THE ROLE OF GONADAL HORMONES IN GENDER ROLE BEHAVIOR

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During the past 40 years a large body of evidence has accrued to indicate that in most animal species virtually all reproductive functions are controlled by steroid hormones secreted by the ovaries and testes (Table I). Such functions include the formation of the sexual phenotypes during embryogenesis, sexual maturation at the time of puberty, various types of sexual behavior including gender identity (the extent to which one perceives oneself as male or female), gender role behavior (the ways that gender identity is communicated to others), sex drive and potentia and a variety of traits such as aggression, the drive for dominance, parenting behavior, and sexually dimorphic stereotypic behaviors (reviewed in reference 1).

TABLE 1. ROLE OF TESTICULAR ANDROGENS IN ANIMALS AND HUMANS

	ANIMALS	HUMANS
MALE PHENOTYPIC SEXUAL DIFFERENTIATION DURING EMBRYOGENESIS	YES	YES
SEXUAL MATURATION AT MALE PUBERTY	YES	YES
MALE SEX DRIVE/POTENTIA	YES	YES
MALE GENDER ROLE BEHAVIOR	YES	?

In humans gonadal steroids are responsible for phenotypic sexual differentiation, sexual maturation, and development of libido and potentia. Whether gonadal steroids are also involved in the development of gender identity and in the control of the patterned activities that constitute gender role behavior in the human is not so clearcut. It is obviously not possible to devise definitive experiments to examine the role of hormones in human behavior. However, on the basis of studies of subjects with a variety of forms of human intersex and/or endocrine abnormalities it is the predominant view that human behavior is more complex than that of other species and that gender identity and gender role behavior are determined primarily, if not exclusively, by psychological and social and psychological factors and that biological forces,

including the action of hormones, play an insignificant role in the process. According to this anthropocentric view, the forces that mediate behavior in animals do not play a significant role in controlling human behavior (reviewed in reference 2).

However, over the years a number of individuals have been reported in the medical literature who were considered female at the time of birth, assigned a female gender, and raised as female but who at the time of expected puberty developed some degree of virilization and subsequently underwent a reversal of gender role behavior and an apparent reversal of gender identity; that is, apparent females turned into anatomical and functional males. It is now established that most such instances are due to either of two autosomal recessive gene mutations that impair testosterone synthesis or metabolism. This phenomenon raises fundamental questions about factors that regulate human sexual behavior.

The cDNAs and genes that encode these two critical enzymes--17β-hydroxysteroid dehydrogenase 3 and steroid 5α-reductase 2--have been cloned by Stefan Andersson and David Russell and their colleagues here at UT Southwestern, and the mutations have been characterized in many affected subjects from our patient materials and in patients from many other institutions. Consequently, we now know a great deal about the pathophysiology and molecular biology of these two disorders.

What I propose today is to consider the implications of these studies for understanding the control of behavior. Gender identity and gender role behavior are normally in accord, but the advantage of focusing on gender role behavior is that there is no ambiguity when an individual changes the legal registration of sex from one gender to another whereas gender identity can be a graded character and difficult to quantify. I will begin by reviewing the animal studies and the apparent differences between animals and humans.

THE SEXUAL BEHAVIOR OF ANIMALS

The role of gonadal hormones in animal behavior has been the subject of several extensive reviews (1-6). For the purposes of this discussion certain aspects of this relationship deserve emphasis (Table II):

Table II. HORMONAL CONTROL OF SEXUAL BEHAVIOR IN ANIMALS

1. Diverse sexually dimorphic behaviors are controlled by gonadal steroids.

2. Androgens dictate male behavior; estrogens (and progestogens) dictate female behavior. Androgens paradoxically may act via conversion to estrogens.

3. Receptors for these hormones are present in the CNS.

4. Behavioral effects are due to peripheral as well as CNS actions of the hormones.

5. In rodents the neonatal surge of testosterone secretion is important in controlling hypothalamic function.

6. Behavioral effects can be organizational or concurrent.

1. Sexually dimorphic behaviors of a variety types are regulated by gonadal steroids, including the songs and mating rituals of birds, copulatory patterns in mammals, and complex forms of ritual behavior such as must 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. Although androgens and estrogens are formed in both males and females and although both hormones may play a role in the physiology of both sexes, androgens (and androgen metabolites including estrogens in some species) dictate male behavior and estrogens and progestogens dictate female behavior.

3. Gonadal steroids act in the central nervous system by the same receptor mechanisms that operate in peripheral tissues (6,7). Intracellular receptors for these hormones are localized within specific regions of the brain. Gonadal steroids may also exert central nervous system effects by other mechanisms such as by influencing ion channels in cell membranes (6).

4. The behavioral effects of steroid hormones are due to complicated interactions between peripheral and central actions of the hormones (2). The best studied paradigm of sexual behavior in the mammal is the mounting reflex of the female rat. When the female in estrus is mounted by a male, she extends the hind legs, elevates the rump, and dorsiflexes the vertebral column. These actions involve not only sensory input from the rump but 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, for example 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 CNS). Whether the neonatal surge in testosterone secretion in the human male infant is of physiological significance is not known.

