Principles of Transgender Medicine and Surgery

Randi Ettner
Stan Monstrey
A. Evan Eyler
Editors

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Chapter 12

Intersex: Definition, Examples, Gender Stability, and the Case Against Merging with Transsexualism

Tom Mazur
Melissa Colsman
David E. Sandberg

INTRODUCTION

Important distinctions between individuals with transsexual and intersex conditions are, at times, blurred in both popular and scientific literature. While individuals with an intersex syndrome may share some features (e.g., gender dysphoria and identity concerns) with those diagnosed with transsexualism, persons with intersex conditions diverge from transsexuals in terms of associated features including prevalence, age of onset, and sex ratio when presenting with a gender identity disorder (GID) (Meyer-Bahlburg 1994).

Historically, in an effort to obtain professional help, some transsexuals claimed to be intersex or hermaphrodites. More recently, the term “intersex” has been subsumed by some writers under the broader term “transgender,” which also includes individuals who “transgress usual gender roles” such as “cross-dressers, drag artists, gender queer, [and] androgynes,” among others (Monro 2005; Raymond 1994). Additionally, some neuroanatomical studies contribute to a merging of the entities into a single category. For example, one postmortem study of the brains of transsexuals showed that the central subdivision of the bed nucleus of the stria terminalis (BSTc) in seven male-to-female (MTF) and one female-to-male (FTM) transsexuals differed from that of a comparison group without GID. Furthermore, the size of this nucleus in the MTF and FTM transsexuals was comparable to female and male comparison groups, respectively (Kruijver...
et al. 2000). Another recent study in rats demonstrated that gene expression prior to the time of prenatal hormone activation may differ in male and female brains (Arnold 2004; Dewing et al. 2003; Vawter et al. 2004). These findings have led to speculation that neuroanatomic substrates in the central nervous system of transsexuals contribute to the development of a form of intersexuality (Meyer-Bahlburg 2005a). Noted scholars in gender research have suggested that transsexualism can be considered to be a neurodevelopmental condition of the brain (Gender Identity Research and Education Society 2002).

Failure to differentiate between individuals with and without a clearly identifiable intersex condition may hamper studies of etiology and optimal clinical management. Given that our understanding of etiologic factors in GID in physically typical individuals (i.e., transsexuals) and in those with intersex conditions is incomplete, it would be prudent to consider them as separate entities when initiating an evaluation of GID in these two groups.

The purpose of this chapter is to propose that intersexuality and transsexuality are different—even though persons classified as either may present with gender dysphoria and/or a desire to change their gender. This chapter will define intersexuality, review the typical sexual differentiation process, provide examples of the most frequently occurring intersex syndromes and related conditions, summarize recent data on gender identity stability and dysphoria in adults whose gender assignment at birth was in question as the result of an intersex condition, compare and contrast the clinical presentation of GID in intersex and nonintersex persons, and discuss evaluation and treatment strategies.

**INTERSEXUALITY DEFINED**

The term “intersex” refers to discordance between any level of genotypic and phenotypic expression of sexually dimorphic features. As such, intersex conditions may or may not include atypical genital appearance. Intersex has been used synonymously with “hermaphroditism,” which refers to congenital ambiguity of the sexual anatomy that, in appearance, is neither fully female nor fully male (Money 2002). Other terms adopted by researchers and clinicians include: disorders of sex development, physical intersex conditions, sex errors of the body, ambiguous genitalia, birth defects of the sex organs, and male and female pseudohermaphroditism. Intersex occurs in genetic males (46XY), genetic females (46XX), individuals with sex chromosome mosaicism (e.g., 45X/46XY), or aneuploidy (i.e., one or more extra or missing chromosomes; for example, Klinefelter syndrome [47XXX] or Turner syndrome [45X]). When ambiguity of the external genitalia is
present, it is typically the result of defects in prenatal sex hormone production or action (MacGillivray and Mazur 2005).

**TYPICAL SEXUAL DIFFERENTIATION PROCESS**

Development of the sexual reproductive system involves the internal (Figure 12.1) and external (Figure 12.2) sex organs. These organs develop through a series of steps. At the outset, sex determination occurs when either a Y- or an X-bearing sperm fertilizes the ovum. If the resulting genetic sex is XY, then the undifferentiated and bipotential gonad develops as a testis. A single gene located on the short arm of the Y chromosome, referred to as the sex-determining region of the Y chromosome, or SRY, is responsible for this event. Testes develop approximately in the sixth to seventh week of pregnancy in an XY embryo. The bipotential gonad develops into an ovary in the absence of SRY (i.e., XX sex chromosomes) (Grumbach, Hughes, and Conte 2003).

The process of sexual differentiation begins once the Leydig cells of the testes secrete two hormones, testosterone and anti-Müllerian hormone (AMH), at weeks eight to nine of pregnancy. Testosterone causes the Wolffian (male) duct to differentiate into the epididymus, vas deferens, seminal vesicles, and ejaculatory ducts. AMH suppresses Müllerian (female) duct development: fallopian tubes, uterus, cervix, and upper third of the vagina. Müllerian duct differentiation unfolds in the absence of hormonal stimulation, (i.e., the ovary is quiescent during this stage of development). In the absence of testosterone exposure, the Wolffian duct regresses.

