The Role of Androgens in Male Gender Role Behavior

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[Abstract] Full Text [PDF]

I. Introduction

In most species all aspects of reproduction are controlled by hormones secreted by the ovaries and testes. Such functions include the formation of the sexual phenotypes during embryogenesis, sexual maturation at the time of puberty, and various forms of sexual behavior including sex drive and potential, gender-typical behavior, and, in some species, traits such as aggression, the drive for dominance, and parenting behavior (reviewed in Ref. 1).

In humans gonadal steroids are responsible for phenotypic sexual differentiation, sexual maturation, and development of libido and potentia. Human sexual behavior also involves gender identity, the perception of oneself as male or female, and gender role behavior (also termed social sex or social identity), the various processes by which gender identity is communicated to others. Gender identity cannot be assessed in animals, and gender role behavior in animals can be difficult to separate from sexual orientation. Whether gonadal steroids are involved in the development of human gender identity and role behavior is difficult to examine. These two aspects of behavior are normally in accord, but most studies on this subject focus on gender role behavior because the change of legal registration of sex from one gender to another is unambiguous, whereas gender identity can be a graded character and difficult to quantify. It is obviously not possible to devise definitive experiments to examine the role of hormones in human behavior but, on the basis of studies of subjects with a variety of forms of human intersex and/or endocrine abnormalities, it has been the predominant view that human behavior is more complex than that of other species and that human gender identity and gender role behavior are determined primarily, if not exclusively, by psychological and social forces (reviewed in Ref. 2). According to this anthropocentric view, the human species has been emancipated from biological controls so that the hormones that mediate this aspect of sexual behavior in animals do not play a significant role in controlling human behavior (3). As summarized by Herdt (4), “the sex of rearing outweighs the biological sex in the development of gender identity and social identity.”

This belief that hormones do not play a significant role in controlling human gender role behavior persists despite a large body of evidence to the contrary, indicating that androgens play an important role in human male gender identity/behavior. This evidence stems largely from the work of Imperato-McGinley and her colleagues (5 6), who documented that genetic males with either of two autosomal recessive mutations that impair androgen synthesis or androgen metabolism during embryogenesis, and hence cause formation of female external genitalia and female sex of rearing in genetic males, may change gender role behavior to male at or after the time of expected puberty. The fact that single gene mutations can be associated with change in gender role behavior raises fundamental questions about the factors that regulate human sexual behavior.

The molecular biology of these two autosomal recessive disorders has been explored in some detail. The cDNAs and genes that encode the two critical enzymes involved, 17ß-hydroxysteroid dehydrogenase 3 and steroid 5-reductase 2, have been cloned, and a great deal has been learned about the underlying pathophysiology. This review is designed to consider some of the implications of these studies for understanding human behavior.

II. Sexual Behavior of Animals
The role of gonadal hormones in animal behavior has been the subject of several extensive reviews (7 8 9 10 11 12 ). For the purposes of this discussion certain aspects of this relationship deserve emphasis:

1. Sexually dimorphic behaviors of a variety of types are regulated by gonadal steroids, including the songs and mating behaviors of birds, copulatory patterns in mammals, and complex forms of ritual behavior such as musth in elephants and male dominance in mice. By way of illustration, male and female rodents differ in the types of sexual postures they assume during coitus; these behaviors can be changed to those of the other sex by appropriate hormonal manipulation.

2. Androgens and estrogens are formed in both males and females, and both hormones may play a role in the physiology of both sexes. However, androgens (and androgen metabolites including estrogens in some species) are the primary determinants of male sexual behavior (13 ).

3. Gonadal steroids act in the central nervous system by the same receptor mechanisms that operate in peripheral tissues. Intracellular receptors for these hormones are expressed within specific regions of the brain (14 15 ), and gonadal steroids may also exert central nervous system effects by other mechanisms such as by influencing ion channels in cell membranes (16 17 18 ).

4. The behavioral effects of steroid hormones are due to interactions between peripheral and central actions of the hormones (2 ). One of the best studied paradigms of sexual behavior in the mammal is the mounting reflex of the female rat. Mounting of a female rat in estrus by a male causes the female to extend the hind legs and elevate the rump, thus dorsiflexing the vertebral column. These actions require sensory input from the rump and involve a well defined neural reflex that includes motor and sensory components and steroid-mediated effects in the central nervous system. While there is no doubt that the central nervous system plays a vital role in the hormonal control of sexual behavior, different behaviors may be influenced to different degrees by central and peripheral actions of the hormones. Even under defined laboratory conditions, it may be difficult to quantify the relative contribution of each to a given action (2 ).

5. In the rodent the surge of testosterone secretion during the neonatal period appears to play a vital role in virilizing hypothalamic function, e.g., in imprinting a tonic pattern of gonadotropin release in contrast to the cyclical secretory pattern in females. (Again, this action may be mediated by estrogenic metabolites of testosterone in the central nervous system.) Whether the neonatal increase in testosterone levels in the human male infant is of physiological significance is not known, but blocking the neonatal surge delays the onset of puberty in male monkeys (19 ).

6. Phoenix and colleagues (20 ) delineated two types of behavioral effects of steroid hormones. Organizational effects are exerted by hormones at a specific time in development; they appear to have permanent effects on function or behavior, effects that persist after the steroid is no longer present. Such organizational effects may be accompanied by changes in anatomical development of the brain (21 ). Activating effects require the continued presence of the steroid for full manifestation of the effects (20 ), e.g., the mounting response of the female rat during estrus. Although the delineation of these two types of behavioral effects is of conceptual importance, there is considerable overlap between them. Organizational effects may be silent in the absence of the proper hormonal signals, and concurrent phenomena such as male copulatory behavior may persist for variable periods after castration. Furthermore, different animal species differ in the extent to which hormones exert permanent organizational effects. In particular, organizational effects appear to be less clear cut in primates than in rodents (22 ); for example, the administration of estrogens in appropriate amounts to male rhesus monkeys of any age elicits a positive release of LH, analogous to the ovulatory surge of LH release in females (7 ).

