those with micropenis or traumatic penile loss. Although there are reports of normal male gender identity and fulfilling heterosexual activity in such patients,<sup>3</sup> female gender role and satisfaction with

sex-of-rearing have also been reported in a small number of individuals.<sup>4</sup>

A few sensationalized cases of extreme gender dysphoria and patient groups advocating a moratorium on early genital surgery have encouraged the medical community to recognize the critical need for long-term outcome data on intersex populations. However, the few existing studies of the claims made by intersex support groups have been limited by small sample size and selection bias.<sup>5</sup> Therefore, we find ourselves currently in a situation with far more questions than answers. How, then, should we begin to address this Challenging Case?

Once the medical diagnosis has been established, parents of an infant with intersex should be given a comprehensive and explicit explanation of normal and abnormal sexual differentiation. Considering the paucity of scientifically validated outcome data in the management of intersex, all available information should be shared, including that which has been highly publicized and is arguably biased. A consistent source of dissatisfaction among adult intersexuals, even among those for whom the psychosexual outcome appears favorable, has been the lack of disclosure by medical professionals (and often parents) regarding their diagnosis and treatment. The perceived secrecy can be experienced as shame. The ideal time at which to establish a culture of full disclosure is in the initial discussions with parents. At that time, information should be provided about the diagnosis and options regarding sex assignment and surgery. Surgical options for this Challenging Case include the technically difficult phalloplasty<sup>6</sup> or the easier vaginoplasty.<sup>7,8</sup> Each procedure is associated with short- and long-term complications. All options should be considered in the case of the infant with aphallia. If the child is reared male, there is the potential for endogenous steroidogenesis and fertility, whereas if the child is reared female, hypogonadism and infertility are guaranteed.

A third option promoted by patient-advocacy groups would be to rear the child as either a boy or as a girl but defer gonadectomy and genital surgery until the child can independently provide informed consent.<sup>9</sup> However, early gonadectomy should be considered in cases of a female sex assignment in light of the postnatal rise of testicular testosterone that may further masculinize sex-dimorphic regions of the brain. Gender-validating surgery has long been considered crucial to the development of uncomplicated gender identity. However, a widely publicized case report of a boy with traumatic amputation of the penis reared as a girl after feminizing genital surgery<sup>10</sup> and the example of physically normal transsexuals who request sex reassignment illustrate that genital appearance consistent with rearing gender is not a guarantee against the development of gender dysphoria later in life.

In light of contemporary controversy, few would hazard the assertion that there is an absolute "right" or "wrong" answer regarding optimal sex assignment in this case. Nonetheless, honesty and empathy go far in establishing an atmosphere of trust within which the parents may become full participants in

the decision-making process. This goal can be facilitated by the inclusion of a mental health professional in the clinical care team. Necessary qualifications of such a team member would be knowledge regarding the process of physical sexual differentiation and its disorders, psychosexual development, and the potential contributions of the social environment and biology to individual variability. In addition, this team member would have more general knowledge and experience in caring for children with congenital health problems and their immediate and extended families. This behavioral specialist can provide psychoeducational counseling at the time of diagnosis to support the objective of fully informed consent for medical management including surgical decisions. The mental health specialist would be available to parents and the child to provide ongoing support to address inevitable concerns regarding the correctness of the sex-assignment decision and to provide the parents with the skills to deliver developmentally appropriate education to the child regarding his/her condition and treatment. Although not yet supported by controlled studies, such a comprehensive clinical care model holds the promise of enhanced quality of life for the affected individual and his/her family.