After completion of the internal sexual reproductive structures, differentiation of the external genitalia begins (week 10). The external genitalia, male and female, are created from a single set of structures, in contrast to the internal genitalia, which differentiate from a double system, Wolffian and Müllerian. Thus, the external genitalia, like the gonads, are bipotential, differentiating and developing into either male or female external sex organs.

Dihydrotestosterone (DHT), the 5-alpha reduced metabolite of testosterone, is responsible for differentiation of the genital tubercle into a penis in an XY fetus (Conte and Grumbach 2004). The labioscrotal swellings fuse to form the scrotum. Urethral-labia folds form the shaft and foreskin of the penis. Male external genital differentiation is complete by weeks twelve to fourteen of pregnancy. Penile enlargement continues during the second and third trimesters of pregnancy.

In an XX fetus, the ovary secretes no masculinizing hormones. The genital tubercle becomes a clitoris. The labioscrotal swellings become the labia
majora. The urethral-labia folds become the labia minora and the clitoral hood. Intersexuality occurs as a consequence of disorders of androgen biosynthesis or action, partial or complete, in genetic males, or excess androgen exposure in genetic females.

**INTERSEX SYNDROMES AND RELATED CONDITIONS**

Atypical sexual development occurs in multiple syndromes and related conditions; the most commonly encountered are summarized in the following text, which uses the endocrine classification system of atypical sexual development found in Conte and Grumbach (2004). The reader is also referred to this review for a more thorough endocrine review; for brief descriptions of the behavioral characteristics of persons diagnosed with these conditions, see Cohen-Kettenis and Pfafflin (2003).

**Disorders of Gonadal Differentiation**

**Klinefelter Syndrome (KS)**

KS is a nonheritable genetic condition in which an extra X chromosome is present (Zurenda and Sandberg 2003a). The most commonly found chromosomal pattern is a single extra X (47XXY), but other variations (e.g., 48XXYY) and mosaicism (e.g., 46XY/47XXY) have been documented. Incidence is estimated at 1:600 live male births (Nielsen and Wohlert 1991). KS is typically diagnosed during puberty when small, firm testicles are palpated on physical exam. Additional features, which assist in making the diagnosis, include tall stature and disproportionately long legs (Ratcliffe, Butler, and Jones 1990). Infertility is almost certain because the testes do not produce a normal volume of sperm. However, assisted reproductive technologies (ART), such as intracytoplasmic sperm injection (ICSI), are helping men with KS to father children with a normal karyotype (Denschlag et al. 2004). Additional features of KS may include unilateral or bilateral breast development (gynecomastia), incomplete masculine body build, and social and/or cognitive-educational problems (Grumbach and Conte 1998). Puberty may also be delayed (Nielsen and Wohlert 1991), and individuals will need testosterone replacement in adolescence and adulthood to prevent osteoporosis and maintain physical energy, sexual function, and a general sense of well being (Zurenda and Sandberg 2003a).

Neurocognitively, individuals with KS characteristically achieve a Full Scale IQ that falls in the average range, but Verbal IQ is typically significantly lower than Performance IQ. This profile is associated with language
and reading problems, speech and language delays in childhood, and poor school performance. Many individuals with KS are described as having a passive personality and a tendency to internalize problems, and exhibit chronic difficulties with peer relationships (Sandberg and Barrick 1995).

Psychosexually, men with KS, on average, exhibit decreased interest in women, less dating, and limited sexual experience (Mazur and Dobson 1995). A twenty-year-long follow-up study showed that 59 percent of KS individuals were married or involved in a long-standing heterosexual relationship (Nielsen and Pelsen 1987). While most persons with KS establish a male gender identity, there are reports of GID in individuals who transition to live fully as female (Seifert and Windgassen 1995; Cossey 1991).

**Turner Syndrome (TS)**

TS is the consequence of a chromosomal genetic abnormality in females characterized by a missing or partially deleted X chromosome (Fennell 2003). Incidence is estimated at 1:2,500 live female births (Fennell 2003; Hook and Warbuton 1983).

Several dysmorphic features characterize the physical appearance of those with TS, including low-set ears and hairline, high-arched palate, webbed (thick) neck, broad chest, and short stature (Fennell 2003; Sybert and McCauley 2004). The number and degree of physically dysphoric features is variable in individuals with TS. Additionally, hearing problems, malformed kidneys, and cardiovascular abnormalities may be present. The Wolffian ducts regress and the Müllerian ducts differentiate normally in TS; individuals with TS typically have streak (nonfunctioning) gonads resulting in infertility. For most women, the external genitalia are normal in appearance. For the majority, endocrinological intervention includes hormone replacement therapy to initiate puberty and to maintain secondary sexual characteristics. Growth hormone is used to treat marked short stature. Various assisted reproductive techniques are now available for achieving pregnancy. For those women who do not have functional ovaries, oocyte or embryo donation can be used to achieve pregnancy (Saenger et al. 2001).