7. Even when hormones are involved in specific aspects of behavior, stereotyping can also play a critical role. For example, development of the characteristic male song pattern in
bird species such as the zebra finch and canary require both the action of androgen in the central nervous system and exposure of the immature male to a mature male of the same species. Otherwise, the male will sing a garbled song instead of learning a song that will attract a female of the same species (23). This androgen action is mediated by estrogenic metabolites formed in the brain (24).

In summary, the role of gonadal steroids in sexual behavior in animals involves, at a minimum, sexual dimorphism of the genital tracts, direct effects on the central nervous system, sensory and motor aspects of neurosensory reflexes, and, probably, integration of the various neural subsystems that control the behavioral process.

III. Control of Libido and Potentia in Humans

For the purposes of this discussion the term libido refers to the instinctive sexual drive, and potentia refers to the ability to perform and complete sexual intercourse. These functions are not considered to be sexually dimorphic, but they are influenced by gonadal hormones. In animals copulation does not occur in the absence of gonadal hormones. In the males of most species, mating capacity is maintained for a limited period after castration, followed by progressive failure, and ovariectomy of female animals causes immediate cessation of female mating behavior (2). In the human, prepubertal castration of boys uniformly prevents the development of normal sex drive, and castration in the adult male produces sequelae similar to those in animals, i.e., a decline in sexual behavior with only occasional castrated men capable of normal sexual activity after 2 yr (25 26). Furthermore, physiological androgen replacement therapy in hypogonadal men causes a rapid and predictable restoration of male sexual drive (27 28). Thus, the hormonal control of male sexual behavior is similar in man and animals. The fact that the administration of an aromatase inhibitor to testosterone-treated, castrated male monkeys impairs male sexual drive indicates that the estrogenic metabolites of testosterone play a critical role in the control of sex drive, (29), but studies of the localization of radioactive steroid hormones in brain indicate that some androgen actions in brain are mediated by testosterone and/or dihydrotestosterone (30 31 32 33).

In contrast, removal of ovarian secretions by ovariectomy or via the natural menopause does not have a consistent effect on sexual activity in women (2). The common interpretation is that once sexual patterns are fixed in women, sexual drive is hormone independent. This interpretation may not be correct because removal of the ovaries does not impair formation of adrenal androgens. Adrenalectomy (34) or hypophysectomy (35) in previously castrated women is reported to decrease sexual desire. Consequently, it is possible that the sexual life of women is as hormone-dependent as that of men. Adrenal androgen (which would be ablated by hypophysectomy or adrenalectomy) could have a direct effect on sexual desire in women or could act as a prohormone for the synthesis in extraglandular tissues of other steroid hormones (36) that could maintain sexual drive in the absence of ovarian hormones. Whether hormones are involved in the genesis of normal sexual drive at female puberty is also unclear.

A similar uncertainty exists as to whether adrenal steroids can affect male sexual behavior. Occasional castrate males of all species sustain a capacity and drive for intercourse for long periods (2 26). In the castrated human male, considerable estrogen and small amounts of testosterone are formed in extraglandular tissues from adrenal androgens (37), and in some animal species estradiol enhances the effect of androgen on male sexual drive (38). Thus, the small amounts of testosterone and/or estrogen formed from adrenal androgens may be enough to sustain libido and potentia in some adult male castrates. In other words, libido and potentia would be preserved in those castrated men able to produce sufficient active hormones by this mechanism.

In summary, gonadal steroids play an important role in the sexual drive of males of all species and in controlling the sexual drive of female animals and possibly of women. Organizational effects do not appear to play as important a role in the control of gonadotropin secretion by gonadal steroids in the primate as in lower animals. In brief, although there may be slight differences, the control of libido and potentia appears to be similar in humans and animals.
IV. Gender Identity/Role Behavior in the Human

In contrast to sexual drive, which is not sexually dimorphic, gender identity is fundamentally different in men and women. Some of the ambiguities in the definition and understanding of gender identity and gender role behavior are due to difficulties in quantifying these parameters and to the fact that gender role behavior is influenced by cultural and social variables, as evidenced by the different actions and activities of the two sexes in different societies. Most studies of the subject have focused on social sex because the change of legal gender is an unequivocal event, but the net consequence may be to underestimate the real frequency of disorders of gender identity because some individuals with discordant gender identity may not change gender role behavior for personal reasons. It is also difficult to investigate the mechanisms that regulate gender identity/role behavior because controlled studies of the process cannot be performed in humans. As a consequence, a major emphasis in the study of human sexual behavior has been the analysis of gender role behavior in subjects with histories of endocrine abnormalities, particularly subjects with abnormalities of sexual development. To understand the limitations and usefulness of studies of these pathological states for the analysis of human behavior, it is necessary to consider briefly how such disorders arise.