6. Phoenix and his colleagues have delineated two types of behavioral effects of steroid hormones (8). Organizational effects are exerted by the 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 (9). Concurrent effects require the continued presence of the steroid for full manifestation of the effects (8), e.g., the mounting response of the female rat during estrus. Although the delineation of these two types of phenomena is of conceptual usefulness, 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. Different animal species differ in the extent to which hormones exert permanent organizational effects. For example, organizational effects in primates appear to be less clearcut than in rodents (10); for example, the administration of estrogens in

appropriate amounts to male rhesus monkeys of any age elicits a positive release of luteinizing hormone, analogous to the ovulatory surge of luteinizing hormone release in females (3).

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 (11).

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

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 is not possible in the absence of gonadal hormones. In the males of most species, mating capacity is maintained for a limited period after orchidectomy, 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 male behavior, 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 two years (12,13). Furthermore, physiological androgen replacement therapy in hypogonadal men causes a rapid and predictable restoration of male sexual drive (14,15). The hormonal control of male sexual behavior is similar in man and animals.

In contrast, removal of ovarian secretions by oophorectomy 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 endocrine independent. This interpretation may be incorrect because removal of the human ovaries does not impair formation of sex steroids by the adrenal glands. Adrenalectomy (16) or hypophysectomy (17) 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 and maintain sexual drive in the absence of ovaries (18). Whether hormones are necessary for the genesis of normal sexual drive at female puberty is also unclear.

A similar problem of interpretation exists as to exactly which hormones regulate male sexual behavior. Occasional castrate males of all species sustain a capacity and drive for intercourse for long periods (2,13). In the castrated human male considerable estrogen and small amounts of testosterone are formed in extraglandular tissues from adrenal androgens (19), and in some animal species estradiol enhances the effect of androgen on male sexual drive (20). Thus, the small amounts of testosterone and/or estrogen formed by this pathway may be enough to sustain libido and potentia in some adult male castrates. In other words, libido and potentia would be preserved only in those castrated men able to produce sufficient hormones by this mechanism.

In summary, testicular hormones play an important role in the sexual drive of males of all species, and ovarian hormones play a critical role in controlling the sexual drive of female animals and possibly in women. Furthermore, permanent imprinting does not appear to play as important a role in the control of gonadotropin secretion by gonadal steroids in the primate as in lower animals. Thus, although there may be slight differences between animals and humans, the control of libido and potentia appears to be similar.

SEXUAL IDENTIFICATION IN THE HUMAN

In contrast to sexual drive, which is not usually considered to be sexually dimorphic, sexual identification is fundamentally different in males and females. Some of the ambiguities in the definition and understanding of gender identity and gender role

behavior are due to the fact that it is difficult to quantify these parameters. Furthermore, gender role behavior is influenced by cultural and social variables, as evidenced by the fact that the actions and activities of the two sexes vary in different societies. Nevertheless, whatever the social and societal differences in gender role behavior, the change of one's legal gender is an unequivocal event. It is equally difficult to devise means of investigating the mechanisms that regulate gender identity/role behavior; appropriately controlled studies that would make possible definition of the determinants of sexual identification cannot be performed in humans. As a consequence, the 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.

Abnormal Sexual Development

Derangements of any of the three primary processes involved in sexual differentiation can cause abnormal sexual development, including disorders of chromosomal sex, gonadal sex, and phenotypic sex (Table III). The pathogenesis, clinical spectrum, 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 (Table IV):

Table III. OCCURRENCE OF AMBIGUOUS GENITALIA IN HUMAN ABNORMALITIES OF SEXUAL DEVELOPMENT

TYPE OF DISORDER	DISORDER	AMBIGUITY OF EXTERNAL GENITALIA
CHROMOSOMAL SEX	KLINEFELTER SYNDROME	NONE
	XX MALE	NONE
	GONADAL DYSGENESIS	NONE
	MIXED GONADAL DYSGENESIS	COMMON
	TRUE HERMAPHRODITISM	OCCASIONAL
GONADAL SEX	PURE GONADAL DYSGENESIS	OCCASIONAL
	ABSENT TESTES SYNDROME	NONE
PHENOTYPIC SEX	FEMALE PSEUDOHERMAPHRODITISM	
	CONGENITAL ADRENAL HYPERPLASIA	COMMON
	NONADRENAL FEMALE PSEUDOHERMAPHRODITISM	COMMON
	DEVELOPMENTAL DISORDERS OF THE MULLERIAN DUCT	NONE
	MALE PSEUDOHERMAPHRODITISM	
	ABNORMALITIES OF ANDROGEN SYNTHESIS	
	SIDE CHAIN CLEAVAGE DEFICIENCY	NONE
	17-HYDROXYLASE/17,20-LYASE DEFICIENCY	NONE
	3β-OH STEROID DEHYDROGENASE DEFICIENCY	COMMON
	17β-OH STEROID DEHYDROGENASE DEFICIENCY	COMMON
	ABNORMALITIES OF ANDROGEN ACTION	
	5α-REDUCTASE DEFICIENCY	COMMON
	DEFECTS OF THE ANDROGEN RECEPTOR	
	TESTICULAR FEMINIZATION	NONE
	REIFENSTEIN SYNDROME	COMMON
	MALE INFERTILITY/UNDERVIRILIZATION	NONE
	PERSISTENT MULLERIAN DUCT SYNDROME	NONE
	SPORADIC HYPOSPADIAS	OCCASIONAL

TABLE IV. ABNORMAL SEXUAL DEVELOPMENT IN HUMANS

1. WIDE PHENOTYPIC VARIABILITY

2. DIFFERENT DISORDERS CAN CAUSE SIMILAR PHENOTYPES.

3. AMBIGUITY OF EXTERNAL GENITALIA AT BIRTH IS DUE TO DEFICIENT TESTOSTERONE SYNTHESIS OR IMPAIRMENT OF ANDROGEN ACTION IN MALE EMBRYOS OR INAPPROPRIATE ANDROGEN SECRETION IN FEMALES.

