Developmental Endocrine Influences on Gender Identity:

Implications for Management of Disorders of Sex Development

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Abstract

When a baby is born, the first medical pronouncement is usually, "It's a boy," or "It's a girl." In most cases, this pronouncement is based simply upon the appearance of the child's external genitalia. Due to variations in the process of sexual differentiation, sometimes the gender that should be assigned is not apparent from inspection of the external genitalia, either because they are "ambiguous" or because their appearance is not congruent with the internal anatomy. Decisions must be made not only about the most appropriate gender to assign the infant but also about the medical and rearing practices that will facilitate optimal psychological development and quality of life for the affected individual. This article will review the approach to managing gender disorders that has evolved since the 1950s. Three issues are identified as central to current shifts that are occurring in the management of these disorders: (a) increased understanding of the biological substrates of gender identity; (b) questions regarding the indications for irreversible cosmetic genital surgeries as a means of reinforcing gender assignments in infancy, and (c) ethical issues pertaining to informed consent and who is entitled to give it, particularly with regard to surgical gender reassignments in infancy. In keeping with the neuropsychiatry theme of this issue, the focus of this article is on prenatal sexual differentiation of the brain as it pertains to the question of psychosexual neutrality at birth.

Key Words: Intersex, sexual differentiation, sex assignment, gender assignment.

Introduction

PARTICULAR TERMS may be defined differently by various authors, so it may be helpful to begin by defining those terms as they will be used here. *Sex* will be used to refer to the biological variables that can be described as either male or female (e.g., genes, chromosomes, gonads, internal and external genital structures), while *gender* will refer to social categories (e.g., man or woman, boy or girl) or factors related to living in the social role of a man or a woman. *Gender identity* refers to one's sense of belonging to the male or female gender category (1), while *gender role* refers to behaviors (mannerisms, style of dress, activities etc.) that convey to others one's membership in one of those categories (1). *Sexual orientation* refers to one's pattern of erotic responsiveness and will be described here as *androphilic* (attracted to men), *gynephilic* (attracted to women), or *bisexual* (attracted to both).

The course of normative development culminates in full concordance among all of the biological variables of sex (i.e., either all male or all female). In *intersex* disorders, however, one or more of those variables is discordant with the others or its differentiation is intermediate between male and female norms. *Intersex* became the preferred term to encompass a variety of syndromes previously classified on the basis of gonadal histology as *true hermaphroditism* in which both testicular and ovarian tissue are present in a single individual, and *pseudohermaphroditism* in which only one type of gonadal tissue is present. Due to disagreements as to whether or not particular disorders should be considered intersexed (2), the term *disorder of sex development* is gaining currency to refer to any congenital condition in which development of chromosomal, gonadal or anatomical sex is atypical (3). It has been estimated that a child is born with external genitalia so noticeably atypical that a specialist in sexual differentiation is consulted about once in every 1,500 – 2,000 births. This article deals primarily with that population, whether or not all meet a particular authority's definition of intersex. For discussion of the definitions and frequency of intersex, the reader is referred elsewhere (2, 4, 5).

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Beginning in the 1950s, John Money and colleagues (6) observed that because intersexes are neither completely male nor completely female they "are likely to grow up with contradictions existing between the sex of assignment and rearing, on the one hand, and various physical sexual variables, singly or in combination." They collected data on the psychosexual development of children born with various intersex conditions in order to determine whether their gender role and identity were more likely to be concordant with the sex of assignment and rearing, or with one or another of the physical variables of sex. Of 105 intersexes studied, only 5 had a gender role or identity that was "ambiguous and deviant from the sex of assignment and rearing." Thus, they concluded, along with Ellis (7), that the sex of assignment and rearing is a much better predictor of gender role and identity than the biological variables of sex.