A. Normal and abnormal sexual development

The embryos of both sexes develop in an identical fashion until the seventh week of gestation. Thereafter, the anatomic and physiological development in the two sexes diverge. As formulated by Jost (39), normal sexual development in the mammal depends on three sequential processes. The first involves the establishment of genetic sex at the time of conception, the heterogametic sex (XY) being male and the homogametic sex (XX) female. In the second phase information encoded on the sex chromosomes causes the establishment of gonadal sex in which the indifferent gonad develops into either an ovary or a testis. The final stage involves the translation of gonadal sex into phenotypic sex. In the presence of an ovary or in the absence of a functional gonad, the development of phenotypic sex proceeds along female lines. Masculinization of the urogenital tract and the external genitalia, in contrast, requires the actions of three hormones, antimullerian hormone, testosterone, and dihydrotestosterone, the 5α-reduced metabolite of testosterone. The formation of antimullerian hormone in the fetal testis is essential for suppression of the mullerian ducts and hence for prevention of development of the uterus and fallopian tubes in the male. Testosterone, which is synthesized primarily in the testes and circulates in the plasma, converts the wolffian ducts into the epididymis, vasa deferentia, and seminal vesicles, and dihydrotestosterone, which is formed predominately in the target cells themselves, induces the formation of the male urethra and prostate and the male external genitalia (Fig. 1).

Derangement of any of the three primary processes involved in sexual differentiation can cause abnormal sexual development, resulting in disorders of chromosomal sex, gonadal sex, or phenotypic sex. The pathogenesis, clinical manifestations, endocrine pathology, and
functional disturbances that accompany these disorders have been reviewed extensively and will not be considered here. However, several aspects of abnormal sexual development are relevant to the analysis of human sexual behavior.

First, the phenotypic manifestations of the various abnormalities differ markedly. For example, men with 47,XXY Klinefelter syndrome or with the 46,XX male syndrome develop as men (albeit infertile) and have endocrine abnormalities only in later life. Likewise, women with 45,X gonadal dysgenesis or with 46,XX or 46,XY pure gonadal dysgenesis have a female phenotype, and most subjects with true hermaphroditism have unequivocal male or female phenotypes. Thus, many if not most individuals with abnormalities of sexual development end up with unambiguous male or female anatomical development; this is the consequence either of the fact that the formation of testicular hormones was sufficient to induce a male phenotype or that the failure of formation/action of testicular hormones was complete enough to result in formation of a female phenotype. Since sex assignment and the sex of rearing are determined by anatomical development, any direct hormonal effects on behavior in most individuals with abnormal sexual development would not be apparent because they would correspond to anatomical development and hence to gender assignment and sex of rearing.

Second, disorders that appear phenotypically similar can result from different mechanisms. For example, men with 45,X/46,XY mixed gonadal dysgenesis can have phenotypes similar to those of men with steroid 5-reductase 2 deficiency or with mutations of the androgen receptor. Since these disorders have distinct pathophysiologies, it is essential that diagnoses be unequivocally established before attempting to draw interpretations as to the behavioral consequences of any given abnormality.

Third, ambiguity of genital development occurs in relatively few disorders of human intersex and is due to one of three mechanisms: 1) The testes do not produce sufficient hormones to virilize the male embryo—either because of developmental abnormality of the testes or because of a defect in one of the enzymes required for testosterone biosynthesis; 2) Sufficient testosterone is synthesized by the testes, but due to impairment of androgen action (usually a defect in the androgen receptor) the hormone cannot virilize the embryo normally; or 3) Overproduction of androgen occurs in the female embryo, as in congenital adrenal hyperplasia due to deficiency of the steroid 21-hydroxylase enzyme. In these disorders gender assignment usually corresponds to the predominant or apparent anatomy. If hormones are involved directly or indirectly in development of gender identity, one would predict that gender identity/behavior would be more likely to be discordant or uncertain in subjects with ambiguous genitalia. Nevertheless, all abnormalities that cause ambiguous genitalia vary in severity among affected individuals and can cause variable phenotypes. For example, the external phenotypes of males with abnormalities of the androgen receptor and of females with steroid 21-hydroxylase deficiency can span the entire spectrum from male to ambiguous to female. One would not expect abnormalities of gender identity in those individuals with normal or near-normal genital development.

Fourth, even when the degree of ambiguity of the external genitalia is similar, disorders can have different times of onset and different long-term endocrine consequences. For example, disorders of androgen synthesis and/or action influence embryonic development beginning at about week 8 of gestation, whereas virilization in females with steroid 21-hydroxylase deficiency does not commence until somewhat later in gestation. Furthermore, as the result of compensatory mechanisms, adult males with 17ß-hydroxysteroid dehydrogenase 3 deficiency, mixed gonadal dysgenesis, or 5-reductase 2 deficiency may have the endocrine profiles of normal (or near normal) adult men despite having profound defects in androgen action during embryogenesis. In contrast, the endocrine defects in the Klinefelter syndrome and in the 46,XX male become progressively more severe with age. Any behavioral consequences of disorders of sexual development would depend on when in development gonadal steroids exert an effect on the behavior in question.

In summary, abnormalities of sexual development differ in their effects on the sexual phenotypes, their effects on hormone levels at various times of life, the times during life when they become manifest, and the ultimate metabolic consequences. Any interpretation
as to possible behavioral consequences of a specific disorder must take these various factors into account. Furthermore, since different abnormalities vary in the severity of their effects on the sexual phenotypes and on endocrine function, some disorders would not be predicted to influence behavior even if hormones are normally involved in controlling the behavior in question. For these reasons, it is necessary to be cautious in interpreting negative results.