4. THE VARIOUS DEFECTS THAT CAUSE ABNORMAL SEXUAL DEVELOPMENT HAVE DIFFERENT TIMES OF ONSET DURING EMBRYOGENESIS.

First, there is considerable variability in the phenotypic manifestations of the various abnormalities. For example, men with 47,XXY Klinefelter syndrome or with the 46,XX male syndrome develop

as men (albeit infertile) and develop 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 male or female phenotypes. Thus, many 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. If hormones are involved in the determination of gender identity/role behavior, the endocrine effects in most individuals with abnormal sexual development would correspond to the anatomical development and hence to the gender assignment at birth.

Second, disorders that appear phenotypically similar can result from different mechanisms. For example, men with 45,X/46,XY mixed gonadal dysgenesis have phenotypes similar to those of men with abnormalities of phenotypic sex, such as steroid 5α-reductase deficiency. 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 (and hence confusion as to gender at birth or in subsequent life) occurs in relatively few of these disorders and is due to any 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 hereditary defect in one of the enzymes required for testosterone biosynthesis; 2.) Sufficient testosterone is synthesized by the testes, but due to an inherited abnormality that impairs androgen action (frequently involving the androgen receptor) the hormone cannot virilize the embryo normally; 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. Consequently, gender identity/behavior would not be expected to be discordant with the sex of rearing in every instance. 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 on about week eight of gestation, whereas virilization in steroid 21-hydroxylase deficiency does not commence until the time of onset of adrenal function late in gestation. Furthermore, adult males with 17β-hydroxysteroid dehydrogenase 3 deficiency, mixed gonadal dysgenesis, or 5α-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 influence 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 has to 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.

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 (Table V):

TABLE V. BEHAVIORAL STUDIES IN INTERSEX SUBJECTS

1. FEMALE PSEUDOHERMAPHRODITES HAVE FEMALE GENDER ROLE BEHAVIOR.

2. EXOGENOUS ESTROGENS OR PROGESTOGENS DURING EMBRYOGENESIS DO NOT INFLUENCE GENDER ROLE BEHAVIOR.

3. GENDER ROLE BEHAVIOR IN TRUE HERMAPHRODITES USUALLY CORRESPONDS TO THE SEX OF REARING.

4. WOMEN WITH GONADAL DYSGENESIS HAVE FEMALE GENDER IDENTITY/ROLE BEHAVIOR.

5. MEN WITH KLINEFELTER SYNDROME HAVE MALE GENDER ROLE BEHAVIOR.

6. 46,XY WOMEN WITH COMPLETE TESTICULAR FEMINIZATION HAVE UNAMBIGUOUS FEMALE BEHAVIOR.

1.) Females exposed to excess androgens as a result of congenital adrenal hyperplasia develop 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 in some studies effects can be delineated on certain aspects of gender role behavior, generally tomboyishness and characteristic male energy expenditure (21-27). (Occasionally, female pseudohermaphrodites have male gender role behavior, but this is probably no more frequent than in the general population.)

2.) Children exposed to exogenous estrogens or progestogens during gestation have appropriate male or female phenotypes; in general, such agents have no or minor effects on sexually dimorphic behavior and no discernable effect on gender identity (28-34).

3.) True hermaphrodites have both testes and ovaries (or ovotestes) and may have male, female, or ambiguous phenotypes. In

such individuals gender identity and gender role behavior usually correspond to the sex of rearing (35).

4.) Women with gonadal dysgenesis have female phenotypes and female gender identity/role behavior (36). Since such women are believed to be estrogen deficient throughout life, it has been inferred that gonadal estrogen plays at best a minor role in the evolution of female gender identity.

5.) Men with Klinefelter syndrome clearly form sufficient androgen to allow normal virilization during embryogenesis but after puberty tend to have diminished androgen production and enhanced estrogen production. Nevertheless, such men appear to have no greater incidence of discordant sexual behavior than controls, suggesting that these hormones play no critical role in gender identity/behavior, at least after the time of expected puberty (37).

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) (38-40).

The conclusion from these various studies is that gender identity and gender role behavior usually develop in conformity with the sex of assignment and rearing (41,42). Similar findings have been reported by workers in different countries studying many types of subjects. In other words, gender identity and role correspond with the predominant anatomical development and hence with the prenatal hormonal milieu. This conformity can withstand various 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 unanimity of opinion in this regard is impressive.

