

The Role of Androgens in Male Gender Role Behavior

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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 potentia, 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 hor-

mones 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, 17 β -hydroxysteroid dehydrogenase 3 and steroid 5 α -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 (7–12). 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

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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 (16–18).

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 (30–33).

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

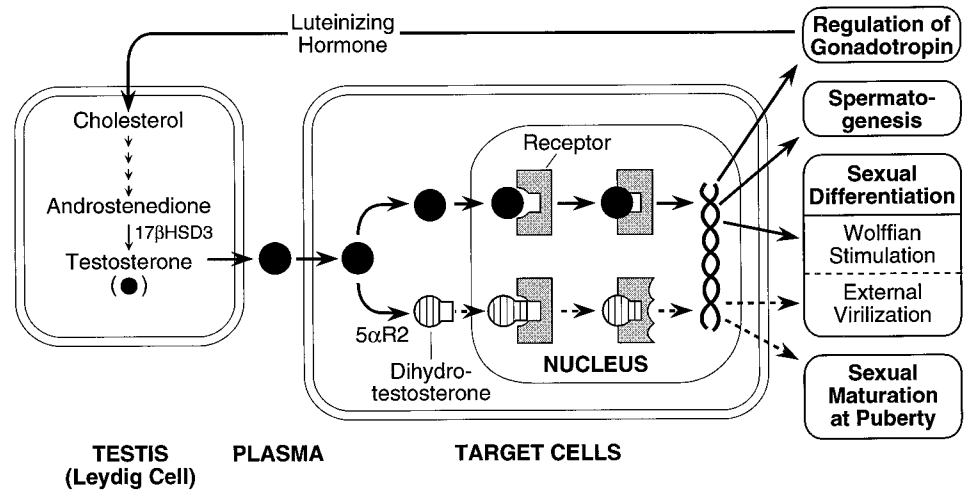
The embryos of both sexes develop in an identical fashion until the seventh week of gestation. Thereafter, the anatomic and physiological development in the two sexes diverge. As formulated by Jost (39), normal sexual development in the mammal depends on three sequential processes. The first involves 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

FIG. 1. Schematic diagram of testosterone biosynthesis in the Leydig cell of the testis and of the mechanism of androgen action within target cells. 17 β HSD3, 17 β -Hydroxysteroid dehydrogenase 3; 5 α R2, 5 α -reductase 2.



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 α -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 com-

pensatory mechanisms, adult males with 17 β -hydroxysteroid dehydrogenase 3 deficiency, mixed gonadal dysgenesis, or 5 α -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 (40–47). [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 (50–56).

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 Klinefelter 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) (60–62).

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 (66–69). 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 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 17 β -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 pseudoher-

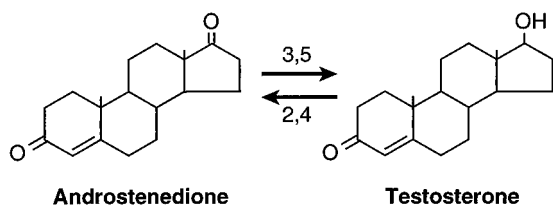


FIG. 2. The 17β -hydroxysteroid dehydrogenase reaction for the interconversion of androstenedione and testosterone. Androstenedione is believed to be converted to testosterone by isoenzymes 3 and 5, and testosterone can be oxidized to androstenedione by isoenzymes 2 and 4.

maphroditism— 5α -reductase 2 deficiency (6, 71) and 17β -hydroxysteroid dehydrogenase 3 deficiency (5, 72, 73) (Fig. 1). A similar change in gender role behavior has been described in genetic males with 3β -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. 17β -Hydroxysteroid dehydrogenase 3 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 (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).]