B. Behavioral studies in subjects with abnormal sexual development

While different forms of abnormal sexual development have been lumped together in some reports, sufficient numbers of individuals with specific diagnoses have been studied to allow a few generalizations:

1. Exposure of females to excess androgens as a result of congenital adrenal hyperplasia causes a variable degree of virilization of the external genitalia. Gender identity in such individuals is usually female even in virilized women and despite the fact that behavioral changes, such as tomboyish behavior and characteristic male energy expenditure, have been described in some studies (40 41 42 43 44 45 46 47 ). [Occasional women with congenital adrenal hyperplasia have male gender role behavior, but this usually occurs in severely virilized women in whom diagnosis and surgical correction of the external genitalia are delayed beyond infancy or in whom glucocorticoid therapy is inadequate (48 49).]

2. Children exposed to exogenous estrogens or progestogens during gestation have appropriate male or female phenotypes; in general, such agents have only minor effects on sexually dimorphic behavior and do not influence gender role behavior/identity (50 51 52 53 54 55 56 ).

3. True hermaphrodites have both testes and ovaries (or ovotestes) and may have male, female, or ambiguous phenotypes. In such individuals, gender role behavior usually corresponds to the sex of rearing, although many of them have anomalous secondary sexual characteristics (57 ).

4. Women with gonadal dysgenesis have female phenotypes and female gender identity/gender role behavior (58 ). Since such women are profoundly estrogen deficient, it has been inferred that ovarian estrogen plays at best a minor role in the evolution of female gender identity.

5. Men with the Klinefelter syndrome form sufficient androgen during embryogenesis to induce formation of a male phenotype but usually have diminished androgen production and enhanced estrogen production after puberty. Nevertheless, most men with Kleinfelter syndrome have male gender role behavior, suggesting that these hormones play no continuing role in gender identity/behavior at or after the time of expected puberty (59 ).

6. 46,XY women with profound androgen resistance due to mutations of the androgen receptor develop a female phenotype and unambiguous female behavior (see below) (60 61 62 ).

The common thread in these various studies involving many types of subjects and many different socioeconomic groups is that gender identity and gender role behavior usually develop in conformity with the sex assignment and the sex of rearing (62 63 ). In other words, gender identity and role behavior correspond with the predominant anatomical development and hence with the prenatal hormonal milieu. This conformity can withstand perturbations that include contradictory patterns in which girls virilize or boys feminize during adolescence, tomboyish energy expenditure in girls, and incomplete development of the secondary sexual characteristics at puberty. Despite the inherent weaknesses in design in all such studies and despite the fact that none of the disorders constitutes a perfect experiment, the consistency of the findings in such studies is impressive.

The problem is that the findings are open to diametrically opposite interpretations. The predominant view—most eloquently formulated by Money (63 ) and Lev-Ran (64 )—is that sex assignment at birth influences parental attitudes and the manner in which infants are
treated from the time of birth, and that these social factors are paramount in determining human gender identity and gender role behavior, so powerful as to be irreversible after early infancy. According to this view, any effects of hormones in influencing gender identity in the human are secondary and probably minor. A diametrically opposite interpretation is possible. Testicular hormones could be important determinants of gender identity/behavior, but since they also control development of the external genitalia (and hence determine sex assignment and the sex of rearing) gender identity and anatomical sex would almost invariably be the same in these various patient groups. In such a view, it is difficult or virtually impossible in most studies of subjects with disorders of intersex to ascertain the extent to which psychological/social and endocrine determinants contribute to this development because the psychological/social forces almost always correspond with the anatomical and endocrine factors.

V. Gender Role Behavior in Individuals with Male Pseudohermaphroditism

Over the years occasional instances have been reported in which individuals with abnormal sexual development have undergone a reversal in gender role behavior (and presumed reversal in gender identity) at some age after gender identity is usually considered to be fixed irreversibly (reviewed in Ref. 65). The majority of these reports were published before the means of making specific diagnoses as to the cause of the abnormal sexual development were widely available, and it is not possible in retrospect to deduce the correct diagnosis in many such reports, indeed even in some relatively recent studies (66 67 68 69). Nevertheless, in analyzing these reports two conclusions seem justifiable: 1) Most such individuals are male pseudohermaphrodites with failure of virilization of the external genitalia and who were given a female sex assignment at birth, and 2) The change in gender role behavior is usually from female to male. The fact that occasional individuals with a disorder of human intersex change gender role behavior long after the time of sex assignment was clearly recognized by the anthropocentric school (63) and was thought to result from childhood stigmatization of such individuals because of their anatomical abnormalities (69).

However, ambiguity of the genitalia cannot be the sole cause of changes in gender role behavior as illustrated by the case described by Stoller (70). This individual was thought to be a normal female at birth and was raised as a girl but exhibited tomboiyish behavior from early childhood that became more and more masculine with time. She was an average student, but as adolescence ensued she became more and more withdrawn. Because of coarsening of the voice she was evaluated and found to be a genetic male with female external genitalia (including an apparently normal clitoris) but with testes in the labia majora. After psychiatric evaluation at age 14 she was told that she was a genetic male [the diagnosis was subsequently established to be 17ß-hydroxysteroid dehydrogenase 3 deficiency (5)]. She promptly changed to male clothing and began to act, behave, and assume the role of a male. The parents decided to move to a new community; the boy’s grades improved, and he participated in men’s sports in high school, obtained a university degree in mathematics, and after urological surgery married. This individual has been studied by several different groups over the years and apparently is a successful and well adjusted man.