This evidence for the early malleability of gender identity instigated a shift away from prior attempts to assign gender to intersexed individuals on the basis of gonadal histology or chromosomal analysis. Instead an "optimal gender policy for psychosocial and medical management" of intersex conditions was developed (8, 9), aimed at optimizing their prognosis with respect to six variables: reproductive potential, sexual function, minimization of medical procedures, gender-appropriate appearance, stable gender identity and psychological well-being. Although it was appreciated at that time that intrauterine hormones might exert sexually differentiating effects on the fetal brain, it was widely accepted that the effects of nurture outweigh those of nature with respect to psychosexual development. Prompt surgical normalization of external genital anomalies was, therefore, viewed as necessary to establish the dominance of nurture over nature. More specifically, external morphology congruent with the assigned gender was viewed as essential both to convince the affected child that he/she was truly a member of the assigned gender and to convince the parents who were responsible for unambiguously rearing the child as a member of the assigned gender (8). Compared to phalloplasty, vaginoplasty provides better cosmetic and functional results, and a small penis was believed to be a tremendous psychosocial burden for a boy (8, 10). Thus, due to the belief in the early malleability of gender, a majority of intersexed infants with an absent or small phallus were assigned as female regardless of the status the other biological variables of sex. Even male infants who were not intersexed but who had a stretched phallus length of less than 2 cm were sometimes reassigned as female (10).

Over the past half century, a variety of lines of converging evidence—including follow-up studies of intersexed individuals and non-intersexed individuals whose gender was surgically reassigned in infancy—suggests that the organizing effects of prenatal endocrine factors on the subsequent emergence of gender identity is much stronger than previously thought (11–13). Consequently, the management of intersex disorders, particularly the initial gender assignment, is increasingly taking into account exposure to these factors. Moreover, the practice of performing cosmetic genital surgeries on infants to reinforce gender assignments is currently being challenged on a variety of medical and ethical grounds including the fact that these surgeries generally cannot be reversed if the affected individual subsequently rejects the assigned gender (14–17). This article will begin by reviewing the neurobiology of gender identity with an emphasis on the role of prenatal endocrine factors, and will conclude by considering this information in the broader context of shifts that are taking place in the management of intersex and other disorders of sex development.

Neurobiology and Gender Identity

Overview of Sexual Differentiation

Hormonal contributions to sexual differentiation of the brain have been extensively reviewed recently elsewhere (18, 19). Animal studies have contributed substantially to the formulation of a prenatal hormonal hypothesis for both sexual orientation and gender identity. The prenatal hormonal hypothesis draws largely on the observation that the balance between male and female copulatory and other reproductive behaviors in animals is strongly influenced by the magnitude and timing of early androgen exposure. In addition, anatomical sex differences in regions of the rodent brain implicated in the regulation of these behaviors have been found to have a similar developmental hormonal dependence. The best studied of these neuroanatomical sex differences, the sexually dimorphic nucleus of the preoptic area (SDN-POA) in rats appears to have a homologue in the primate (20) and human (12, 21, 22) hypothalamus. The human nucleus, known as the third interstitial nucleus of the anterior hypothalamus (INHA3), is larger in males than in females (12, 21, 22). It has been reported to vary with sexual orientation such that it is larger in gynephilic compared to androphilic individuals (12). In addition, the size of a portion of the bed nucleus of the stria terminalis has been reported to be sexually dimorphic in rats

and humans, and to vary in humans as a function of gender identity but not sexual orientation (13, 23). Specifically, the nucleus was reported to be larger in individuals with a male as opposed to a female gender identity, regardless of their genetic, gonadal or hormonal status and regardless of the direction of their sexual orientation (13, 23). These human studies must be viewed tentatively pending corroboration, and, to date, there have been no empirical investigations into the prenatal hormonal dependence of the putative hypothalamic dimorphisms in humans.