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 5α -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 be-

TABLE 1. Comparison of human 17β -hydroxysteroid dehydrogenase isoenzymes

	Isoenzyme				
	1	2	3	4	5
Size (amino acids)	327	387	310	737	323
Chromosome location of gene	17q21	16q24	9q22	5q2	10p14, 15
Tissue expression	Ovary, placenta	Endometrium, placenta, liver	Testis	Ubiquitous	Liver, skeletal muscle
Subcellular localization	Cytosol	Microsomes	Microsomes	Peroxisomes	Cytosol
Substrate preference	C_{18} steroids	C_{18} , C_{19} , C_{21} steroids	C_{18} , C_{19} steroids	C_{18} steroids	C_{19} , C_{21} steroids
Preferred cofactor	NADPH	NAD	NADPH	NAD	NADPH
Catalytic preference	Reduction	Oxidation	Reduction	Oxidation	Reduction
Activity in 17β HSD deficiency	Normal	Normal	Impaired	—	—

TABLE 2. 17β -Hydroxysteroid dehydrogenase 3 deficiency

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

havior (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 5α -reductase 2 deficiency

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

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).

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) dihydrotest-

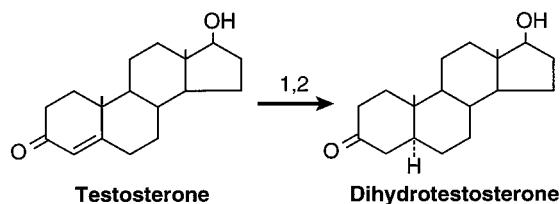


FIG. 3. The 5α -reductase reaction involved in the conversion of testosterone to dihydrotestosterone. Both isoenzymes 1 and 2 can perform this conversion.

TABLE 3. Comparison of human 5α -reductase isoenzymes

	Isoenzyme	
	1	2
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

osterone. 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

TABLE 4. 5 α -Reductase 2 deficiency

Inheritance	Autosomal recessive
Phenotype	Males
	Male Wolffian structures 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 5. Features common to 5 α -reductase 2 deficiency and 17 β -hydroxysteroid dehydrogenase 3 deficiency

1. Impairment of virilization during embryogenesis is limited to the external genitalia.
2. 46,XY males are given gender assignments and raised as females.
3. Considerable virilization takes place at the time of expected puberty.
4. In both disorders an alternate pathway exists so that the defects are incomplete, namely testosterone is formed in 17 β HSD3 deficiency, and dihydrotestosterone is formed in 5 α R2 deficiency.
5. Change in gender role behavior from female to male is common but not universal.

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 17 β -hydroxysteroid dehydrogenase 3 and steroid 5 α -reductase 2 deficiencies

5 α -Reductase 2 deficiency and 17 β -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 a 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 17 β -hydroxysteroid dehydrogenase 3 deficiency, and dihydrotestosterone can be formed by enzyme 1 in 5 α -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 indi-

viduals 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.

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).

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.

VI. Discussion

What generalizations can be drawn about behavior from the findings in these two single gene disorders? First, it seems

TABLE 6. Androgen receptor mutations

Inheritance	X-linked trait
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 7. Estrogen formation in normal men and in subjects with male pseudohermaphroditism

Group	Estradiol ($\mu\text{g/day}$)	Estrone ($\mu\text{g/day}$)
Normal men (4)		
Total	45	60
Extraglandular aromatization	39	60
Secretion	6	0
Testicular feminization (4)		
Total	77	114
Extraglandular aromatization	33	101
Secretion	44	13

Mean values have been taken from P. C. MacDonald *et al.* (37). The number of individuals studied in each group is given in parentheses.

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 estrogen 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

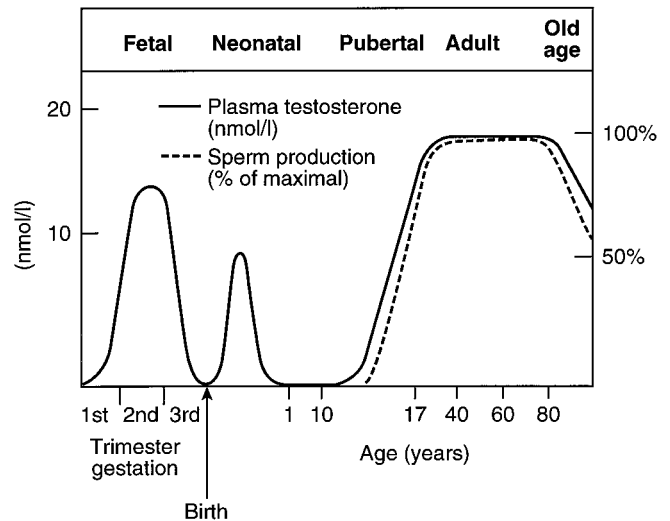


FIG. 4. The phases of male sexual life as indicated by mean plasma testosterone level as a function of age. Sperm production occurs only during the adult phase. [Modified from Griffin JE, Wilson JD 1980 The testis. In: Metabolic Control and Disease, Bondy PK, Rosenberg LE (eds) with permission from W.B. Saunders, Philadelphia. Based on the formulation of J.S.D. Winter *et al.*: *J Clin Endocrinol Metab* 42:679-686, 1976.]

