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Postnatal Gonadal Steroid Effects on Human Behavior

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In many mammalian species, prenatal or early postnatal exposure to sex steroid hormones exerts an organizing effect on certain aspects of central nervous system (CNS) function and alters CNS responsiveness to later hormone stimulation (*1, 2*). For many sexually dimorphic behaviors (those differing in males and females), it seems necessary that the male CNS be exposed to increased levels of gonadal steroids during early development and that the female not experience this early hormonal stimulation. For some behaviors, this early hormonal exposure is all that appears to be of consequence. For example, prenatal exposure of female rhesus monkeys to gonadal steroids appears to be the only requisite for their increased male-like play behavior as juveniles and increased aggressive behavior in adulthood. Administration of gonadal steroids in postnatal life also can be behaviorally activating; for example, the expression of male-like sexual behavior in adult female rhesus monkeys requires concurrent androgenic stimulation in adulthood in addition to prenatal exposure to testosterone.

Another type of gonadal steroid activation appears not to require a specific early hormonal exposure for its effect. For example, long-term testosterone treatment of normal adult female hamsters and ovariectomized adult female rhesus monkeys results in the display of some male-like sexual behaviors—such as male mounting and intromission patterns in hamsters, and yawning, sex exploration, and sex display in monkeys—even though these animals were not exposed to testosterone before or immediately after birth. Therefore, in the few mammalian species studied, long-term exposure to gonadal steroids in adulthood also can elicit certain sexually dimorphic behaviors in the absence of organization or alteration of CNS responsiveness by these hormones during early development.

Many investigators are attempting to extend the data regarding the postnatal gonadal steroid activation of sexually dimorphic behaviors from animals to man. Relevant information is being obtained by the observation of behavior and concomitant evaluation of hormone levels in subjects whose hormonal status or behavioral repertoire furnishes an opportunity to study conditions other than normal ones. These include individuals

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who exhibit unusually high or aberrant levels of sexually dimorphic behavior or who suffer from clinical endocrine syndromes that mimic certain experimental animal manipulations. In this article we survey three areas of research on human subjects in order to illustrate (i) the diversity of putative postnatal gonadal steroid influences on human sexually dimorphic behavior, and (ii) the methodologic difficulties in assessing both the endocrine and the behavioral components of these psychoendocrine interactions.

Summary. Gonadal steroid hormones, active during fetal life, continue after the birth of a fetus to influence the central nervous system and affect behavior. The characteristically different circulating concentrations of male and female steroid hormones in men and women appear to be partial determinants of certain sexually dimorphic behaviors, interacting in a complex way with psychological and sociocultural factors as well as with other biological factors. This interaction is highlighted in research on testosterone and aggression in men, mood and the menstrual cycle in women, and pubertal sex role reversal in pseudohermaphrodites.

Testosterone and Aggression in Men

Testosterone is thought to have an activating effect on human aggressive behavior. Its action on the CNS appears to contribute to the heightened self-assertiveness and other-directed activity of boys and men compared to girls and women. However, the question arises whether, among men, inter-individual differences in the amount of testosterone reaching the brain and interacting with receptors play some role in determining inter-individual differences in aggressive and hostile feelings and subsequent behavior. Approaches to this question have included correlating circulating testosterone in blood with subjectively felt hostility and overtly aggressive behavior in normal and antisocial men, examining men with genetic differences in testosterone production for differences in aggressive behavior, and elucidating the effects on behavior of administered testosterone and antiandrogenic agents.

Studies relating measures of testosterone secretion to measures of hostility, aggressive behavior, and social dominance in men can be divided into those in which psychological rating scales were used to quantify hostility in otherwise normal subjects, and those in which indices of overtly aggressive and violent acts in antisocial individuals, mainly prisoners, were used (*3, 3a*). In the former group of studies, done on normal volunteers such as male college students, older men, and athletes, the results have been variable. In these subjects there was no consistent correlation between circulating testosterone and various measures of hostility or aggression (*3, 3a*). Because normal individuals generally do not show overtly aggressive behavior, reliance must be placed on self-report measures such as the Buss-Durkee hostility inventory, a 75-item paper-and-pencil test that subjectively assesses such factors as assaultive behavior, indirect and verbal hostility, irritability, and resentment. One problem with this and other self-report tests is that they may reflect more the immediate state of the individual rather than any relatively stable, long-term behavior patterns.