The fact that a single gene mutation could be associated with a reversal of gender role behavior has far reaching implications for understanding gender behavior, and in the ensuing years it has been established that female-to-male reversal of gender role behavior appears to be a common feature of two autosomal recessive forms of male pseudohermaphroditism—5-reductase 2 deficiency (6 71) and 17ß-hydroxysteroid dehydrogenase 3 deficiency (5 72 73) (Fig. 1). A similar change in gender role behavior has been described in genetic males with 3ß-hydroxysteroid dehydrogenase deficiency (74), an even rarer autosomal recessive form of male pseudohermaphroditism, and in a few individuals with mixed gonadal dysgenesis (65). This review focuses on the two more common disorders, and we will compare the consequences of mutations in these two enzymes with those of mutations of the androgen receptor on gender role behavior.

A. 17ß-Hydroxysteroid dehydrogenase 3 deficiency
The 17ß-hydroxysteroid dehydrogenase reaction is the terminal step in the synthesis of testosterone in the Leydig cell and of estradiol in the granulosa cell, and the rate of the back reaction in extraglandular tissues plays a major role in determining the steady state levels of these steroids in tissues (Fig. 2). Isoenzymes that perform these reactions are encoded by at least five genes (75) (Table 1), and mutations of the type 3 isoenzyme (76) are responsible for a rare, autosomal recessive form of male pseudohermaphroditism originally described by Saez and colleagues in 1971 (77). The typical features of this disorder are summarized in Table 2. In brief, affected 46,XY infants have female external genitalia, despite the presence of testes and male wolffian structures; they are usually assigned a female gender at birth and raised as females. They usually come to medical attention because of virilization at puberty or because of failure to menstruate. On endocrine evaluation they have low testosterone levels (for men), normal ratios of plasma testosterone to dihydrotestosterone, and variable estrogen levels. The diagnosis is made by finding androstenedione levels that are usually 10 times normal [Stoller’s patient had typical endocrine features for this disorder (5)].

![Figure 2. The 17ß-hydroxysteroid dehydrogenase reaction for the interconversion of androstenedione and testosterone. Androstenedione is believed to be converted to testosterone by isoenzymes 3 and 5, and testosterone can be oxidized to androstenedione by isoenzymes 2 and 4.](image)

<table>
<thead>
<tr>
<th>Isoenzyme</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td>Size (amino acids)</td>
<td>327</td>
<td>387</td>
<td>310</td>
<td>737</td>
<td>323</td>
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<tr>
<td>Chromosome location of gene</td>
<td>17q21</td>
<td>16q24</td>
<td>9q22</td>
<td>5q2</td>
<td>10p14, 15</td>
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<td>Testis</td>
<td>Ubiquitous</td>
<td>Liver, skeletal muscle</td>
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<tr>
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<td>Microsomes</td>
<td>Microsomes</td>
<td>Peroxisomes</td>
<td>Cytosol</td>
</tr>
<tr>
<td>Substrate preference</td>
<td>C_{18} steroids</td>
<td>C_{18}, C_{19}, C_{21} steroids</td>
<td>C_{18}, C_{19} steroids</td>
<td>C_{18} steroids</td>
<td>C_{19}, C_{21} steroids</td>
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<tr>
<td>Preferred cofactor</td>
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<td>NAD</td>
<td>NADPH</td>
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<tr>
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<td>Oxidation</td>
<td>Reduction</td>
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<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>—</td>
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Table 1. Comparison of human 17ß-hydroxysteroid dehydrogenase isoenzymes.
### Table 2. 17ß-Hydroxysteroid dehydrogenase 3 deficiency

A characteristic feature of the disorder is that the defect in virilization (and the abnormality in testosterone levels) becomes less severe with time, and many affected individuals eventually have near-normal male plasma testosterone levels (78). Testosterone in these individuals can be formed by two mechanisms. Namely, some mutant enzymes are nevertheless capable of some testosterone synthesis when LH and androstenedione levels are high, whereas individuals with more severe mutations appear to convert androstenedione to testosterone in extraglandular tissues by the action of one or more of the unaffected isoenzymes, probably isoenzyme 5 (78). The consequence is that an alternate pathway for testosterone formation is present in all patients and that testosterone formed in this way can cause considerable virilization after the time of expected puberty.

This disorder is rare and believed to be even less common than 5-reductase 2 deficiency. Andersson and colleagues (76 78 79) have identified 16 different mutations in affected subjects that cause 12 different amino acid substitutions, 3 splice junction abnormalities, and 1 small deletion that causes a frame shift. The latter types of mutations are believed to preclude the formation of functional enzyme, but the missense mutations impair enzyme function to variable degrees (78 79).

In addition to the Stoller patient, several individuals identified and raised as females have undergone a changed gender role behavior from female to male at the time of expected puberty (72 73 76 80). In some case reports affected individuals were too young to assess gender identity, and a few affected subjects have been raised from the beginning as male. However, in a number of families, affected adult individuals have female sexual identity/role behavior (75 78). If one excludes case reports in infants and small children, gender role reversal appears to occur in about half of affected males. Because change in gender role behavior is so common in this disorder, careful psychiatric evaluation must be obtained before any corrective surgery is undertaken. Although it is not certain why this behavioral change occurs only in some patients, this difference is not due to variations in the severity of the mutation. Changes in gender role behavior have occurred in one individual who is believed to make no functional isoenzyme 3 as a result of a splice junction defect (72 76) and in the Arab family from Gaza who make a kinetically abnormal enzyme that nevertheless can function partially (73 76). While affected males from the Gaza family usually change gender role behavior from female to male, it is interesting that two Brazilian sisters with the identical mutation (R80Q homozygotes) have female gender role behavior (76). Furthermore, in at least one family with another mutation (A203V), one affected individual changed gender role behavior to male whereas the other is a married female (76).