Neurocognitively, individuals with TS characteristically achieve a Full Scale IQ that falls in the average range, but Performance IQ is typically significantly lower than Verbal IQ. TS is associated with a variety of learning problems such as poor math skills, which may be related to poor visual-perceptual abilities (Mazur and Dobson 1995; Sandberg and Barrick 1995; Sybert and McCauley 2004). Hyperactivity and inattentiveness in childhood are noted in the literature (Sandberg and Barrick 1995). Women with TS exhibit difficulties in establishing satisfying long-term social relation-
ships and are at risk for having low self-esteem (Sandberg and Barrick 1995; Sybert and McCauley 2004).

Psychosexually, gender identity in TS is unambiguously female. To our knowledge, there are no reports of a woman with TS transitioning to live in the male gender.

**True Hermaphroditism (TH)**

TH is associated with a number of chromosomal patterns: 46XX (most common), combined 46XX/46XY chimerism, or 46XY (rare). Stated to be “uncommon,” but “reported in more than 400 individuals,” the incidence of TH is unknown (Grumbach, Hughes, and Conte 2003, p. 908).

TH is defined by the presence of both testicular and ovarian tissue in the same individual (Grumbach, Hughes, and Conte 2003). The internal reproductive ducts differentiate in accordance with the gonad on that side of the body, i.e., female internal reproductive structures if an ovary is present. The external genitalia in these individuals may range from typical male to typical female. Breast development is common and menses may occur in more than half of individuals with TH. Clinical management depends on the age at diagnosis and functional capacity of the reproductive structures.

Individuals diagnosed with TH have been assigned to either the male or the female gender. Comprehensive reviews of long-term psychosocial or psychosexual outcomes in TH have not been performed (Meyer-Bahlburg 2005a).

**Female Pseudohermaphroditism**

**Congenital adrenal hyperplasia (CAH).** CAH is the result of an enzyme deficiency (most commonly 21-hydroxylase) that occurs in both males and females. CAH is inherited as an autosomal recessive disorder and has an estimated incidence of 1:15,000 live births (Speiser and White 2003), with considerable variation between ethnic/racial populations.

Genetic males with CAH show no ambiguity of their external sex organs at birth. In contrast, the prenatal androgen excess in genetic females results in varying degrees of masculinization of the external genitalia. In the most extreme form (Prader stage 5), the genitalia of the 46XX infant look typically male, with the urethral meatus terminating at the tip of an enlarged phallic structure and fused labia which resemble a scrotum. There are no gonads in the scrotum, as the internal genital ducts are typically female, with ovaries and uterus in the typical position. CAH is associated with excess of adrenal androgen production in utero and, sometimes, an accompa-
nying deficiency in the salt-retaining hormone, aldosterone. Depending upon the degree of aldosterone deficiency, an electrolyte imbalance due to salt loss can occur, which can be life threatening. Endocrine intervention is lifelong: cortisol replacement controls excess androgen production and, if needed, mineralocorticoid treatment controls salt loss.

Neurocognitively, individuals with CAH characteristically achieve a Full Scale IQ that falls in the average range; however, some affected individuals may demonstrate decreased global IQ or specific cognitive deficits resulting from salt-wasting crises during infancy (Zurenda and Sandberg 2003b). Females with CAH represent the most systematically studied of all intersex syndromes, with emphasis on behaviors that show significant gender-related variation. Some 46XX CAH infants have been gender-assigned male, but the Standard of Care calls for a female assignment. Gender identity is characteristically female, gender role behavior is often masculine or “tomboyish,” and there is a higher likelihood of CAH females experiencing bisexual or homosexual erotic/romantic dreams, fantasies, and sexual attraction, when compared to unaffected women (Zurenda and Sandberg 2003b). Dessens, Slijper, and Drop (2005) reviewed the extensive literature on CAH and found that the majority (94.8 percent) of 46XX CAH-reared females established a female gender identity with no dysphoria. However, thirty of 250 (5.2 percent) individuals had “serious problems” of gender identity. This percentage is higher than the prevalence of FTM transsexuals in the general population of 46XX females. They also reported that four of thirty-three 46XX CAH individuals (12.1 percent) assigned male at birth and reared as male had serious gender problems; one identified as female and the other three experienced gender dysphoria.

Male Pseudohermaphroditism

Androgen insensitivity syndrome (AIS). AIS is an X-linked disorder which occurs as a result of a mutation of the androgen receptor (AR) gene, making the tissue completely or partially unresponsive to the influence of androgens, although testes form and synthesize androgens normally.

In complete androgen insensitivity syndrome (CAIS), the external genitalia have a typical female appearance because of the lack of tissue responsiveness to androgens. Likewise, the Wolffian ducts fail to develop but the Müllerian ducts regress, due to the action of AMH. Breasts develop under the influence of androgens that are metabolized into estrogen. The diagnosis is usually made at puberty when lack of menstruation becomes a concern. Gender assignment is always female, gender identity is unambiguously female, gender role is feminine, and their sexual orientation in both

Partial androgen insensitivity syndrome (PAIS) results in an individual born with ambiguous external genitalia. The genital tubercle is enlarged but is not typically of normal male size, a partially fused labia/scrotum may be present, and severe hypospadias is often present. Infants with PAIS have been gender assigned as males and as females (Conte and Grumbach 2004). The incidence of PAIS is unknown.