In contrast, studies of plasma testosterone in overtly aggressive, assaultive, and violent male prisoners have been somewhat more consistent in demonstrating a relation between such behaviors and increases in circulating testosterone (*3, 3a*). Plasma testosterone concentrations often do not differ between fighting and nonfighting prisoners, nor do they correlate with psychological test scores, including those from the Buss-Durkee inventory. However, groups of prisoners with long and vivid histories of more violent and aggressive crimes in adolescence or before their incarceration (such as rapist-murderers) have been found to have significantly higher mean levels of circulating testosterone than prisoners without such histories. Thus, in populations predisposed by social factors to develop antisocial behavior, testosterone might be an additional, endocrine factor placing some persons at risk to commit more aggressive crimes.

The relation between testosterone and behavior is clearer in individuals with pathologic alterations of testosterone levels, including those changes secondary to genetic anomalies, and in individuals with induced alterations in testosterone levels. A large reduction in circulating testosterone diminishes a number of behavioral characteristics in men, including aggressiveness and sexual appetite. These effects are considerably more pronounced if the hormone reduction occurs before puberty than if it occurs after puberty; the profound effects of castration on prepubertal boys have been known for 2000 years. Certain chromosomal abnormalities can produce prepubertal hypogonadism, notably 47,XXY (Klinefelter's syndrome) and its variants (*4–6*). In this syndrome, a dysgenesis of the testes begins in late fetal development and continues throughout childhood and puberty, so that in the adult XXY male the endocrine function of the testes is frequently reduced.

Individuals who are XXY manifest characteristic physical features including small testes, lack of sperm production, and a tall, eunuchoid body build with little facial hair. Depending on the sources of the sample studied (such as mental institutions and military populations), varying degrees of mental retardation and psychiatric disturbance also have been noted (*7*). Average behavioral traits described for several samples of Klinefelter's patients include passivity, dependence, mental slowness and shallowness, and diminished sexual drive with indeterminant sexual orientation, although specific individuals may show none of these characteristics and appear relatively normal behaviorally.

These patients often respond both physically and behaviorally to treatment with testosterone (*8*). Development of a masculine body build with increased muscle mass and male secondary sex characteristics, and increased sexual interest including heterosexual fantasies, penile erections, and overt sexual behavior, can result from this hormone treatment. Exogenously administered testosterone frequently has these same effects in hypogonadal men, regardless of the cause of their hypogonadism (*9*).

Whereas androgen deficiency states such as Klinefelter's syndrome have been well documented, and the clinical improvements in sexual behavior resulting from testosterone treatment of hypogonadal men have been frequent, conditions of androgen excess with concomitant behavioral disturbances have not yet been documented. Toward this end, the relation between testosterone and behavior has been examined in men with another chromosomal abnormality, the 47,XYY karyotype. Whereas Klinefelter's (XXY) patients have at least one additional X chromosome, XYY subjects have an extra Y chromosome. After the initial reporting of this karyotype in 1961, chromosomal surveys of hospital inmates with persistently violent behavior revealed a number of new cases. This suggested a putative relation between the extra Y chromosome and hyperaggressive behavior in men (*10, 11*),

analogous to the increased aggression that follows the experimental breeding of an extra Y chromosome in Japanese fighting fish (*12*).

The hypothesis has been proposed that increased testosterone secretion might be a hormonal mediator of such behavior, but the endocrine data on XYY individuals are conflicting. Plasma testosterone in XYY's, while showing a large variability among subjects, was almost always comparable to that in control subjects and rarely above the normal range (*3a, 13*). One methodologic problem is that most hormone measurements have been made on a single blood sample taken from each subject, which is similar to the methodologies used in the aforementioned studies of testosterone concentrations in prisoners with histories of violent crimes. Another concern is that the behavior disturbances of XYY individuals, while impulsive and antisocial, show a dearth of violent acts toward other persons (*10, 11*). Many XYY subjects also are mentally retarded and institutionalized, both of which factors may contribute to their impulsive, antisocial behavior.