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.

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 5α -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

1. Phoenix CH, Goy RW, Young WC 1967 Sexual behavior: general aspects. In: Martini L, Ganong WF (eds) Neuroendocrinology. Academic Press, New York, vol 2:163–196
2. Davidson JM 1972 Hormones and reproductive behavior. In: Levine S (ed) Hormones and Behavior. Academic Press, New York, pp 63–103
3. Money J 1994 The concept of gender identity disorder in childhood and adolescence after 39 years. *J Sex Marital Ther* 20:163–171
4. Herdt G 1997 Same Sex Different Cultures. Westview Press, Boulder, CO, p 47
5. Imperato-McGinley J, Peterson RE, Stoller R, Goodwin WE 1979 Male pseudohermaphroditism secondary to 17β -hydroxysteroid dehydrogenase deficiency: gender role change with puberty. *J Clin Endocrinol Metab* 49:391–395
6. Imperato-McGinley J, Peterson RE, Gautier T, Sturla E 1979 Androgens and the evolution of male-gender identity among male pseudohermaphrodites with 5α -reductase deficiency. *N Engl J Med* 300:1233–1237
7. Resko JA 1975 Fetal hormones and their effect on the differentiation of the central nervous system in primates. *Fed Proc* 34:1650–1655
8. Beach FA 1977 Courtship and mating. In: Beach FA (ed) Human Sexuality in Four Perspectives. Johns Hopkins Press, Baltimore, pp 247–267
9. Whalen RE 1977 Brain mechanisms controlling sexual behavior. In: Beach FA (ed) Human Sexuality in Four Perspectives. Johns Hopkins Press, Baltimore, pp 215–246
10. Goy RW, Bercovitch FB, McBair MC 1988 Behavioral masculinization is independent of genital masculinization in prenatally androgenized female rhesus macaques. *Horm Behav* 22:552–571
11. Wallen K 1996 Nature needs nurture: the interaction of hormonal and social influences on the development of behavioral sex differences in rhesus monkeys. *Horm Behav* 30:364–378
12. Adkins-Regan E 1988 Sex hormones and sexual orientation in animals. *Psychobiology* 16:335–347
13. Zumpe D, Michael RP 1985 Effects of testosterone on the behavior of male cynomolgus monkeys (*Macaca fascicularis*). *Horm Behav* 19:265–277
14. Clancy AN, Bonsall RW, Michael RP 1992 Immunohistochemical labeling of androgen receptors in the brain of rat and monkey. *Life Sci* 50:409–417
15. Clancy AN, Michael RP 1994 Effects of testosterone and aromatase inhibition on estrogen receptor-like immunoreactivity in male rat brain. *Neuroendocrinology* 59:552–560
16. McEwen BS 1980 Gonadal steroids: humoral modulators of nerve-cell function. *Mol Cell Endocrinol* 18:151–164
17. Celotti F, Massa R, Martini L 1979 Metabolism of sex steroids in the central nervous system. In: DeGroot LJ (ed) Endocrinology, Grune and Stratton, New York, pp 48–53
18. Wehling M 1997 Specific, nongenomic actions of steroid hormones. *Annu Rev Physiol* 59:365–393
19. Mann DR, Gould KG, Collins DC, Wallen K 1989 Blockade of neonatal activation of the pituitary-testicular axis: effect on peripubertal luteinizing hormone and testosterone secretion and on testicular development in male monkeys. *J Clin Endocrinol Metab* 68:600–667
20. Phoenix CH, Goy RW, Gerall AA, Young WC 1959 Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology* 65:600–667
21. Gorski RA, Gordon JH, Shryne JE, Southam AM 1978 Evidence for a morphological sex difference within the medial preoptic area of the rat brain. *Brain Res* 148:333–346
22. Reiter EO, Grumbach MM, Kaplan SL, Conte FA 1975 The response of pituitary gonadotropes to synthetic LRF in children with glucocorticoid-treated congenital adrenal hyperplasia: lack of effect of intrauterine and neonatal androgen excess. *J Clin Endocrinol Metab* 40:318–325
23. Arnold AP 1980 Sexual differences in the brain. *Am Sci* 80:165–173
24. Schlinger BA 1998 Sexual differentiation of avian brain and behavior. *Annu Rev Physiol* 60:407–429
25. Beach FA 1948 Hormones and Behavior. Harper (Hoeber), New York, pp 20–29
26. Bremer J 1959 Asexualization. A Follow-up Study of 244 Cases. Macmillan, New York
27. Davidson JM, Camargo CA, Smith ER 1979 Effects of androgen on sexual behavior in hypogonadal men. *J Clin Endocrinol Metab* 48:955–958
28. Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ 1992 A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *J Androl* 13:297–304
29. Zumpe D, Bonsall RW, Michael RP 1993 Effects of the nonsteroidal aromatase inhibitor, fadrozole on the sexual behavior of male cynomolgus monkeys (*Macaca fascicularis*). *Horm Behav* 27:200–215
30. Rees HD, Bonsall RW, Michael RP 1988 Localization and identification of nuclear radioactivity in the pituitary gland and genital tract after administration of ^3H -testosterone, ^3H -dihydrotestosterone, or ^3H -estradiol to male rhesus monkeys. *Cell Tissue Res* 254:139–146
31. Michael RP, Bonsall RW, Rees HD 1986 The nuclear accumulation of [^3H]testosterone and [^3H]estradiol in the brain of the female primate: evidence for 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
34. Waxenberg SE, Drellich MG, Sutherland AM 1959 The role of hormones in human behavior I. Changes in female sexuality after adrenalectomy. *J Clin Endocrinol Metab* 19:193–202
35. Schon M, Sutherland AM 1960 The role of hormones in human behavior. III. Changes in female sexuality after hypophysectomy. *J Clin Endocrinol Metab* 20:833–841
36. Siiteri PK, MacDonald PC 1973 Role of extraglandular estrogen in human endocrinology. In: Greep RO, Astwood EB (eds) Handbook of Physiology. American Physiological Society, Washington, DC, Sect 7, vol 7:615–629
37. MacDonald PC, Madden JD, Brenner PF, Wilson JD, Siiteri PK 1979 Origin of estrogen in normal men and in women with testicular feminization. *J Clin Endocrinol Metab* 49:905–916
38. Wilson JD 1979 Metabolism of testicular androgens. In: Greep RO, Astwood EB (eds) Handbook of Physiology. American Physiological Society, Washington DC, vol 5:491–508