A recent literature review of gender identity stability in individuals diagnosed with CAIS and PAIS showed self-initiated gender change and was observed only among those with PAIS, and the change occurred in both directions (Mazur 2005a). AR gene mutations were documented in PAIS individuals who changed gender and in those who did not. A specific AR-gene mutation was not associated with gender identity outcomes. This finding is similar to Wilson’s (2001) finding that gender change is not related to the severity of the AR-mutation.

5-alpha-reductase deficiency (5-ARD). 5-ARD is an enzyme deficiency secondary to a gene deletion or mutation in 46 XY individuals. It is an autosomal recessive disorder, which results in an inability of testosterone to be converted to DHT by peripheral tissue in utero. DHT is required for the development of external male genitals and prostate. Consequently, infants with 5-ARD are born with ambiguous external genitalia. The underdeveloped penis resembles a clitoris and the scrotum appears as labia majora; as such, infants may have been assigned either a female or a male gender at birth. The natural course of this condition is a virilizing puberty with voice deepening, phallic enlargement, increased muscle mass, and the development of male-pattern facial and body hair growth. This masculinization is probably due to increase in an enzyme that converts pubertal testosterone into DHT (Wilson 2001).

A second autosomal recessive disorder similar to 5-ARD is 17β-hydroxysteroid dehydrogenase-3 deficiency (17β-HSD-3). External genitals appear ambiguous or not completely masculinized and either male or female gender may be assigned. The prevalence in the general population for both of these autosomal recessive disorders is unknown (Cohen-Kettenis 2005; Conte and Grumbach, 2004).

There has been considerable controversy over the stability of gender identity and gender role behavior of these individuals, especially as they transition through puberty. Recently, Cohen-Kettenis (2005) reviewed the
world literature on this topic. Fifty-six percent (62 of 110) of those individuals diagnosed with 5-ARD changed gender from female to male and 39 percent (19 of 49) of those diagnosed with 17β-HSD-3 changed from female to male. Cohen-Kettenis (2005) also identified twenty-eight individuals diagnosed with either 5-ARD or 17β-HSD-3 who were assigned and reared as male. None of them changed to the female gender or appeared to have any wish to do so. Gender change, in those initially assigned as female who did gender reassign, could not be explained by prenatal exposure to androgens or to the degree of external masculinization.

**Unclassified Forms of Abnormal Development**

*Hypospadias.* Hypospadias refers to the positioning of the urinary meatus (opening) at some point on the undersurface of the penis, rather than at its tip. Hypospadias is a feature of many malformation syndromes, but it can also occur alone (i.e., isolated hypospadias). A multifactoral etiological model has been proposed for hypospadias. The exact cause of isolated hypospadias, which occurs in 1:300 newborn males (Conte and Grumbach 2004), remains unknown in most cases.

Classified according to the position of the urinary meatus, the mildest and most common form (85 percent) is glandular or coronal hypospadias (Grumbach, Hughes, and Conte 2003). Research indicates that hypogonadalization associated with hypospadias does not interfere with developing gender-typical (masculine) behavior in boys during middle childhood (Sandberg et al. 1995). Individuals with hypospadias report relatively normal sexual behavior and function and, as a group, they do not report any more behavioral/emotional problems than comparison groups (Mureau 1995).

*Micropenis.* Micropenis refers to a completely formed penis, with the urethral meatus at the tip of the glands, that measures at or below 2.5SD in length for age and stage of puberty when stretched from the pubis ramus to the tip of the glands (i.e., a penis <1.9cm in a newborn or <9.3cm in an adult qualifies as a micropenis) (Lee et al. 1980). Micropenis can result from a heterogeneous group of disorders; the most common of which is fetal testosterone deficiency (Conte and Grumbach 2004). A micropenis does not necessarily occur as part of a syndrome; rather, it can occur in isolated form or be associated with a number of other conditions. For this reason, the incidence is not known.

Using the *Adjustment Self-Report Questionnaire*, Lee and Houk (2004) reported no significant differences between a small group of adult males with isolated micropenis and controls regarding psychosocial and psycho-
sexual functioning. They also failed to identify any differences in psychiatric symptoms between these two groups using the Hopkins Symptoms Checklist. Money and Norman (1988) found an association between micropenis and central nervous system (CNS) impairments in four cases, all with CHARGE syndrome (coloboma, heart disease, atresia cloanae, retarded growth/development or CNS anomalies, genital hypoplasia, and ear anomalies).

Newborns with a micropenis have been assigned at birth to either the female or the male gender. In a review of extant literature with respect to gender stability in individuals with a micropenis reared as male or female, there was not a single documented case of gender change among the eighty-nine individuals studied, ten of whom were assigned to the female gender (Mazur 2005a).