The problem is that this conclusion is open to diametrically opposite interpretations. The predominant view--most eloquently formulated by John Money and his disciples--is that sex assignment at birth influences parental attitudes and the manner in which infants are treated from the very first 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 (41,42). 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 determine anatomical development, and hence sex assignment and the sex of rearing, gender identity and anatomical sex would almost invariably be the same. In such a view, it is difficult, virtually impossible, to ascertain in such studies the extent to which psychological/social and endocrine determinants contribute to this development because the psychological/social forces generally correspond with the anatomical and endocrine factors.

Reversal of Gender Role Behavior and Apparent Reversal of Gender Identity

Occasional instances have been reported over the years 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 43). The majority of these reports were published before the means of making specific diagnoses as to the cause of the abnormal sexual development were available, and it is not possible in retrospect to deduce the correct diagnosis in most such reports, indeed even in some relatively recent studies (44,45). Nevertheless, in analyzing these reports two conclusions seem justifiable: 1.) Most such individuals had ambiguous genitalia and were assigned a female sex assignment at birth, and 2.) the change in gender role behavior at puberty is almost always 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 (41) and was thought to result from childhood stigmatization of such individuals because of their anatomical abnormalities (45).

However, ambiguity of the genitalia cannot be the sole cause of changes in gender role behavior as illustrated by the famous case described by Robert Stoller (46). This individual was thought to be a normal female at birth and was raised as a girl but exhibited tomboyish 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 17β-hydroxysteroid dehydrogenase deficiency (47)]. She promptly went home, 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 man 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 become apparent that female to male reversal of gender role behavior appears to be a common feature of two autosomal recessive forms of male pseudohermaphroditism--5α-reductase deficiency (48-50) and 17β-hydroxysteroid dehydrogenase 3 deficiency (47,51,52), and the majority of instances of change in gender role behavior in individuals with male pseudohermaphroditism are associated with these two conditions (Fig 1). Nevertheless, a similar change in gender role behavior has been described in 3β-hydroxysteroid dehydrogenase deficiency (53), an even rarer autosomal recessive form of male pseudohermaphroditism, and in individuals who have severe hypospadias of uncertain provenance (54,55). Because of the frequency we will concentrate on the first two disorders, and we will compare the differences in the effects of mutations in these two enzymes and mutations of the androgen receptor on gender role behavior.

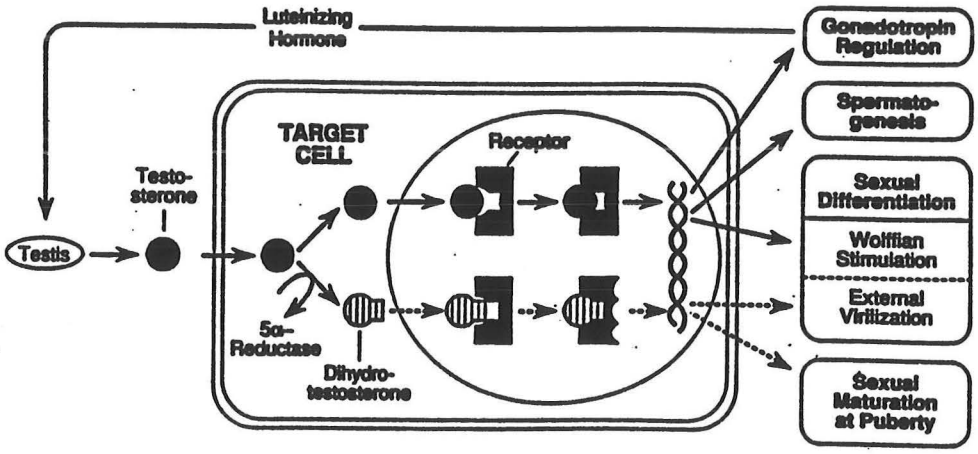

FIG. 1. Schematic diagram of the mechanism of androgen action.

The cloning of the genes that encode these proteins and the construction of gene maps of the various mutations makes it possible to examine the behavioral consequences of these mutations in a new way. I will review 5α-reductase deficiency and 17β-hydroxysteroid dehydrogenase deficiency only briefly to set the stage for consideration of the effects on behavior.

17β-hydroxysteroid Dehydrogenase Deficiency

The 17β-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 (56) (Table VI), and mutations of the type 3 enzyme (57) are responsible for a rare, autosomal recessive form of male pseudohermaphroditism, 17β-hydroxysteroid dehydrogenase deficiency originally described by Saez and his colleagues in 1971 (58). The characteristic features of this disorder are summarized in Table VII. In brief, these 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 begin to virilize at puberty, a phenomenon that usually brings them to medical attention. On endocrine evaluation they have low testosterone levels (for men), normal testosterone/dihydrotestosterone ratios, and variable estrogen levels. The diagnosis is made by finding androstenedione levels that are usually ten times normal (Stoller's patient had typical findings and course for this disorder).