39. **Jost A** 1972 A new look at the mechanism controlling sex differentiation in mammals. *Johns Hopkins Med J* 130:38–53
40. **Baker SW** 1980 Psychosexual differentiation in the human. *Biol Reprod* 22:61–72
41. **Money J, Hampson JG, Hampson JL** 1955 Hermaphroditism: recommendations concerning assignment of sex, change of sex, and psychologic management. *Bull Johns Hopkins Hosp* 97:301–319
42. **Ehrhardt AA, Epstein R, Money J** 1968 Fetal androgens and female gender identity in the early-treated adrenogenital syndrome. *Johns Hopkins Med J* 122:160–167
43. **Ehrhardt AA, Evers K, Money J** 1968 Influence of androgen and some aspects of sexually dimorphic behavior in women with the late-treated adrenogenital syndrome. *Johns Hopkins Med J* 123:115–122
44. **Money J** 1968 Sex reassignment as related to hermaphroditism and transsexualism. In: Green R, Money J (eds) *Transsexualism and Sex Reassignment*. Johns Hopkins Press, Baltimore, pp 91–113
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
47. **Hines M, Kaufman FR** 1994 Androgen and the development of human sex-typical behavior: rough-and-tumble play and sex of preferred playmates in children with congenital adrenal hyperplasia (CAH). *Child Dev* 65:1042–1053
48. **Lim YJ, Batch JA, Warne GL** 1995 Adrenal 21-hydroxylase deficiency in childhood: 25 years' experience. *Pediatr Child Health* 31:222–227
49. **Meyer-Bahlburg HFL, Gruen RS, New MI, Bell JJ, Morishima A, Shimshi M, Bueno Y, Vargas I, Baker SW** 1996 Gender change from female to male in classical congenital adrenal hyperplasia. *Horm Behav* 30:319–332
50. **Yalom ID, Green R, Fisk N** 1973 Prenatal exposure to female hormones. Effect on psychosexual development in boys. *Arch Gen Psychiatry* 28:554–561
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 psychological development in humans and animals: with a note on the state of the field. In: Sachar EJ (ed) *Hormones, Behavior, and Psychopathology*. Raven Press, New York, pp 69–94
53. **Reinisch JM** 1977 Prenatal exposure of human foetuses to synthetic progestin and oestrogen affects personality. *Nature* 266:561–562
54. **Meyer-Bahlburg HFL, Grisanti GC, Ehrhardt AA** 1977 Prenatal effects of sex hormones on human male behavior: medroxyprogesterone acetate (MPA). *Psychoneuroendocrinology* 2:383–390
55. **Ehrhardt AA, Grisanti GC, Meyer-Bahlburg HFL** 1977 Prenatal exposure to medroxyprogesterone acetate (MPA) in girls. *Psychoneuroendocrinology* 2:391–398
56. **Lish JD, Ehrhardt AA, Meyer-Bahlburg HFL, Rosen LR, Gruen RS, Veridiano NP** 1991 Gender-related behavior development in females exposed to diethylstilbestrol (DES) *in utero*: an attempted replication. *J Am Acad Child Adolesc Psychiatry* 30:29–37
57. **Ramsay M, Bernstein R, Zwane E, Page DC, Jenkins T** 1988 XX true hermaphroditism in Southern African blacks: an enigma of primary sexual differentiation. *Am J Hum Genet* 43:4–13
58. **Ehrhardt A, Greenberg N, Money J** 1970 Female gender identity and absence of fetal gonadal hormones: Turner's syndrome. *Johns Hopkins Med J* 126:237–248
59. **Federman DD** 1967 *Abnormal Sexual Development. A Genetic and Endocrine Approach to Differential Diagnosis*. WB Saunders, Philadelphia
60. **Masica DN, Money J, Ehrhardt AA** 1971 Fetal feminization and female gender identity in the testicular feminizing syndrome of androgen insensitivity. *Arch Sex Behav* 1:131–142
61. **Ahlquist JAO** 1994 Gender identity in testicular feminisation (letter). *Br Med J* 308:1041
62. **Money J, Ogunro C** 1974 Behavioral sexology: ten cases of genetic male intersexuality with impaired prenatal and pubertal androgenization. *Arch Sex Behav* 3:181–205
63. **Money J** 1977 Determinants of human gender identity/role. In: Money J, Musaph H (eds) *Handbook of Sexology*. Elsevier, Amsterdam, pp 57–79
64. **Lev-Ran A** 1974 Gender role differentiation in hermaphrodites. *Arch Sex Behav* 3:391–424