Mayer-Rokitansky-Kuster-Hauser (MRKH). MRKH, marked by the absence of the vagina with abnormal or absent Müllerian structures, is a congenital syndrome that occurs in genetic females. The incidence is estimated at between 1:4000 (Rock and Breech 2003) and 1:5000 (Evans, Poland, and Boving 1981; Grumbach, Hughes, and Conte 2003) female births. Associated features include amenorrhea with normal ovarian function. Renal and skeletal abnormalities may be present. Hearing loss occurs in approximately 25 percent of women with MRKH (Grumbach, Hughes, and Conte 2003).

Follow-up studies describing the psychological health of women with MRKH are limited. With psychological support and proper medical intervention to create a vagina, a normal sexual life can be expected (Bean 2003). Gender identity is firmly established as female with no known published reports of gender change.

Penile agenesis. Penile agenesis (or aphallia) refers to complete absence of the penis as part of a developmental pelvic field defect (Cendron 2001). The incidence of penile agenesis is not known. There may be associated anomalies such as failure of one or both testes to descend, renal abnormalities, and pulmonary problems. In the most pure form, there is absolutely no penile tissue in the normal position, two testes in a fully formed scrotum and the urethral opening on or in the anus (Cendron 2001). To our knowledge, there are no psychosexual and neurocognitive studies of a group of these individuals due to the rarity of the condition.

Penile agenesis is different from penile ablation: penile ablation is not the result of an anomaly of genital development but refers to traumatic loss of the penis resulting from, for example, an accident during circumcision.

Cloacal extrophy of the bladder (CE). CE, affecting both genetic males and genetic females, is a severe variant of a defect to multiple organ systems.
involving, among others, the bladder complex, abdominal wall, and pubic bones (Gearhart 2001). It appears that the bladder and abdominal wall are turned inside out, thus exposing the bladder. In males, the penis is often aplastic and split into halves. Classical bladder exstrophy is less severe than CE, but severe malformations can occur in this condition as well. Exstrophy of the bladder is a rare, congenital anomaly occurring in live births in a 1:25,000 to 1:40,000 ratios. There is a male predominance over female in a ratio of about 2:1 (Dominguez 2003).

**Adult Gender Identity Outcomes**

Table 12.1 summarizes the results on gender stability and change in those intersex conditions recently reviewed in the world literature and referred to in the previous section. Several conclusions can be drawn from inspection of this table: (1) self-initiated gender change occurs in intersex syndromes and related conditions; (2) the prevalence of individuals who change gender varies by syndrome; (3) self-initiated gender change is not universal for any one syndrome or condition; (4) gender change is more frequent in XY persons than in those with an XX chromosomal pattern; (5) self-initiated gender change occurs in both directions, that is, male-to-female and female-to-male, although it more frequently occurs in the direction of female-to-male as exemplified in Meyer-Bahlburg’s (2005b) review of penile agenesis, classical and cloacal exstrophy, and penile ablation; and (6) there are no published reports of gender change in micropenis regardless of whether the person was assigned and reared as male or female.

**GID in Intersex and Nonintersex Conditions**

Clinical investigators have been unable to determine whether the etiology of GID is biological, psychological/environmental, or both. However, there are several factors associated with GID in intersex and nonintersex individuals (Cohen-Kettenis and Pfafflin 2003; Zucker 2004). While there are some overlapping features in the putative etiology of GID in persons with intersex and nonintersex conditions, the presence of factors unique to those with intersex suggests the possibility that the pathway to GID differs between groups (Tables 12.2 and 12.3).

Meyer-Bahlburg (1994) reported that GID in individuals without intersex conditions appears quite early in life, that is, before the age of six years; in contrast, most marked gender problems appear for individuals with intersex during adolescence. With regard to the sex ratio, in persons without intersex conditions, boys far outnumber girls; in those with intersex
### TABLE 12.1. Gender Stability in Intersex and Related Conditions

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>N</th>
<th>Initial Assignment</th>
<th>n</th>
<th>%a</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen-Kettenis (2005)</td>
<td>5-ARD</td>
<td>110</td>
<td>F</td>
<td>62</td>
<td>56</td>
<td>F → M</td>
</tr>
<tr>
<td></td>
<td>17β-HSD-3</td>
<td>49</td>
<td>F</td>
<td>19</td>
<td>39</td>
<td>F → M</td>
</tr>
<tr>
<td>Dessens et al. (2005)</td>
<td>CAH (46,XX)</td>
<td>250</td>
<td>F</td>
<td>4</td>
<td>2</td>
<td>F → M</td>
</tr>
<tr>
<td></td>
<td>CAH (46,XX)</td>
<td>33</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Mazur (2005a)</td>
<td>CAIS</td>
<td>156</td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>PAIS</td>
<td>99</td>
<td></td>
<td>9</td>
<td>9</td>
<td>F → M (3) M → F (6)</td>
</tr>
<tr>
<td></td>
<td>Micropenis</td>
<td>79</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Micropenis</td>
<td>10</td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Meyer-Bahlburg (2005b)</td>
<td>Penile agenesis</td>
<td>16</td>
<td>F</td>
<td>2</td>
<td>12</td>
<td>F → M</td>
</tr>
<tr>
<td></td>
<td>Penile agenesis</td>
<td>17</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Penile ablation</td>
<td>7</td>
<td>F</td>
<td>2</td>
<td>29</td>
<td>F → M</td>
</tr>
<tr>
<td></td>
<td>Cloacal extrophy</td>
<td>51</td>
<td>F</td>
<td>11</td>
<td>22</td>
<td>F → M</td>
</tr>
<tr>
<td></td>
<td>Cloacal extrophy</td>
<td>15</td>
<td>M</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td></td>
<td>Classical extrophy</td>
<td>3</td>
<td>F</td>
<td>2</td>
<td>67</td>
<td>F → M</td>
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<td></td>
<td>Classical extrophy</td>
<td>279</td>
<td>M</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