Table VI. COMPARISON OF HUMAN 17β-HYDROXYSTEROID DEHYDROGENASE ISOZYMES

	Type 1	*Type 2*	*Type 3*	*Type 4*	*Type 5*
Cloning strategy	Antibody screening	Expression cloning	Expression cloning	cDNA probe	cDNA probe
Size (amino acids)	327	387	310	736	323
Gene (exons)	6	5	11	—	9
Chromosome localization	17q21	16q24	9q22	—	10p14,15
Tissue localization	Ovary, placenta	Endometrium, placenta, liver	Testis	Ubiquitous	—
Cellular localization	Cytosol	Microsomes	Microsomes	Peroxisomes	—
Preferred substrate	Estrogens	Androgens, estrogens, progestogens	Androgens, estrogens	Estrogens	—
Preferred cofactor	NADPH	NAD^+	NADPH	NAD^+	NADPH
Catalytic preference	Reduction	Oxidation	Reduction	Oxidation	Reduction
17β-HSD deficiency	Normal	Normal	Mutated	—	—

HSD, hydroxysteroid dehydrogenase.

TABLE VII. 17β-OH STEROID DEHYDROGENASE 3 DEFICIENCY

KARYOTYPE	46,XY
GENETICS	AUTOSOMAL RECESSIVE
PHENOTYPE	MALE WOLFFIAN STRUCTURES FEMALE UROGENITAL SINUS AND EXTERNAL GENITALIA
ENDOCRINOLOGY	TESTOSTERONE PRODUCTION AND LEVELS LOWER THAN NORMAL MEN ESTROGEN LEVELS LOW OR NORMAL DIHYDROTESTOSTERONE LEVELS NORMAL
GENDER ASSIGNMENT AT BIRTH	FEMALE

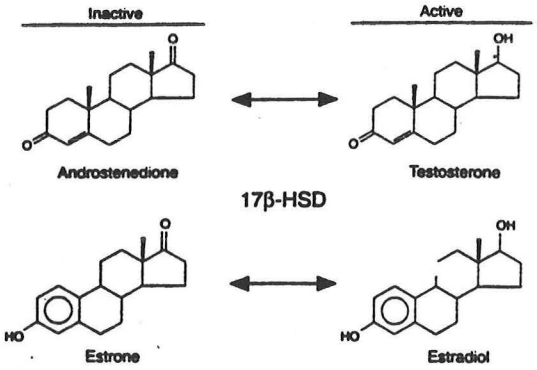

Figure 2 The principal enzymatic reactions catalyzed by the 17β-hydroxysteroid dehydrogenase enzymes.

Figure 2

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 (59). Testosterone in these individuals can be formed by two mechanisms. Some have mutant enzymes that are nevertheless capable of some testosterone synthesis when luteinizing hormone and androstenedione levels are high. Individuals with more severe mutations appear to

convert androstenedione to testosterone in extraglandular tissues by the action of by the action of one or more of the unaffected isoenzymes. The critical point is that there is an alternate pathway for testosterone formation in all patients.

This disorder is rare and is believed to be less common than 5α-reductase deficiency. When the cDNA for enzyme 3 was cloned, we had fibroblasts from only four affected families in our repository, and we obtained suitable material from other investigators for analysis of additional individuals and or families. Consequently, David Russell and Stefan Andersson were able to construct a gene map of fourteen different mutations identified to date (Fig. 3). (56,57,59).

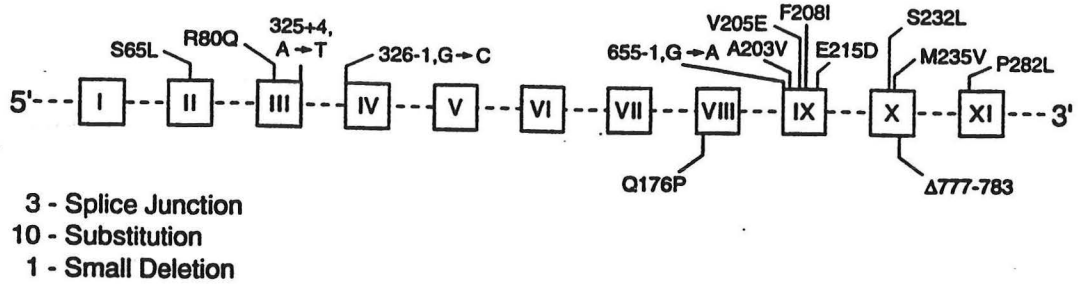

Figure 3. Mutations in the 17β-hydroxysteroid dehydrogenase 3 gene in subjects with 17β-hydroxysteroid deficiency.

Figure 3

In four families in addition to the Stoller patient, individuals identified and raised as females have undergone a changed their gender role behavior from female to male at the time of expected puberty (51,52,57,60). In some of the reports affected individuals were too young to assess gender identity, and in a few instances subjects have been raised from the first as male. However, in a number of families affected adult individuals are said unequivocally to have female sexual identity/role behavior (reviewed in 59). If one excludes case reports in infants and small children, gender role reversal appears to occur in approximately one in three families; clearly, this phenomenon is common enough that psychiatric evaluation should be obtained before corrective surgery is undertaken. Although it is not certain why this behavioral change occurs only in some patients, this

difference is not due to differences in the severity of the mutation. Changes in gender role behavior have occurred in one individual who is believed to make no functional enzyme 3 as a result of a splice junction defect (51,57) and in the Arab family from Gaza who make a kinetically abnormal enzyme that nevertheless can function partially (52,57).