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#### Dr Jorge J. Daaboul

This case serves as a model for the current debate on the management of the child with “ambiguous genitalia” or, to use the term that has acquired wide currency in the last 5 years, intersex. In the 1950s, a management strategy for children with intersex was formulated that included early sex assignment with early surgical correction to assure consonance be-

tween the assigned gender and the physical appearance of the child. To assure gender-appropriate parenting, parents were often not fully informed of the child’s condition, because it was felt that if the parents had any doubts about the child’s gender, they might send the child mixed signals, resulting in an insecure gender identity.<sup>1</sup> With small modifications, this management strategy remained in place until the mid-1990s and is still accepted in many centers in the United States and around the world.<sup>2,3</sup>

In the mid-1990s, social scientists, a number of intersex activists, and some physicians called for a revision of this management strategy. The debate focused on management strategy continues to this date. It has led physicians to be more open and share more information with patients about their condition and about the consequences of medical and/or surgical therapy. However, the focus of management has remained fixed on determining which medical and/or surgical interventions will yield an optimal outcome for each intersex condition. The general feeling is that the current debate on intersex will be resolved when the appropriate outcome studies are done and that, when these data are generated, physicians will, in effect, be able to use an algorithm to determine a child’s sex-of-rearing and the appropriate medical and surgical interventions that the child will require to make her/him a well-adjusted individual with a secure gender identity and adequate sexual function.

Although I believe that studies are important and necessary to establish the efficacy of the various medical, surgical, and psychological interventions that are used in the management of the child with intersex, I believe that the data will yield results that confirm an enormous variability in how individuals with identical intersex conditions develop psychologically. Even the limited studies available (eg, behavioral characteristics of girls with congenital adrenal hyperplasia<sup>4</sup>) point to widely divergent outcomes. There are conditions such as complete androgen-insensitivity syndrome for which outcomes are almost universally predictable. But for most intersex conditions, the psychological outcome will be so variable that, for each specific case, the outcome will be unpredictable.

Therefore, the current medical model with its focus on diagnosis and medical-surgical treatment does not assure the best possible outcome for children with intersex conditions. The appropriate care model is one in which the focus is shifted away from the precise medical diagnosis and toward the parents’ conception of what their child has, what they believe their child’s gender to be, and how they see their child’s future in the context of their family and of society. Each set of parents, with their unique sociocultural beliefs and backgrounds, would then make all decisions regarding the care of their child. These decisions will be unique to each family and will reflect each family’s unique perspective on the incredibly complex issues of sex and gender. This task should be facilitated by health care professionals expert in the field of family counseling and child

development who are, in addition, familiar with intersex conditions.<sup>5</sup>

To apply this reasoning to the Challenging Case, there is no "right" medical-surgical procedure for the infant with aphallia. Rather, after informing the family of what is known and not known about the outcomes of this condition, the caregiver should explore with the family members their feelings about what they believe is best for their child and respect their decision.

In summary, it is my opinion that when all the outcome data on intersex are collected and analyzed, we will discover that there will be no one answer or management protocol per intersex condition but rather many answers, each unique to a given family.

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#### Martin T. Stein

Children who are born with intersex conditions bring enormous challenges to the fields of developmental endocrinology and child development. The

commentaries that accompany this case emphasize contemporary social and ethical issues that have not always been considered in the early medical decision-making process. In addition, cultural differences with regard to the acceptance of intersex conditions may not conform to those of Western society and should be taken into consideration.<sup>1</sup>

The contemporary dialogue on an approach to the child with an intersex condition is a credit to our colleagues in pediatric endocrinology who have responded to recent scientific discoveries (both biological and psychological) and the concerns of patients and their families. Dr Robert Blizzard, in a recent commentary in *Pediatrics*, wrote: "There exists a series of conundrums regarding gender assignment, gender identity, gender role, and sexual preference that need solving before we can be comfortable in providing reasonable answers to the questions posed by parents of intersexed patients and those of the patients themselves."<sup>2</sup>(p620)

This is an area in which a developmental-behavioral pediatrician can contribute in significant ways. With an emphasis on the interactions between biological and psychosocial aspects of child development, the issues raised by the birth of a child with an intersex condition are particularly suitable to the clinical perspectives of a developmental-behavioral pediatrician. The commentaries invite an interdisciplinary approach that should be seen as an opportunity for participation.

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