a percentages rounded to the nearest whole number  

b four of 33 (12.1 percent) were reported to have "serious gender problems; one individual lived as a male, but was convinced he was a woman starting at age 26 when he began to menstruate"
TABLE 12.2. Putative Etiologic and Associated Physical Factors in GID: Intersex and Nonintersex

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intersex</th>
<th>Nonintersex</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biologic</strong></td>
<td>1. Prenatal hormones</td>
<td>1. Prenatal hormones</td>
</tr>
<tr>
<td></td>
<td>2. Puberty discordant for assigned sex</td>
<td>2. Handedness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Sibling sex ratio/birth order</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Birth weight</td>
</tr>
<tr>
<td><strong>Psychosocial</strong></td>
<td>1. Late correction or uncorrected genitalia</td>
<td>1. Social reinforcement</td>
</tr>
<tr>
<td></td>
<td>2. Stigmatization regarding genitalia</td>
<td>2. Prenatal sex preference</td>
</tr>
<tr>
<td></td>
<td>4. Parental psychopathology</td>
<td></td>
</tr>
</tbody>
</table>


conditions, there are more reports of individuals initially assigned female who change to male than the reverse (Table 12.1). As such, Meyer-Bahlburg concluded that it is unlikely that GID is the same entity for persons with intersexuality as those without such a condition.

The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (American Psychiatric Association, 2000), classifies individuals expressing marked discomfort with their apparent or assigned gender, and who demonstrate persistent identification with the opposite sex, under the category of Gender Identity Disorder (GID; 302.6 Gender Identity Disorder in Children or 302.85 Gender Identity Disorder in Adolescents or Adults). Symptoms qualifying for the diagnosis of GID are observed among individuals born physically typical as well as in those born with a disorder of somatic sex development (i.e., intersexuality). Because the DSM-IV-TR is largely a nontheoretical diagnostic scheme based on descriptions of symptom clusters rather than on a unified psychopathological concept (Rutter and Tuma 1988), it would be incorrect to assume that the etiology of GID in individuals born with an intersex condition is the
### TABLE 12.3. Comparison of Intersex and Nonintersex Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Intersex</th>
<th>Nonintersex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reproductive anatomy</td>
<td>Atypical/discordant</td>
<td>Typical/concordant</td>
</tr>
<tr>
<td>2. Gender assignment at birth</td>
<td>Delayed or reassigned</td>
<td>Unambiguous and immediate</td>
</tr>
<tr>
<td>3. Medical care associated with intersex condition</td>
<td>Routine contact throughout lifetime</td>
<td>No routine contact</td>
</tr>
<tr>
<td>a. Contact with health care professionals (e.g., endocrinologist, urologist)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Surgical decisions and procedures</td>
<td>During infancy and childhood</td>
<td>None</td>
</tr>
<tr>
<td>c. Medication</td>
<td>May begin during infancy and continue throughout lifetime</td>
<td>None</td>
</tr>
<tr>
<td>d. Puberty</td>
<td>May be induced by exogenous hormones</td>
<td>Induced by endogenous hormones</td>
</tr>
<tr>
<td>4. Gender dysphoria</td>
<td>Adolescence or later</td>
<td>Early childhood</td>
</tr>
<tr>
<td>a. Age of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Sex ratio</td>
<td>More common in those assigned female at birth</td>
<td>More common in males</td>
</tr>
<tr>
<td>5. Self-initiated gender change</td>
<td>May occur</td>
<td>May occur</td>
</tr>
</tbody>
</table>

Evaluation and Treatment Strategies

While the final explanation of GID in both groups awaits further research, it must be emphasized that persons with an intersex condition experiencing GID have different histories from those born without a somatic intersex condition (Tables 12.2 and 12.3). The intersex condition, from the very moment of birth, triggers a series of events that are not experienced by
either nonintersex individuals or their parents. These events relegate the affected individual and parents, at least through infancy, childhood, and adolescence, to monitoring by health care professionals, much like a person with a chronic illness. For the individual born with ambiguous genitalia, the question that immediately faces medical personnel and parents is to which gender to assign the infant. The history may even include a change of the initial gender of announcement, with parents having to reannounce the gender of their child to siblings, grandparents, and friends. There may also be an immediate necessity for lifesaving medication as in the case of infants with salt-wasting CAH. Eventually, there are issues surrounding surgical reconstruction of the genitals, hormone treatment to induce puberty, and general state of good health (i.e., continued hormone replacement to maintain physical health).