65. **Wilson JD** 1982 Gonadal hormones and sexual behavior. In: Besser GM, Martini L (eds) *Clinical Neuroendocrinology*. Academic Press, New York, vol 2:1–29
66. **Money J, Devore H, Norman BF** 1986 Gender identity and gender transposition: longitudinal outcome study of 32 male hermaphrodites assigned as girls. *J Sex Marital Ther* 12:165–181
67. **Brown JB, Fryer MP** 1964 Plastic surgical correction of hypospadias with mistaken sex identity and transvestism resulting in normal marriage and parenthood. *Surg Gynecol Obstet* 118:45–46
68. **Berg I, Nixon HN, MacMahon R** 1963 Change of assigned sex at puberty. *Lancet* 2:1216–1219
69. **Money J, Norman BF** 1987 Gender identity and gender transposition: longitudinal outcome study of 24 male hermaphrodites assigned as boys. *J Sex Marital Ther* 13:75–92
70. **Stoller RJ** 1964 A contribution to the study of gender identity. *Int J Psychoanal* 45:220–226
71. **Kuttent F, Mowszowicz I, Wright F, Baudat N, Jaffial C, Robin M, Mauvais-Jarvis P** 1979 Male pseudohermaphroditism: a comparative study of one patient with 5 α -reductase deficiency and three patients with the complete form of testicular feminization. *J Clin Endocrinol Metab* 49:861–865
72. **Akesode FA, Meyer III WJ, Migeon CJ** 1977 Male pseudohermaphroditism with gynaecomastia due to testicular 17-ketosteroid reductase deficiency. *Clin Endocrinol (Oxf)* 7:443–452
73. **Rosler A, Kohn G** 1983 Male pseudohermaphroditism due to 17 β -hydroxysteroid dehydrogenase deficiency: studies on the natural history of the defect and effect of androgens on gender role. *J Steroid Biochem* 19:663–674
74. **Mendonca BB, Bloise W, Arnhold JJP, Batista MC, de Almeida Toledo SP, Drummond MCF, Nicolau W, Mattar E** 1987 Male pseudohermaphroditism due to nonsalt-losing 3 β -hydroxysteroid dehydrogenase deficiency: gender role change and absence of gynaecomastia at puberty. *J Steroid Biochem* 28:669–675
75. **Andersson S, Russell DW, Wilson JD** 1996 17 β -Hydroxysteroid dehydrogenase 3 deficiency. *Trends Endocrinol Metab* 7:121–126
76. **Geissler WM, Davis DL, Wu L, Bradshaw KD, Patel S, Mendonca BB, Elliston KO, Wilson JD, Russell DW, Andersson S** 1994 Male pseudohermaphroditism caused by mutations of testicular 17 β -hydroxysteroid dehydrogenase 3. *Nat Genet* 7:34–39
77. **Saez JM, de Peretti E, Morera AM, David M, Bertrand J** 1971 Familial male pseudohermaphroditism with gynaecomastia due to a testicular 17-ketosteroid reductase defect. *J Clin Endocrinol* 32:604–610
78. **Andersson S, Geissler WM, Wu L, Davis DL, Grumbach MM, New MI, Schwarz HP, Blethen SL, Mendonca BB, Bloise W, Witchel SF, Cutler Jr GB, Griffin JE, Wilson JD, Russell DW** 1996 Molecular genetics and pathophysiology of 17 β -hydroxysteroid dehydrogenase 3 deficiency. *J Clin Endocrinol Metab* 81:130–136
79. **Moghrabi N, Hughes IA, Dunaif A, Andersson S** 1998 Deleterious missense mutations and silent polymorphisms in the human 17 β -hydroxysteroid dehydrogenase 3 gene (HSD17B3). *J Clin Endocrinol Metab* 83:2855–2860
80. **Lanes R, Brown TR, de Bustos EG, Valverde B, Pieretti RB, Bianco N, Ortega G, Migeon CJ** 1983 Sibship with 17-ketosteroid reductase (17-KSR) deficiency and hypothyroidism. Lack of linkage of histocompatibility leucocyte antigen and 17-KSR loci. *J Clin Endocrinol Metab* 57:190–196
81. **Russell DW, Wilson JD** 1994 Steroid 5 α -reductase: two genes/two enzymes. *Annu Rev Biochem* 63:25–61
82. **Wilson JD, Griffin JE, Russell DW** 1993 Steroid 5 α -reductase 2 deficiency. *Endocr Rev* 14:577–593
83. **Griffin JE, McPhaul MJ, Russell DW, Wilson JD** 1999 The androgen resistance syndromes: steroid 5 α -reductase 2 deficiency, testicular feminization, and related disorders. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, Childs B (eds) *The Metabolic and Molecular Basis of Inherited Disease*, ed 8. McGraw-Hill, New York, in press
84. **Thigpen AE, Silver RI, Guileyaedo JM, Case ML, McConnell JD,**