The mammalian embryo is initially sexually bipotential (19). In the course of normal male differentiation a testis-determining gene, SRY, which is normally on the Y chromosome directs the development of testes. Subsequently, testicular secretions orchestrate the differentiation of the male genitalia and brain. Müllerian inhibitory substance, a nonsteroidal testicular secretion, induces regression of female internal genital structures, while the 5α-reduced metabolite of testosterone, 5α-dihydrotestosterone (DHT), is required for the development of male internal genital structures and for the differentiation of male external genitalia. Activation of androgen receptors by testosterone itself or by DHT appears to contribute to the masculinization of brain structure and function in some species (24). In laboratory rodents the conversion of testosterone to estrogen by aromatase enzymes within the brain plays a greater role, although the activation of both androgen and estrogen receptors may be required for full masculinization (24, 25). Not only do males and females have different hormonal requirements, but animal studies suggest that the various aspects of somatic and brain sexual differentiation occur during differing periods of development in a sequence of temporally overlapping steps (24, 26). Thus, various parameters hypothesized to reflect sexual differentiation of the brain (e.g., gender identity and sexual orientation) could vary independently from one another and from genital morphology. In the absence of the cascade set in motion by the testis-determining gene, female development ensues, at least to a first approximation.

Human testes begin to secrete androgens by the seventh or eighth week of gestation (27), a process that is initially regulated by human chorionic gonadotropin secreted by the placenta (28). By the fifteenth week of gestation, the regulation of androgen secretion is taken over by gonadotropin from the fetal pituitary, which is in turn regulated by the fetal hypothalamus. Gonadotropin secretion decreases toward the end of gestation. Thus, fetal androgen in males is elevated between weeks 8–24 of gestation, with peak levels occurring between weeks 14–16 (29). In males, the level of testosterone increases from birth to a peak at 1–3 months and then decreases to prepubertal levels by 4–6 months (30). The ovary is relatively quiescent prenatally but secretes substantial levels of estradiol during the first 6–12 months after birth. A sharp reduction of gonadal activity then occurs in both sexes until 10 or 12 years of age, when sex-characteristic adult hormonal profiles emerge (19). Thus, hormonal influences could conceivably influence psychosexual differentiation prenatally (8–24 weeks of gestation), during the first 6–12 months postnatally, and again at puberty.

Human Studies Relevant to Biology and Gender Identity

Clinical data spanning more than half a century, relevant to the question of early hormonal influences on gender identity, have been reviewed extensively by Zucker (8). The following is a summary and update of that review, with an emphasis on cases that were followed at least into late adolescence and in which an assessment of gender identity and role were documented. The syndromes are grouped into those in which the developing brain was exposed to either a full or a partial complement of masculinizing influences. This division is based on the hypothesis that the likelihood of problems with the acceptance of a female gender assignment is related to the degree of early brain masculinization. Various syndromes will be described first, with their implications regarding gender differentiation discussed at the end of this section. For discussion of disorders of sex development not reviewed below, the reader is referred elsewhere (3, 31–33).

Syndromes with a Normal Complement of Masculinizing Hormonal Influences Prenatally

Ablatio penis does not refer to a disorder of sex development but instead refers to the accidental or traumatic loss of the penis in infancy in otherwise normal males. Four cases reassigned to the female gender prior to 2 years of age have been reported (8). Of these, at least 2 had switched to a male gender identity by or during puberty, while 2 had retained a female identity at last follow-up (ages 17 and mid-20s). Detailed information is available for only two of these cases. The first detailed case was first described by Money and Ehrhardt (1) and has been widely publicized as the case of John/Joan. This case will be discussed in some detail because of the inordinate impact it has had on the field.