5α-Reductase Deficiency

The conversion of testosterone to dihydrotestosterone changes a weak to a more potent hormone and is essential for many androgen actions (reviewed in 61) (Fig. 4). This reaction is irreversible and is mediated by two enzymes that are encoded by separate genes (Table VIII). Enzyme 2 is the principle 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 may play a role in androgen metabolism in sebaceous glands and in the CNS.

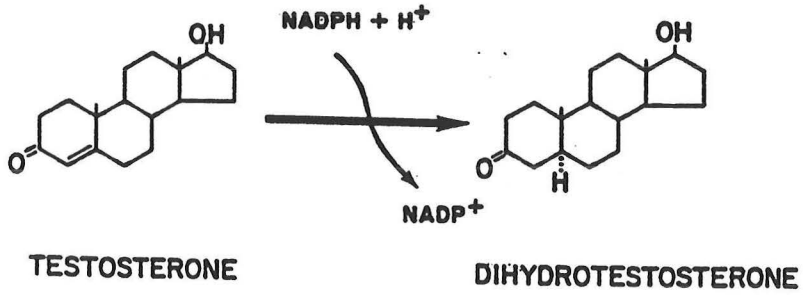

Fig. 4. The 5α-Reductase Reaction

Table VIII. COMPARISON OF HUMAN STEROID 5α-REDUCTASE ISOZYMES

Size	259 amino acids M,=29,462	254 Amino acid M,+28,398
pH optima	Neutral to basic	Acidic
Gene, chromosome location	SRD5A1, 5P15	SRD5A2, 2p23
Gene structure	5 exons/4 introns	5 exons/4 introns
Activity in 5α-reductase deficiency	Normal	Mutated
Expression in prostate	Low	High
Inhibition by finasteride	$K_i \geq 300$ nM	K_i=3-5 nM

5α-reductase deficiency causes an autosomal recessive form of male pseudohermaphroditism in which the virilization of the external genitalia is impaired and in which affected males are assigned a female gender at birth and raised as females (the mutation appears to be silent in women) (Table IX). When the cDNAs for these genes were cloned it was found as expected that the mutations involve the gene for enzyme 2 (reviewed in 62), and, David Russell and his colleagues have constructed a gene map of these various mutations (Fig. 5).

Table IX. STEROID 5α-REDUCTASE 2 DEFICIENCY

Karyotype	46,XY
Genetics	Autosomal Recessive
Phenotype	Male Wolffian Structures
	Female Urogenital Sinus and External Genitalia
Endocrinology	Normal Male Testosterone
	Normal Estrogen Dynamics
	Decreased Plasma Dihydrotestosterone
Gender Assignment at Birth	Female

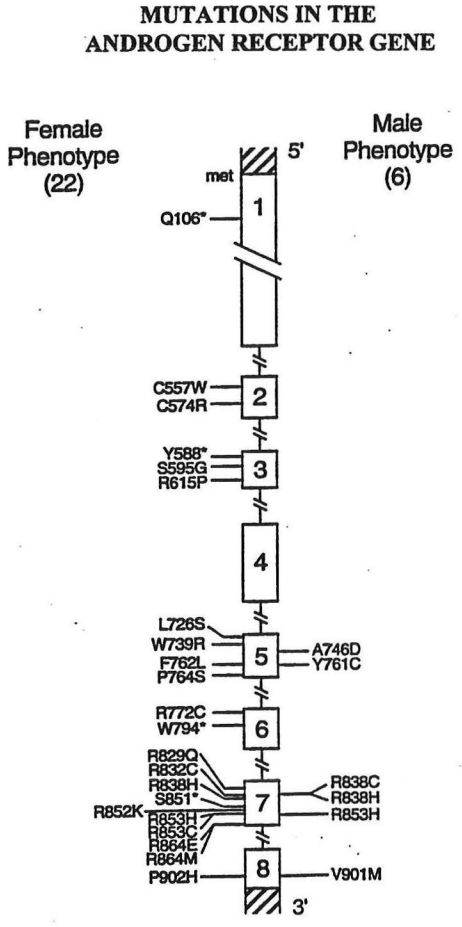

Figure 5

As with 17β-hydroxysteroid dehydrogenase deficiency these individuals virilize to a greater or lesser extent at the time of expected puberty, and on endocrine evaluation 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 kinetic abnormalities 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 (62). It is of interest in this regard that the activity of enzyme 1, the principal isoenzyme in non-genital skin, is initially low and increases at the time of expected puberty (63), probably explaining why impairment of virilization in these subjects is more complete during embryogenesis than in postembryonic life.

Imperato-McGinley et al (47,48) 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, namely in 19 of 29 families in which individuals raised as females were of sufficient age to change gender role (62). Thus, reversal of gender role behavior appears to be more common in this disorder than in 17β-hydroxysteroid dehydrogenase deficiency, but, as in 17β-hydroxysteroid dehydrogenase deficiency, 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 (Dominican Republic Family) and in a family with a splice junction abnormality that is thought to prevent formation of functional enzyme (62). 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 (64).

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 (65); 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.