- Russell DW 1993 Tissue distribution and ontogeny of steroid 5 α -reductase isozyme expression. *J Clin Invest* 92:903-910
85. Mendonca BB, Inacio M, Costa EMF, Arnhold IJP, Silva FAQ, Nicolau W, Bloise W, Russell DW, Wilson JD 1996 Steroid 5 α -reductase 2 deficiency: diagnosis, psychological evaluation, and management. *Medicine* 75:64-76
 86. Mendez JP, Ulloa-Aguirre A, Imperato-McGinley J, Brugmann A, Delfin M, Chavez B, Shackleton C, Kofman-Alfaro S, Perez-Palacios G 1995 Male pseudohermaphroditism due to primary 5 α -reductase deficiency: variation in gender identity in seven Mexican patients from five different pedigrees. *J Endocrinol Invest* 18:205-213
 87. Canto P, Vilchis F, Chavez B, Mutchinick O, Imperato-McGinley J, Perez-Palacios G, Ulloa-Aguirre A, Mendez JP 1997 Mutations of the 5 α -reductase type 2 gene in eight Mexican patients from six different pedigrees with 5 α -reductase-2 deficiency. *Clin Endocrinol (Oxf)* 46:155-160
 88. Al-Attia HM 1996 Gender identity and role in a pedigree of Arabs with intersex due to 5 α reductase-2 deficiency. *Psychoneuroendocrinology* 21:651-657
 89. Foucault M 1980 Herculine Barbin: Being the Recently Discovered Memoirs of a Nineteenth-Century French Hermaphrodite. Pantheon Books, New York
 90. Dreger AD 1998 Hermaphrodites and the Medical Invention of Sex. Harvard University Press, Cambridge, MA
 91. Price P, Wass JAH, Griffin JE, Leshin M, Savage MO, Large DM, Bu'Lock DE, Anderson DC, Wilson JD, Besser GM 1984 High dose androgen therapy in male pseudohermaphroditism due to 5 α -reductase deficiency and disorders of the androgen receptor. *J Clin Invest* 74:1496-1508
 92. Köbberling J, König A, Meyer JE 1972 Transsexualismus bei testiculärer feminisierung. *Klin Wochenschr* 50:696-701
 93. Gooren L, Cohen-Kettenis PT 1991 Development of male gender identity/role and a sexual orientation towards women in a 46,XY subject with an incomplete form of the androgen insensitivity syndrome. *Arch Sex Behav* 20:459-470
 94. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lubahn DB, Korach KS 1994 Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med* 331:1056-1061
 95. Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J, Korach K, Simpson ER 1997 Effect of testosterone and estradiol in a man with aromatase deficiency. *N Engl J Med* 337:91-95
 96. Bilzkeian JP, Morishima A, Bell J, Grumbach MM 1998 Increased bone mass as a result of estrogen therapy in a man with aromatase deficiency. *N Engl J Med* 339:599-603
 97. Meyer III WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA 1986 Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 15:121-138
 98. Meyer-Bahlburg HFL 1994 Intersexuality and the diagnosis of gender identity disorder. *Arch Sex Behav* 23:21-40