One of a pair of normal monozygotic 46XY twins suffered accidental penile ablation at the age of seven months. A decision for gender reassignment was made at 17 months, with orchiectomy and preliminary vaginoplasty occurring at 21 months (1, 8, 31). Follow-up at seven years suggested that the patient had accepted the female gender identity and that the twin brother was a normal male (1). Two years later, the patient was described as having tomboyish traits but that "Her activity is so normally that of an active little girl...." (34). It was concluded that "...gender identity is sufficiently incompletely differentiated at birth as to permit successful assignment of a genetic male as a girl…." (34). Over the next two decades that conclusion was cited in innumerable medical review articles and textbooks, and formed the crux of theories concerning the malleability of gender and surgical gender reassignment in intersexes (35). Follow-up when the patient was in his early 30s, however, revealed that he had rejected the female identity, resisted feminizing estrogen therapy, and had begun to live as a male by the age of 14. At that time he received a mastectomy and began testosterone replacement therapy and surgical procedures for phallus reconstruction (11, 35). He married a woman at age 25 and adopted her children. His suicide in 2004 has been attributed by some to the contribution of gender reassignment and its aftermath to his anguished history (36).

In the second detailed case, the patient's penis was destroyed during an electrocautery circumcision at 2 months (37) and surgical reassignment was begun at 7 months. At 26, she was reported to be confident of her female gender. Although she was sexually active with a man, she reported primarily gynephilic fantasies and described her sexual orientation as bisexual.

Cloacal exstrophy, a disorder of embryogenesis involving the genitourinary and intestinal tracts, affects both genetic males and females. Its incidence is believed to be less than one in 400,000 births. In genetic males, the external genitalia are often grossly anomalous or absent; however, testicular function is generally believed to be normal (38, 39). Genetic males with this disorder are often reassigned as female, castrated to prevent emergence of masculine secondary sexual characteristics, and treated with estrogen at puberty to stimulate the development of female secondary sexual characteristics. No detailed post-pubertal follow-up studies have been published on reassigned individuals. In one case report, an affected male reared as female from birth lived as a woman for 52 years. Then, upon the death of her parents, she underwent reconstruction as a man. In a series of 10 affected 46XY individuals between the ages of 4 and 14 who were castrated and unequivocally raised as girls from birth, all were close to the male range in attitudes, activities and behaviors (38). Three had declared themselves to be male (at ages 8, 9, and 12 years, respectively). In a detailed clinical study of affected adolescents who were reared as males, all were described as exhibiting psychosexual dysfunction and anxiety leading to social and sexual developmental impairment (40). Nevertheless, all retained a male gender identity.

Penile agenesis is a condition in which the penis fails to differentiate, although the scrotum is normal and contains normally functioning testes (41). No hormonal abnormality of prenatal onset has been reported in patients with this rare disorder of mixed etiology. Although more than 20 cases have been reported (8), post-pubertal follow-up with assessment of gender identity is available for only a few. Of 4 assigned males, all had retained a male identity at last follow-up, at ages 13, 15, 22 and 45, respectively. Of more than a dozen assigned and reared as females, post-pubertal assessment is available for only two. Of those, one was reported to be content with her female assignment at age 13. The other identified as female at age 15 but was living as a man at age 27.

Syndromes with an Incomplete Complement of Masculinizing Influences

Congenital adrenal hyperplasia, which occurs approximately once in 13,000 births (4), involves an enzymatic abnormality in cortisol synthesis that results in an overproduction of androgens beginning during the fetal period (42). In genetic males, no genital abnormality ensues; however, in genetic females varying degrees of external genital masculinization occur ranging from mild clitoral enlargement to complete fusion of the labioscrotal folds with a phallic urethra (43). There is at times uncertainty regarding gender assignment at birth. Cortisol replacement therapy can minimize further virilization after birth and allow normal ovarian function and fertility to emerge with puberty. In one large cohort 9% of genetic females were assigned and reared as males without reported complications (42). As early detection increases due to state-mandated neonatal screening, the proportion assigned as male is likely to decrease in keeping with the optimal gender policy, which places emphasis on female reproductive potential.