### B. Steroid 5-reductase 2 deficiency

The conversion of testosterone to dihydrotestosterone (Fig. 3) changes a weak hormone to

| Inheritance | Autosomal recessive |
| Phenotype | Males |
| | Male Wolffian structures |
| | Female urogenital sinus and external genitalia |
| | (Females asymptomatic) |
| Hormone profile | Low testosterone levels |
| | High androstenedione levels |
| | Low or normal estrogen levels |
| | Normal testosterone/dihydrotestosterone ratios |
| Gender assignment at birth | Female |
a more potent hormone and is essential for many androgen actions (reviewed in Ref. 81 ).
This reaction is irreversible and is mediated by two enzymes that are encoded by separate
genes (Table 3). Enzyme 2 is the principal enzyme in the male urogenital tract and plays a
critical role in the virilization of the external genitalia and urogenital sinus during
embryogenesis. Enzyme 1, which after puberty is expressed in many tissues, may play a
role in androgen metabolism in sebaceous glands and in the central nervous system.

Figure 3. The 5α-reductase reaction involved in the conversion of testosterone to
dihydrotestosterone. Both isoenzymes 1 and 2 can perform this conversion.

<table>
<thead>
<tr>
<th>Isoenzyme</th>
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<td>1</td>
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</table>

| Size (amino acids) | 259 | 254 |
| pH Optimum         | Neutral to basic | Acidic |
| Chromosome location of gene | 5p15 | 2p23 |
| Gene organization  | 5 Exons/4 introns | 5 Exons/4 introns |
| Expression in prostate | Low | High |
| Activity in 5α-reductase deficiency | Normal | Impaired |

Table 3. Comparison of human 5α-reductase isoenzymes

5α-Reductase deficiency causes an autosomal recessive form of male
pseudohermaphroditism in which the phenotype resembles that in 17β-hydroxysteroid
dehydrogenase 3 deficiency. Namely, virilization of the external genitalia is impaired, and
affected males are usually assigned a female gender at birth and raised as females (the
mutation appears to be silent in women) (Table 4). When the cDNAs for these genes were
cloned, it was found as expected that the mutations involve the gene for enzyme 2
(reviewed in Ref. 81 ), and 45 different mutations have been described to date, including
35 different missense mutations, 3 premature stop codons, 3 small deletions and 1
deletion of the entire coding sequence, 1 small insertion, and a change from a stop codon
to a missense code (82 83 ).
Female urogenital sinus and external genitalia  
(Females asymptomatic)

| Hormone profile |  |
|-----------------|  |
| Normal male testosterone levels |  |
| Normal estrogen levels |  |
| Decreased dihydrotestosterone levels |  |

Gender assignment at birth  
Female

**Table 4. 5α-Reductase 2 deficiency**

As with 17β-hydroxysteroid dehydrogenase 3 deficiency, these individuals virilize to a greater or lesser extent at the time of expected puberty. They have normal male levels of plasma testosterone and low (but not absent) dihydrotestosterone. The measurable plasma dihydrotestosterone (and the subsequent partial virilization at puberty) can arise by two mechanisms; in individuals with mild kinetic abnormalities of enzyme function some dihydrotestosterone may be derived from the mutant enzyme 2, whereas in individuals with mutations that prevent formation of a functional enzyme 2 plasma dihydrotestosterone can be derived from enzyme 1 (82). It is of interest in this regard that the activity of enzyme 1, the principal isoenzyme in nongenital skin, is initially low and increases at the time of expected puberty (84), probably explaining why impairment of virilization in these subjects is more complete during embryogenesis than at the time of expected puberty.

Imperato-McGinley et al. (6) reported that 18 of 19 affected individuals from one family with 5α-reductase deficiency in the Dominican Republic were initially raised as females but subsequently changed gender role behavior to male at the time of expected puberty. A similar phenomenon has been described in other parts of the world: about two-thirds of individuals raised as females change to male gender role after the time of expected puberty (82). In one study of 16 patients from 10 families studied by the same psychologist, 3 individuals retained a female gender role, 12 changed to male gender role, and one was raised as a male (85), and in a study of 10 affected individuals from 8 families studied in another unit, 6 changed gender role behavior to male, 3 have female gender role behavior, and 1 was raised as a male (86 87). Thus, reversal of gender role behavior may be even more common in this disorder than in 17β-hydroxysteroid dehydrogenase 3 deficiency. As in 17β-hydroxysteroid dehydrogenase deficiency, however, change in gender role behavior is not a simple function of the severity of the mutation, since the phenomenon occurs with mutations that partially impair the kinetics of the 5α-reductase and in at least one family with a splice junction abnormality that is thought to prevent formation of functional enzyme (82). Furthermore, families have been reported in which some, but not all, affected individuals undergo the change in social sex (85 88).

It is of interest that the earliest description of gender role reversal and possibly of 5α-reductase deficiency appears to be Herculine Barbin, a French woman who lived during the 19th century and who is believed to be the first person to have changed legal sex from one gender to the other; her phenotype, including evidence from autopsy, is compatible with the diagnosis (89 90).