Summary of the Behavioral Effects of 17β-hydroxysteroid Dehydrogenase and 5α-reductase Deficiencies

5α-reductase 2 deficiency and 17β-hydroxysteroid dehydrogenase 3 deficiency share several common features (Table X). 1.) In both 46,XY males are given gender assignments at birth; in a sense, gender role change, when it occurs, is a correction of a incorrectly assigned gender. 2.) In both the impairment of virilization during embryogenesis is limited to the external genitalia; the internal urogenital tract is male in character (testes, epididymis, vas deferens, seminal vesicle, and ejaculatory ducts), 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 unaffected isoenzymes in 17β-hydroxysteroid dehydrogenase 3 deficiency, and dihydrotestosterone can be formed by enzyme 1 in 5α-reductase 2 deficiency. The consequence is that in the post-pubertal steady state in both conditions testosterone and dihydrotestosterone levels can be normal or near normal. 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 X. FEATURES COMMON TO STEROID 5α-REDUCTASE 2 DEFICIENCY AND 17β-OH-STEROID DEHYDROGENASE 3 DEFICIENCY

1. 46,XY MALES ARE GIVEN GENDER ASSIGNMENTS AS FEMALES.

2. IMPAIRMENT OF VIRILIZATION DURING EMBRYOGENESIS IS LIMITED TO THE EXTERNAL GENITALIA.

3. CONSIDERABLE VIRILIZATION TAKES PLACE AT THE TIME OF EXPECTED PUBERTY.

4. IN BOTH DISORDERS, AN ALTERNATE PATHWAY EXISTS. TESTOSTERONE IS FORMED BY 17β-OH-SD 2 IN 17β-OH-SD 3 DEFICIENCY, AND DIHYDROTESTOSTERONE IS FORMED BY STEROID 5α-R1 IN STEROID 5α-R2 DEFICIENCY.

5. GENDER ROLE CHANGE AT PUBERTY IS COMMON BUT NOT UNIVERSAL.

6. BY HISTORY THE CHANGE IN GENDER ROLE BEHAVIOR IS THE RESOLUTION OF AN AMBIGUOUS GENDER IDENTITY.

Androgen Receptor Mutations

Although mutations that impair the function of the androgen receptor (Figure 1) can cause similar phenotypes to those of the two enzyme deficiencies (Table XI), gender role behavior in these subjects almost invariably corresponds to the gender assignment at birth (66). Namely, if the impairment of receptor function is severe enough at birth to cause the syndrome of complete testicular feminization and a female sex assignment (Figure 5), such individuals not only maintain the female sex assignment as adults but rank high by all psychological criteria (38,39). Rare women with the syndrome of incomplete testicular feminization (whose mutated androgen receptors have partial residual function and who typically virilize partially at puberty) have been described in whom gender identity was male despite being reared as female (67,68); the significance of this phenomenon is not clear. Men with partial androgen resistance and even less severe impairment of receptor function have sufficient virilization to result in a male sex assignment at birth and have unequivocal male gender role behavior (66).

Table XI. ANDROGEN RECEPTOR MUTATIONS

KARYOTYPE	46,XY
GENETICS	X-LINKED
PHENOTYPE	VARIABLE FROM WOMEN WITH TESTICULAR FEMINIZATION TO UNDER VIRILIZED MEN
ENDOCRINOLOGY	NORMAL MALE TESTOSTERONE AND DIHYDROTESTOSTERONE INCREASED ESTROGEN PRODUCTION
GENDER ASSIGNMENT AT BIRTH	VARIES WITH THE ANATOMY

The fact that complete testicular feminization is always associated with a female gender role/identity despite the presence of testes and normal adult male levels of plasma testosterone clearly 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 (19) (Figure 6) , any role of androgens in gender role behavior cannot involve the conversion of androgens to estrogens in the brain, as appears to be the case in some animal species (7,11).