As a consequence, the context within which a child with an intersex condition grows and develops is much different from that for a child without a somatic intersex condition. Therefore, the clinician needs to obtain a thorough history including chromosomal pattern, diagnosis, etiology (if known), surgeries, hormone treatment, pubertal development, and history of medications taken (up to and including current prescriptions). When obtaining a medical history, particular attention should be paid to factors believed to be associated with gender change in persons with intersex. Questions to ask might include the following: Did the person have late (after age of three years) or no genital surgery? If the person is an adolescent or adult, is their puberty (secondary sexual characteristics) discordant with their assigned gender? Is the person sexually attracted to individuals of the same gender, meaning the gender to which the person with intersex was initially assigned?

Cohen-Kettenis (2005) hypothesized three factors as a possible explanation of self-generated gender change from female to male in 5-ARD or 17ß-HSD-3 individuals. A masculine appearance in childhood coupled with masculine (tomboyish) behavior due, "perhaps," to prenatal androgen exposure, influences a gender change with the onset of physical changes brought about by puberty. The third factor, pubertal development, intensifies an "already existing gender discomfort" (dysphoria). This combination of a masculinized appearance, atypical gender-role behavior, and pubertal hormones precipitates a self-initiated gender change in a subgroup of these individuals.

It has also been suggested that uncorrected or late-corrected genital appearance may lead to parental confusion (or rejection) over the gender of rearing, as well as to the child’s own confusion (Meyer-Bahlburg et al. 1996; Money, Devore, and Norman 1986). A discordant puberty may then
exacerbate this confusion and, in some, contribute to the development of
GID (Cohen-Kettenis 2005). There is thus a developmental sequence of
events that results in a “crystallized” gender dysphoria with the wish to self-
reassign gender. Part of obtaining a detailed history of the condition is to as-
certain what the person has been told (or not told) by parents and physicians
about the person’s medical history. More important than what they have
been told is how they understand their intersex condition. For example, a
patient who states, “I was told that I really was born a boy but reared as a
girl,” demonstrates a lack of specific knowledge about the diagnosis and
sequelae of the condition.

Adults born with an intersex or related condition are at risk for misunder-
standing their medical history, if accurate information about their birth cir-
cumstances and the rationale for the medical treatment in childhood is ei-
ther not provided or withheld. Consequently, gender confusion, even GID,
may result. Also, consider that due to the complexity of the information in-
volved, a person may misinterpret accurate information. Therefore, a main
difference between assessing a person with a possible GID, who also has an
intersex condition, and assessing one who does not is in discerning to what
degree the presenting gender problem is associated with, possible confu-
sion, or lack of information about the intersex condition. Such an assess-
ment requires that the clinician understand what is known etiologically
about intersex conditions, know how and why the somatic discordance oc-
curs, and, most importantly, be able to provide this information to the client,
who is likely to have gaps in knowledge or misinformation.

An important distinction between the clinical management of individu-
als with intersex and the management of those with nonintersex is psycho-
education about their medical history and the known associated behavior.
Such information may help resolve a person’s gender concerns and/or clar-
ify the history. Several helpful resources are available for clinician and
patient use (Appendix A).

In the event the patient wants to proceed with reassignment, a compre-
prehensive understanding of the medical condition and treatment history is es-
sential, not only to increase self-knowledge but, in certain cases, to ensure
prolonged good health (i.e., the rationale for endocrine life-sustaining inter-
vention in salt-wasting CAH, pubertal induction, or maintaining bone
strength). Therefore, the first step in managing GID diagnosed in a person
with an intersex condition, regardless of age, is not to implement therapeu-
tic support for a change of gender, but rather to obtain the medical history
and make sure that the person has a thorough and accurate understanding of
the condition. In children and adolescents, this includes parental under-
standing as well.
Discussion

The purpose of this chapter was to provide an overview of "intersex" as traditionally defined. A sketch of differentiation and development of the internal and external sexual/reproductive system was given to provide a background upon which to appreciate the various intersex syndromes in genetic males and females as well as related conditions. Selected examples of these syndromes and conditions were presented. Data on the stability of adult gender identity in the most commonly studied intersex syndromes indicate that gender dysphoria and self-initiated gender change do occur in individuals with intersex conditions, although the frequency varies by syndrome. Furthermore, there is no syndrome or condition where self-initiated gender change is universal.