It should be emphasized that no prospective studies have been done in either of these disorders so that it is not possible to be certain that gender identity before expected puberty was ever unambiguously female. Indeed, several such persons have stated in retrospect that they had been aware of uncertainties as to their correct gender from a very early age (91); consequently, one cannot be certain that this is a change in gender identity as contrasted to a resolution of a confused gender identity—only that gender role behavior changes from that of the sex of rearing to that of the genetic, gonadal, and endocrine sex of the individual. This change could either be the result of a change in gender identity or the resolution of an uncertain gender identity as virilization progresses at the time of expected puberty.
C. Features common to 17ß-hydroxysteroid dehydrogenase 3 and steroid 5-reductase 2 deficiencies

5-Reductase 2 deficiency and 17ß-hydroxysteroid dehydrogenase 3 deficiency share several common features (Table 5):
1) In both, 46,XY males are given gender assignments at birth; in this sense, gender role change, when it occurs, is a correction of an incorrectly assigned gender.
2) In both disorders the impairment of virilization during embryogenesis is limited to the external genitalia; the internal urogenital tract (testes, epididymis, vas deferens, seminal vesicle, and ejaculatory ducts) is male in character, and the testes usually descend into the inguinal canals or labia majora.
3) In both disorders considerable virilization takes place at the time of expected puberty, particularly the growth of a phallus capable of erection; indeed, penile erections are the rule.
4) In both disorders an alternate pathway exists; testosterone can be formed by an alternate pathway in 17ß-hydroxysteroid dehydrogenase 3 deficiency, and dihydrotestosterone can be formed by enzyme 1 in 5R2-reductase 2 deficiency. Consequently, in the postpubertal steady state in both conditions, testosterone and dihydrotestosterone levels can be in the normal or near-normal male range, causing affected individuals to undergo considerable virilization.
5) Change in gender role behavior in the two disorders at expected puberty is common but not universal; the reason for this inconsistency is not readily apparent and cannot be explained in any straightforward way by variations in the severity of the mutations themselves. Whether this inconsistency might be explained by variability in the completeness of compensation by the alternate pathways in the two disorders is unknown.

Table 5. Features common to 5R-reductase 2 deficiency and 17ß-hydroxysteroid dehydrogenase 3 deficiency.

| Inheritance | X-linked trait |

D. Androgen receptor mutations

Although mutations that impair the function of the androgen receptor (Fig. 1) can cause a phenotype that is similar to those caused by the two enzyme deficiencies (Table 6), gender role behavior in these subjects almost invariably corresponds to the gender assignment at birth (83): if the impairment of receptor function is severe enough at birth to cause the syndrome of complete testicular feminization and a female sex assignment, such individuals not only maintain the female sex assignment as adults but rank high in feminine traits as defined by psychological criteria (60 61). Rare women with the syndrome of incomplete testicular feminization (whose mutated androgen receptors have partial residual function and who virilize to a variable degree at puberty) have been described in whom gender identity was male despite being reared as female (92 93); the significance of this phenomenon is not clear. Many men with partial androgen resistance and even less severe impairment of receptor function virilize sufficiently during embryogenesis to result in a male sex assignment at birth and characteristically have unequivocal male gender role behavior as adults (83).
Phenotype Males
Variable from women with testicular feminization to undervirilized men

Hormone profile
Normal male testosterone and dihydrotestosterone levels
Increased estrogen production and levels

Gender assignment at birth
Varies with the anatomy

Table 6. Androgen receptor mutations

The fact that complete testicular feminization is associated with a female gender role/identity despite the presence of testes and normal adult male levels of plasma testosterone indicates that any involvement of androgens in gender role behavior must involve the androgen receptor. Furthermore, since the extraglandular conversion of androgens to estrogens is normal in women with testicular feminization (Table 7) (37 ), the role of androgens in gender role behavior cannot involve the conversion of androgens to estrogens, as appears to be the case in some animal species (17 23 24 ). This conclusion is supported by the fact that a man with a mutation that impaired function of the estrogen receptor (94 ) and two men with profound aromatase deficiency (95 96 ) have been reported to have male gender identity.

<table>
<thead>
<tr>
<th>Group</th>
<th>Estradiol (µg/day)</th>
<th>Estrone (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal men (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Extraglandular aromatization</td>
<td>39</td>
<td>60</td>
</tr>
<tr>
<td>Secretion</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Testicular feminization (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
<td>114</td>
</tr>
<tr>
<td>Extraglandular aromatization</td>
<td>33</td>
<td>101</td>
</tr>
<tr>
<td>Secretion</td>
<td>44</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 7. Estrogen formation in normal men and in subjects with male pseudohermaphroditism.

VI. Discussion

What generalizations can be drawn about behavior from the findings in these two single gene disorders? First, it seems inescapable that androgen action is important for male gender role behavior and probably for male gender identity as well. This does not necessarily mean that androgens can change gender identity/role behavior, only that they may interfere with the development of a gender assignment not in accord with the genetic/endocrine sex. Second, this action cannot be mediated by the conversion of androgens to estrogen; male gender identity appears to be normal in men with mutations of the estrogen receptor (94 ) or of aromatase (95 96 ), and gender identity is female in 46,XY women with testicular feminization despite normal or elevated plasma estrogen.
levels (for men) and normal rates of estrrogen formation by extraglandular aromatase (36
37). Third, the androgen effect must be mediated by the androgen receptor since
profound impairment of receptor function causes complete testicular feminization that is
characterized by female gender identity/role behavior despite normal male levels of plasma
testosterone (60 61). It also follows that even partial androgen receptor function is usually
adequate to support male gender role behavior, since most men with mutations that only
partially impair androgen receptor function (Reifenstein syndrome) have unequivocal male
behavior even in the presence of incomplete external virilization and considerable
feminization at the time of expected puberty.