Affected individuals who were reared as females have been studied extensively with regard to cognitive profiles (44), childhood gender conformity (45), gender identity (46), and sexual orienta-

tion (47). The vast majority of affected individuals retain their female gender identity into adulthood although with a statistically increased incidence of gender nonconformity (45, 46), gender dysphoria (48) or ambivalence about gender (49) in childhood and gynephilia in adulthood (46, 47). Four cases, however, have been described in which a male identity emerged gradually between late adolescence and adulthood despite having been assigned as female within a few weeks of birth (50). Gender dysphoric subjects appear to be less willing to participate in follow-up studies compared to subjects without gender dysphoria (8). The proportion of affected individuals who change from female to male gender identity is difficult to know with any degree of certainty; however, various authors have estimated that proportion to be as low as 2% and no higher than 10% (3, 8). Both estimates are much higher than the rate (approximately 1 per 34,000) of transsexuality among normal females (8).

Complete androgen insensitivity is believed to have a minimal incidence of one per 99,000 births but may be as high as one per 13,000 (4). In this condition 46XY individuals develop normally functioning testes but lack functional androgen receptors (24). They develop normal female external genitalia because their tissues are unable to respond to androgens. They are capable of responding to Müllerian inhibitory substance, however, so their internal female genital structures regress. Untreated, they develop breasts and female-typical fat distribution at puberty in response to estrogens derived from testosterone synthesized by their testes. Historically, these individuals were assumed to be normal females at birth and did not come to medical attention until testes descended into the labia, or until they failed to menstruate or conceive children. The published literature does not contain any reports of affected individuals changing to a male gender identity (9). Thus, in the absence of functional androgen receptors, female gender identity appears to be the rule in individuals with an XY karyotype and normally functioning testes. While it has been suggested that in the absence of functioning androgen receptors, these individuals would have female-typical brain differentiation (19), in laboratory rodents androgens appear to orchestrate differentiation of the male brain primarily by interaction with estrogen receptors after conversion to estrogen by aromatase enzymes in the brain (24). It has, therefore, been suggested that humans, in contrast to rodents, require functional androgen receptors for male brain development (24).

Partial androgen insensitivity refers to disorders in which there is a partial resistance to androgens, which results in external genitalia that are only partially masculinized. No reliable statistics are available for the frequency of this disorder, which is generally believed to occur with a lower incidence, perhaps one tenth that of complete androgen insensitivity (4). The degree of external genital masculinization varies with the degree of androgen resistance, leading to considerable phenotypic variation and overlap in appearance with other syndromes. Affected individuals have been assigned and reared as either males or females depending in part on the degree of external genital virilization. In one series of 6 individuals assigned as female (8), 5 retained the female gender identity into adulthood. Following a long history of masculine gender role interests and gynephilia, the sixth requested gender reassignment at age 30. Another report describes 10 affected individuals of whom eight were reared as boys, one as a "hermaphroditic girl" and one as a girl (51). At follow-up between 13–39 years it was concluded that gender identity differentiated in accordance with the gender of rearing. A third report describes 8 patients, 7 of whom were assigned as female at birth (48) and followed up between the ages of 6–23. Details on gender identity were not given; however, the authors concluded that the female assignment had been wrong on the basis of the patients' "boyish behavior.... In particular, the wild, rough play ... [which was] difficult for their parents to regulate."

5α-reductase deficiency affects 46XY individuals. During fetal development the gonads differentiate into normal testes and secrete appropriate amounts of testosterone; however, due to the deficiency of 5?-reductase, affected individuals are unable to convert testosterone to dihydrotestosterone in amounts sufficient for the external genitalia to masculinize normally. Consequently the newborn may have a phallus that more closely resembles a clitoris than a penis, and unfused labioscrotal folds resembling labia majora. In the absence of sophisticated diagnostic testing, affected individuals have often been assumed to be females at birth and have been reared accordingly (52, 53). At puberty, however, testosterone and not dihydrotestosterone is the essential androgen for growth of the male external genitalia and the emergence of male secondary sex characteristics (54). Thus, a masculinizing puberty ensues: the phallus markedly enlarges, the testes descend into the labioscrotal folds, the beard grows, the voice deepens and a masculine habitus develops (52, 53).