While a chapter on intersex in a book on transsexualism might be surprising to some, its inclusion is important for several reasons. As mentioned, current reviews of various intersex and related conditions document that self-initiated gender change does occur and that gender dysphoria without gender change probably occurs as well. A recent survey (Mazur et al. 2005b) of the membership of the Harry Benjamin International Gender Dysphoria Association (HBIGDA), the professional organization dedicated to the treatment of individuals with gender identity problems and dysphoria, indicated that ninety-three members (40 percent of respondents) had provided service, in the past two years, to individuals with an intersex condition or who were born with a sex-atypical variant of genital differentiation. While the majority of HBIGDA members had seen just a few such individuals, ten members had seen more than ten affected persons and fifteen were members of a "gender team" involved in gender assignment decisions for newborns with an intersex condition. Seventy-three percent indicated that they wanted continuing education on the topic of intersexuality.

Another reason for the relevance of this chapter for those who work in the area of gender identity and dysphoria pertains to the multiple use of the term "intersex." Originally, intersex was used interchangeably with the term "hermaphroditism." Over time, other terms or phrases were created to describe intersex or hermaphroditic conditions. All terms referred to an anomaly of the sexual/reproductive system where, in most cases, the sex of the infant could not be immediately determined. All of these terms focused on an identifiable problem of physical development/differentiation of the sexual/reproductive system, regardless of whether a diagnosis or etiology could be determined. Recently, the term "intersex" has been used to refer to individuals with no discernable physical problem. One way of understanding this broadening of "intersex" is to recall Szasz's words (1970) over
thirty years ago as he addressed the use of language in psychiatry. He sug-
gested that language has three main functions: to transmit information, to
induce mood, and to promote action. Lumping individuals with intersex
with those who are nonintersex but experiencing problems of gender, or
who challenge conventional gender boundaries, enlarges the base of minor-
ities, which, hopefully, increases their political influence and the opportu-
nity to gain “rights” previously denied to them. Such blurring of distinc-
tions and inconsistent language use for political (or other) uses can be
advantageous; however, merging categories can complicate the work of
both scientists and clinicians who are charged with the tasks of elucidating
conditions’ etiologies and developing effective treatment strategies.

APPENDIX A

Androgen Insensitivity Syndrome Support Group (AISSG)
www.medhelp.org/www/ais

AISSG is a consortium of worldwide support groups that originated in
the United Kingdom in 1988. AISSG provides information and support to
young people, adults, and families affected by complete and partial Andro-
gen Insensitivity Syndromes, Swyer’s Syndrome (XY Gonadal Dysgen-
esis), 5-alpha Reductase Deficiency, Leydig Cell Hypoplasia, Mayer-Ro-
kitansky-Kuster-Hauser (MRKH) Syndrome, Mullerian Dysgenesis,
Mullerian Duct Aplasia, Vaginal Atresia, and other related conditions.

Congenital Adrenal hyperplasia Research Education and Support
(CARES)
www.caresfoundation.org

CARES Foundation provides information to individuals and families
about how to manage Congenital Adrenal Hyperplasia (CAH). CARES has
also strongly advocated for the expansion of newborn screening for congen-
tital and life-threatening disorders to include CAH.

The Center for Young Women’s Health
www.youngwomenshealth.org/search.html

The Boston Children’s Hospital center provides information on a variety
of medical conditions relevant for young girls and women. A second Web

We thank Ms. Elaine Mosher, MLS, Emily Foster Health Sciences Library of The
Women and Children’s Hospital of Buffalo for her library assistance.
site, www.childrenshospital.org/az/Site2067/mainpageS2067P0.html provides general information on ambiguous genitalia.

Hospital for Sick Children
www.sickkids.ca/childphysiology/default.asp

This animated, interactive Web site at The Hospital for Sick Children in Toronto, Canada teaches about the workings of the human body. It shows how various systems and organs develop and perform. The section on genital development depicts typical development and differentiation of the internal and external sex organs in an animated, interactive manner. The site also explains via animation how CAH and AIS develop. Other conditions will be displayed as the site expands.

Intersex Society of North America (ISNA)
www.isna.org

Started by a group of intersex patient advocates, ISNA is devoted to systemic change to end shame, secrecy, and unwanted genital surgeries for people born with an anatomy that someone decided is not standard for male or female.

The Johns Hopkins Hospital


Klinefelter Syndrome and Associates (KS and Associates)
www.genetic.org/ks

KS and Associates focuses on individuals who have an extra X chromosome (47XXY) and variations. This Web site provides information about when 47XXY was first discovered, common characteristics of Klinefelter syndrome, ongoing research and treatment, and support and educational services.

Magic Foundation
www.magicfoundation.org

MAGIC stands for Major Aspects of Growth in Children. Click on Genital and Reproductive Anomalies in Children (GRAC) link for information on a variety of intersex syndromes and related conditions.
Middlesex Centre
www.uclh.nhs.uk/gps+healthcare+professionals/clinical+services/womens+health+(ega)/gynaecology++middlesex+clinic

The Middlesex Centre is located at the Elizabeth Garrett Anderson Hospital, in London, England. It has multidisciplinary teams which provide clinical care, diagnosis, information, and highly specialized treatment to individuals with various intersex syndromes in the United Kingdom.

REFERENCES


ment and diagnosis in child psychopathology (pp. 437-452). New York: The Guilford Press.