This is not to say that there are not formidable unresolved aspects of this problem. For
example, it is not known whether this action of androgen takes place during
embryogenesis, during infancy, or at the time of expected puberty, the phases of male life
associated with high levels of plasma testosterone (Fig. 4). As stated above, several such
individuals have reported that they were conscious of gender conflicts from early infancy
(91), implying that the effect is either prenatal or occurred during the neonatal period.
Virilization at the time of expected puberty may influence this process but is probably not
critical because in some individuals [such as Stoller’s patient (70)], there is no evidence of
genital ambiguity when the change in gender role behavior occurred. Likewise, in animal
studies effects of androgens on behavior can sometimes be identified in the absence of
virilization of the urogenital tract (10). It is also unclear whether the effect of androgen on
gender behavior is mediated at the level of the central nervous system, the urogenital
tract, or both; nor is it intuitively clear how to investigate this issue in humans. Finally, it is
not known whether this androgen action is mediated by testosterone or by
dihydrotestosterone; insight into the latter question may be possible with the availability of
potent inhibitors of both isoenzymes or double-knockout animals in which both 5-reductase
isoenzymes are missing. These model systems may make it possible to investigate the
effects of testosterone and dihydrotestosterone independently.

**Figure 4.** The phases of male sexual life as indicated by mean plasma testosterone level
as a function of age. Sperm production occurs only during the adult phase. [Modified from
Griffin JE, Wilson JD 1980 The testis. In: Metabolic Control and Disease, Bondy PK,
Rosenberg LE (eds) with permission from W.B. Saunders, Philadelphia. Based on the

No matter how important the implications of the findings in these two disorders may be
for understanding the control of gender role and gender identity in the human, it is highly
unlikely that abnormalities in androgen action are a common cause of transsexual
behavior. Meyer et al. (97) studied 60 male-to-female transsexuals and 30 female-to-male
transsexuals; only two of these individuals (both female-to-male) had an underlying
endocrine abnormality so that, at best, less than a tenth of female-to-male transsexuals can be explained by disordered action of androgen.

In keeping with this concept, Meyer-Bahlburg (98 ) argued convincingly that disorders of gender identity in subjects with male pseudohermaphroditism are fundamentally different than gender identity disorders in subjects that do not have a problem of human intersex in that the former group make the change in gender role behavior with greater ease. Consequently, it is unlikely that studies of this type can provide insight into transsexualism per se, the etiology of which is believed to be outside the endocrine domain.

VII. Conclusions

Genetic and endocrine evidence indicates that androgen action plays an important role in male gender role behavior; since gender identity and gender role behavior are normally in accord, androgen action is probably an equally important determinant of male gender identity. At the same time, it is also clear that androgen is not the sole determinant of these processes; the fact that many individuals with mutations of the 5c-reductase and 17β-hydroxysteroid dehydrogenase enzymes do not undergo a change in gender role behavior means that other factors—social, psychological, or biological—are of equal or greater importance in modulating human sexual behavior. Indeed, the sex of rearing may be more important in this regard than the endocrine milieu under ordinary circumstances, and it may not be a coincidence that many (although not all) of the instances of reversal of gender role behavior in these two disorders have occurred in countries and/or ethnic groups in which men play a dominant role; in this situation, endocrine factors may be more important determinants of behavior than would be the case in more egalitarian societies.

Endocrine and psychological factors must interact to influence these behaviors. Perhaps the most appropriate animal model for this aspect of human behavior is the song bird in which androgen action in the central nervous system and a pattern of behavior learned from a male of the same species are both necessary to learn a song that will attract a female of the same species (23 ). It may never be possible to assign quantitative importance to the roles of the two processes in human behavior, but it may be possible to determine how, where, and when in development androgen plays its role in this process.

References

10. Goy RW, Bercovitch FB, McBrair MC 1988 Behavioral masculinization is independent of genital masculinization in prenatally androgenized female rhesus
macaques. *Horm Behav* 22:552–571


25. Beach FA 1948 *Hormones and Behavior*. Harper (Hoeber), New York, pp 20–29


the aromatization hypothesis. *Endocrinology* 118:1935–1944

32. **Michael RP, Bonsall RW, Rees HD** 1987 Sites at which testosterone may act as an estrogen in the brain of the male primate. *Neuroendocrinology* 46:511–521

33. **Michael RP, Rees HD, Bonsall RW** 1989 Sites in the male primate brain at which testosterone acts as an androgen. *Brain Res* 502:11–20


45. **Slijper FME** 1984 Androgens and gender role behavior in girls with congenital adrenal hyperplasia (CAH). *Prog Brain Res* 61:417–422

46. **Hurtig AL, Rosenthal IM** 1987 Psychological findings in early treated cases of female pseudohermaphroditism caused by virilizing congenital adrenal hyperplasia. *Arch Sex Behav* 16:209–223


51. **Reinisch JM** 1974 Fetal hormones, the brain, and human sex differences: a heuristic, integrative review of the recent literature. *Arch Sex Behav* 3:51–90

52. **Reinisch JM** 1976 Effects of prenatal hormone exposure on physical and


64. Lev-Ran A 1974 Gender role differentiation in hermaphrodites. Arch Sex Behav 3:391–424


gynaecomastia due to testicular 17-ketosteroid reductase deficiency. *Clin Endocrinol (Oxf)* 7:443–452


77. Saez JM, de Peretti E, Morera AM, David M, Bertrand J 1971 Familial male pseudohermaphroditism with gynecomastia due to a testicular 17-ketosteroid reductase defect. *J Clin Endocrinol* 32:604–610


88. Al-Attia HM 1996 Gender identity and role in a pedigree of Arabs with intersex due
to 5α-reductase-2 deficiency. Psychoneuroendocrinology 21:651–657


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