The prevalence of this disorder in the general population is unknown (4). It has been studied extensively in the village of Las Salinas, Dominican Republic, where its prevalence is unusually high

due to consanguineous marriages (52, 53). Of 18 individuals who reportedly had been assigned and reared as females from birth, 17 changed to a male gender identity and 16 to a male gender role at puberty. The authors suggested that male gender identity and gynephilia "appear to be testosterone and not dihydrotestosterone related...and that sex of rearing as females...appears to have a lesser role than the presence of two masculinizing events—testosterone exposure *in utero* and again at puberty with the development of a male phenotype." Because the studied individuals came from inter-related families living in the same village, questions have been raised about the possibility of ambiguities in the gender socialization of many of the affected individuals (53, 55). Similar accounts of gender change from female to male have been made in cohorts from Mexico, Papua New Guinea and Brazil (8, 54, 56).

17β-hydroxysteroid dehydrogenase deficiency usually results from a missense mutation (54) and occurs with unknown frequency. The mutation results in a deficiency of the enzyme that catalyzes the terminal step in testosterone synthesis. Affected 46XY infants are born with female external genitalia despite the presence of testes and male internal structures (54). The deficit in testosterone produces a corresponding deficit in its androgenic and estrogenic metabolites believed to play a role in masculinization of the brain. The deficiency usually becomes less severe with time and many affected individuals eventually have male-typical testosterone levels. They are usually assigned as female at birth and come to medical attention because of virilization at puberty or a failure to menstruate. Between 40% and 50% of affected individuals, even one who made essentially no hydroxysteroid dehydrogenase (17β-HSD) (54), have been reported to switch from a female to male identity postpubertally.

Micropenis is a condition in which penile length is at or below the 10th percentile for age-graded norms (8). Androgens are necessary at two points in fetal development for a normal penis to form: early in fetal life to sculpt the bipotential genital precursor into a penis and scrotum and subsequently in fetal life to enlarge the penis. Micropenis is believed to occur in XY individuals if androgen levels are insufficient for the penile growth after the initial masculinization of the external genitalia has already occurred. Of 16 reported cases who were assigned and reared female, follow-up is available only for 8 (ages 10–25), all of whom were described as having appeared to have developed a female identity, although a detailed history was obtained from only one adult subject (8). In contrast, adulthood follow-up is available for 22 affected individuals who were assigned and reared as males (8). Of these, all were judged to have retained a male gender identity. One, however, expressed feelings of inferiority related to his small penis and reported childhood fantasies of gender reassignment. After gynephilic experimentation, he exhibited an androphilic orientation in adulthood. In one group study of 9 individuals in which all retained a male identity, childhood gender nonconformity was noted in 4, an androphilic orientation in three and gynephilic orientation in six. In a second group study of 12, all retained a male identity and a gynephilic orientation was assumed for at least nine, seven of whom were married or cohabitating with a woman.

Summary and Implications of Clinical Observations

The above review underscores the paucity of intersexed and gender reassigned cases for which detailed follow-up is available into adulthood. Moreover, it is clear that an individual may undergo a transition in gender identity while restricting the social contexts in which gender role behavior reflects that transition, and that such transitions may occur as late as middle age. The likelihood of rejecting female assignment appears to be increased in androgen-responsive individuals born with testicular tissue the longer that tissue is left in place, even prior to puberty. This could reflect the duration of reinforcement of a male identity prior to reassignment or ambivalence resulting in delays in the reassignment. Alternatively, it could reflect increased masculinization of the brain during the early postnatal surge of testosterone secretion (30). The data on individuals with 5?-reductase and 17β-HSD deficiencies suggest that the probability of switching to a male gender identity and role after female reassignment is increased further in androgen-sensitive individuals whose testes are left in place until puberty. The data do not justify the conclusion that prenatal androgen exposure produces a brain that is hardwired for male gender identity at birth. Instead, an effect of prenatal androgens may be reinforced by the elevated androgen secretion that occurs in the neonatal period and again at puberty.