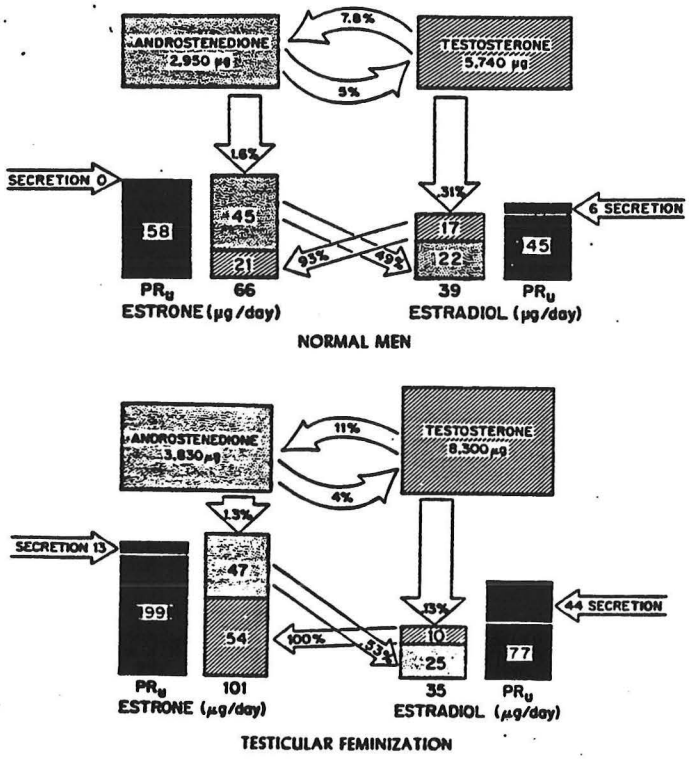

FIG. 6 Summary of the sources of estrogen formation in normal young adult men and in women with testicular feminization. PR-E_1 and PR-E_2 (PR_u) were measured by isotope dilution methods (▬). The estimation of the contribution of plasma precursors A and T to E_1 and E_2 production was calculated from the plasma PR of the precursors and the transfer constants of conversion of precursor to product. The PR_u of E_1 is the average of the values of the subjects of this study measured from isotope dilution techniques and does not equal exactly that computed to have arisen from the utilization of plasma precursors at extraglandular sites. The portion of E_2 production attributed to glandular secretion is the mean excess of the PR_u-E2 over that computed to have arisen by extraglandular formation from plasma precursors.

GENERAL CONCLUSIONS

What generalizations can be drawn from the findings in these two relatively rare disorders? (Table XII) First, it seems inescapable that androgen action is important for male gender role behavior and probably for male gender identity as well. 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 (69), and gender identity is female in 46,XY women with testicular feminization despite normal or above normal plasma estrogen levels and normal rates of extra-glandular aromatase (18,19). 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 (38,39). It also follows that even partial androgen receptor function in many instances is adequate to cause male gender role behavior, since most men with Reifenstein syndrome have unequivocal male behavior even in the presence of profound defects in external virilization.

TABLE XII. CONCLUSIONS

1. ANDROGEN ACTIONS IS AN IMPORTANT DETERMINANT FOR MALE GENDER ROLE BEHAVIOR AND PROBABLY FOR MALE GENDER IDENTITY.

2. THIS ACTION IS NOT MEDIATED BY CONVERSION OF TESTOSTERONE TO ESTRADIOL.

3. THE ANDROGEN RECEPTOR MUST BE INVOLVED IN THIS ACTION.

This is not to say that there are not formidable unresolved aspects of this problem (Table XIII). For example, it is not known whether this action of androgen takes place during embryogenesis, during infancy, or at the time of expected puberty. (Figure 7). As stated above, several such individuals have reported that they were conscious of gender conflicts from early infancy (65), and in some (such as Stoller's patient) there was no evidence of genital ambiguity when the change in gender role behavior occurred. It is also not clear whether this effect of androgen 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 5α-reductase isoenzymes are missing. These model systems may make it possible to investigate the effects of testosterone and dihydrotestosterone independently.

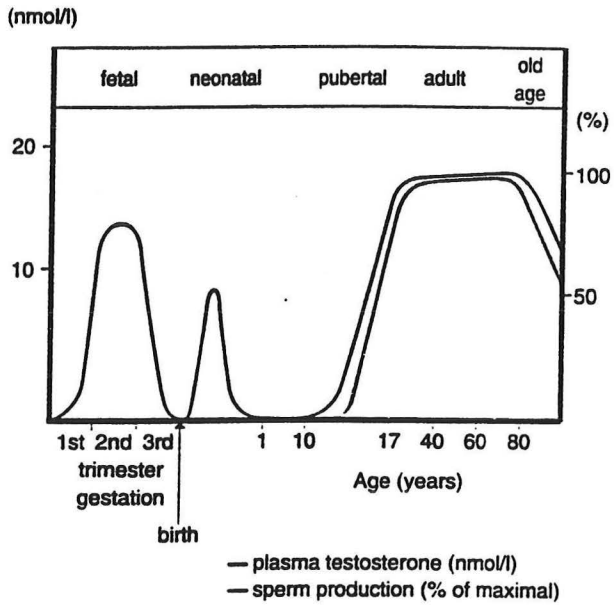

Fig. 7. Phases of male sexual function, as indicated by mean plasma testosterone level and sperm production at different phases of life. Modified from JE Griffin and JD Wilson (1980) by courtesy of WB Saunders Company.

Table XIII. SOME UNRESOLVED ISSUES ABOUT THE ROLE OF ANDROGEN IN GENDER ROLE BEHAVIOR

1. Do the androgen effects take place prenatally or postnatally?
2. Do androgens act at the level of the CNS or peripheral target tissues or both?
3. Is the action of androgen mediated by testosterone or dihydrotestosterone?

CAVEAT

As important as I believe the implications of the findings in these two disorders to be for understanding the control of gender role and gender identity in the human, it would be a mistake to imply that these disorders are a common cause of transsexual behavior. Walter Meyer and his colleagues at the UT Medical Branch 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 an action of androgen (70). Furthermore, Meyer-Bahlburg has 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 (71). 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.

SUMMARY

Genetic and endocrine evidence indicate 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 must be 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 5α-reductase and 17β-hydroxysteroid dehydrogenase do not undergo a change in gender role behavior means that other factors--social, psychological, or biological--are of equal importance in modulating human sexual behavior. It may not be a coincidence that the majority (admittedly 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 play a more important role in influencing behavior than would be the case in more egalitarian societies.

Intuitively, it seems likely that 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 (11). It may never be possible to assign quantitative importance to the roles of the two processes in human behavior, but it should be possible to determine how, where, and when in development androgen plays its role in this process.

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