Fifth International Symposium on Neurobiology and Neuroendocrinology of Aging Bregenz, Austria—July 23–28, 2000

The topics will include, among others, interrelationships between the different types of pathologies that contribute to cognitive decline and dementia, brain glucose and energy metabolism in sporadic Alzheimer, genetics of Alzheimer disease, behavioral changes during aging, cell cycle regulation in aging, estrogens and aging, reproductive aging in men, transgenic animals as models for degenerative diseases, circadian disturbances in the elderly, aging and hypothalamic control of episodic release of pituitary hormones, nutraceutical formulations that slow aging and treat age-related diseases, caloric restriction, and demography of longevity.

The invited speakers include: P. Berger, Austria; J. A. Edwardson, UK; S. Hoyer, Germany; J. P. Huston, Germany; A. Iguchi, Japan; P. Jansen-Dürr, Austria; M. Jucker, Switzerland; A. Maggi, Italy; M. A. Pericak-Vance, USA; B. Sommer, Switzerland; R. E. Tanzi, USA; E. J. W. Van Someren, The Netherlands; J. D. Veldhuis, USA; B. Villeponteau, USA; R. Weinruch, USA; J. R. Wilmoth, USA.

The site of the Symposium will be the Mehrerau Monastery (built in 1090), which lies on the eastern shore of the Lake of Constance (the Bodensee) in the city of Bregenz, Austria.

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