Implications Regarding Hormonal Pathways Involved in Gender Differentiation

Although individuals with complete androgen insensitivity possess normal testes and all the hormones and metabolic machinery necessary to mas-

culinize the rodent brain (i.e., testosterone, aromatase enzyme, estrogen receptors), all reported cases have been reared unambiguously as females, have retained that identity into adulthood, and have been described as having stereotypically feminine interests and behaviors as children (8). Thus, if prenatal hormones exert an organizing influence on the human brain with respect to gender, masculinization of the brain in this regard must be mediated primarily via androgen receptors. The evolution of masculine behavior and male identity among individuals with 5α-reductase deficiency suggests that those androgen receptors may be activated by testosterone in the absence of 5α- reduction. Moreover, the outcomes among individuals with 17β-HSD, and presumably very little testosterone production *in utero*, suggest that very little testosterone is required to bias gender identity in the male direction. Compared to gender identity, sexual orientation appears to be even more sensitive to androgenic influences, as evidenced by the proportion of androgenized females who develop a bisexual or gynephilic orientation while retaining a female gender identity. On the other hand, that the androgenic requirements for male gender identity and gynephilia appear to be so low detracts from the hypothesis that either androphilia or transgenderism in otherwise normatively developed XY men results from an early androgen deficiency. The variability of gender outcomes even among related intersexed individuals known to share identical genetic mutations, suggests the importance of psychological, social and cultural factors as co-mediators of gender development. The current dominance of the hormonal theory of sexual differentiation may give the impression that gonadal secretions are fully responsible for all aspects of brain sexual differentiation. Recent work, primarily in animals, however, suggests that XX and XY brain cells behave differently, in part, because of the cell-autonomous actions of X and Y genes (18). The possibility that such actions could contribute to gender identity is only now beginning to be considered. As discussed elsewhere (57), cognitive and experiential factors must also be considered.

Implications for Gender Assignment

While this review strongly suggests that biological factors contribute to gender identity, the exact nature and magnitude of their impact are uncertain. During infancy it is not possible to predict a given individual's ultimate gender identity with certainty. A small minority of individuals (i.e., transgendered individuals) who appear normatively developed at birth develop a gender identity incongruent with the known biological variables of sex. Nevertheless, development of a male identity is strongly correlated with exposure to androgenic influences in early development. Thus, it would seem imprudent to assign infants with a small or absent phallus to the female gender if they were exposed to a full complement of masculinizing influences prenatally (e.g., individuals with penile agenesis, micropenis, cloacal exstrophy). As reviewed above, male assignment of these individuals is not without complications; however, it minimizes surgery (e.g., castration to prevent masculinization at puberty) and in many cases preserves fertility (3). Similarly, preservation of fertility as males is possible for individuals with 5α-reductase deficiency and may also be possible with 17β-HSD deficiency (3). Current estimates suggest that a majority of these individuals who are reared as females, eventually live as males. Barring cultural indications to the contrary, male assignment should be the rule.

There are no known cases of 46XY individuals with complete androgen insensitivity assuming a male gender identity. These individuals, who will be infertile regardless of assignment, should always be assigned female. In order to preserve fertility, female assignment is also currently recommended by most authorities in all 46XX cases of congenital adrenal hyperplasia (3). This recommendation holds even for those cases involving extreme masculinization of the external genitalia (3) and who, according to the above review, could likely live successfully as infertile men and are at high risk of rejecting the female assignment. Guidelines for the initial gender assignment are less straightforward in other syndromes, especially those involving exposure to intermediate levels of masculinizing influences prenatally (e.g., partial androgen insensitivity, abnormalities of gonadal differentiation or function), and for whom there is no potential for fertility. In such cases, decisions must be made on an individual basis using all that is known about the child's particular disorder, how the child's disorder is likely to influence his or her gender identity, and how the family's cognitive capacity and beliefs will impact their nurturing of the child. The aim is to optimize the prognosis with respect to the endpoints identified by the optimal gender policy as described above.

Ethical Issues in Management of Disorders of Sex Development

A distinction must be made between gender assignment (a social labelling process) and the cos-

metic genital surgeries that may be done in an effort to reinforce that assignment. While it is generally agreed that parents have a legal right to determine the nature of their child's medical care, some recipients of childhood surgeries have raised the complex question of whether their parents had an ethical right to consent to irreversible genital/gonadal procedures done for non-medically threatening conditions. They hold that because genitals are concealed from the public by clothing, gender assignment and social reinforcement of that assignment can be accomplished without surgery (58, 59). While atypical genitals rarely cause illness or pain, surgery and its associated scarring may cause pain, diminution of sexual pleasure, and anorgasmia as well as other complications (17). Genitoplasty frequently involves multiple procedures throughout childhood and even the best surgical efforts sometimes fail to produce acceptable functional or cosmetic results (60, 61). Furthermore, surgery is difficult or impossible to reverse and, as children or adults, individuals with disorders of sex development may reject the gender that was assigned in infancy. Some have, therefore, suggested that elective genital surgeries should not be considered until the affected individual is old enough to possess the intellectual capacity to make an informed decision (62). In appropriate cases, puberty and the development of secondary sex characteristics may be delayed medically so that a patient's decision-making is not rushed. Many believe, however, that early surgery to address genital anomalies relieves parental distress and, thereby, improves bonding between parent and child as well as the parents' ability to nurture the child (3, 50). Systematic evidence supporting this belief is critically lacking, however. To date no studies have addressed whether this important issue is better addressed by surgery as opposed to psycho-education and counseling of the parents.

Beyond the issue of who is ethically entitled to consent to procedures employed in intersex management is the issue of what constitutes informed consent. While physicians may understandably fear that particular details of their child's sexual anomalies may exacerbate parental anxiety, parents cannot make informed decisions if information is withheld from them. Informed consent requires full disclosure of relevant information, such as physical findings, karyotype and diagnosis, as well as the known potential risks and benefits of withholding or performing each intervention that may be considered. For example, early castration requires subsequent postpubertal hormone replacement therapy, which poses its own risks. These may include elevated rates of cardiovascular disease, cancers (63, 64), or osteoporosis secondary to poor compliance with hormone replacement. Some have suggested further that in order to give informed consent, parents should also be made aware of the lack of scientific agreement on theories of gender development as well as the paucity of outcome studies following particular procedures commonly employed in intersex management (14). In some cases full disclosure of the intersex status to the parents and/or affected individual has been withheld for fear that it would introduce ambiguities into the reinforcement of the assigned gender and lead to an unstable gender identity (65). Not only is age-appropriate disclosure of one's biological status a prerequisite for informed consent, it precludes the possibility that a patient will discover his or her intersex status in an uncontrolled setting in which a catastrophic psychological reaction is possible.

Conclusions

Detailed long-term follow-up and assessment of quality of life have been reported for exceedingly few individuals with disorders of sex development. More research is clearly needed to elucidate, on a syndrome-by-syndrome basis, what clinical practices are likely to yield the best quality of life in affected individuals. Three issues are central to current shifts that are occurring in the management of these disorders: (a) increased understanding of the biological substrates of gender identity; (b) the indications for cosmetic genital surgeries in the management of these disorders; and (c) ethical issues pertaining to informed consent and who is entitled to give it. In addition, a re-examination of many aspects of intersex management has been precipitated by input from advocacy groups comprising adults with disorders of sex development and the parents of intersexed children (66, 67, 68). One such group, which also includes health care providers, The Consortium on the Management of Disorders of Sex Development, has recently published clinical guidelines for health care professionals (59) and a handbook for parents (58). Among other sets of published guidelines, these uniquely reflect the input of those with the highest stake in intersex management decisions—the recipients of interventions based on those decisions.

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