Just as the administration of testosterone has been used to normalize sexual drive and sexual activity in hypogonadal men, the administration of antiandrogenic agents, such as cyproterone and medroxyprogesterone, has been used to reduce aberrant sexual behaviors in men with these antisocial tendencies (*14, 15*). These compounds have antigonadotropic and progestogenic as well as antiandrogenic properties, lowering both circulating gonadotropins and testosterone. Individuals treated with these agents generally have had normal basal circulating testosterone levels, and have required a reduction of 50 to 75 percent, to within the hypogonadal range, to effect a behavioral improvement.

The genetic and behavioral characteristics of patients successfully treated with antiandrogenic agents are varied and include XYY men. Individuals with compulsive sexual thoughts, often of a paraphilic nature, and with impulsive and aggressive overt sexual behaviors have been treated successfully. The behavioral effects of the antiandrogens appear to be specific for disordered sexual thoughts and behaviors; these drugs are less effective in reducing nonsexual violent outbursts. (Their effect on nonsexual antisocial behaviors may be related to their progestational characteristics, which include a general lowering of neuronal excitability.)

Money *et al.* (*15*) described the behavioral characteristics of a number of successfully treated patients. The panoply of paraphilias included homosexual and heterosexual pedophilia, homosexual masochism, homosexual incest and transvestism, and heterosexual exhibitionism. Not only were these overt behaviors controlled with antiandrogen treatment, but erotic mental imagery also was reduced. Money *et al.* pointed out that the insistent and compulsive mental imagery of the illegal erotic practices was especially disturbing to the patients, who were relieved by the reduction of this imagery with treatment. Actual erotic practices were reduced by 50 to 100 percent. For such individuals, the most effective treatment has been pharmacotherapy with antiandrogens combined with a well-designed, strong program of counseling and psychotherapy.

Thus, there is a demonstrated activating effect of androgens on certain aggressive behaviors in men, but only when the amount of circulating androgen is altered to a great extent. More subtle effects of inter-individual differences in androgen secretion within the generally accepted normal range also may occur, but these have not yet been satisfactorily documented, and, if they indeed do occur, appear to be strongly modulated by psychosocial factors.

Mood and the Menstrual Cycle

A second important area of presumptive hormonal influence on sexually dimorphic behavior occurring in women concerns changes in feelings, behavior, and social interactions in relation to the menstrual cycle. In some women, negative (dysphoric) affects occur regularly for 7 to 10 days prior to the onset of menses (*16*). Transient alterations in psychological state also may be associated with menstruation itself, as well as with the presumed time of ovulation, or midcycle. Disturbances occurring around the time of menstruation include the physically painful syndrome occurring during menses (dysmenorrhea) and dysphoric premenstrual affective changes, the so-called premenstrual tension syndrome (PMTS). There may be an overlap in symptoms when negative affects are associated with the discomfort of dysmenorrhea and when there is premenstrual pain or fluid retention.

In dysmenorrhea, somatic changes seem to be of primary importance. In dysmenorrheic women the incidence of primary psychopathology, such as neuroticism, is not increased, and it is uncommon for emotional changes to appear during menses unless there are physical symptoms. In contrast, the relation of PMTS to physical changes, psychiatric disorder, and sociocultural factors is less clear. Premenstrual negative, dysphoric affects have been attributed to fluid retention and edema, but some women become severely incapacitated psychologically while suffering little physical discomfort (*17*). The importance of personality features and preexisting psychopathology, the specific behavioral consequences of hormonally induced changes in the CNS, and the effects on women of negative sociocultural attitudes toward menstruation have been studied as potential contributing factors in PMTS (*18*). However, there has been disagreement on the phenomena that constitute this syndrome. Some investigators have studied groups of psychiatric patients, students, or prison inmates, who may not be comparable to other, larger groups of women with PMTS, and the severity of affective and behavioral disturbances in PMTS can vary widely among individuals. Recent observations of only those behavior changes specific to the premenstruum, classified according to psychiatric research diagnostic criteria (RDC) (*19*), revealed no overt psychiatric disorder during the follicular phase in 42 women, but, if the RDC duration-of-symptoms criterion was reduced from 2 weeks to 2 days, all met the diagnosis of major depressive disorder during the premenstruum (*20*). However, their dysphoria was predominantly irritability, tension, and affective lability, and none could be classified as having the endogenous subtype of major depressive disorder.

Since the early reports of premenstrual syndromes, their possible relation to gonadal steroid and other hormone dysregulations has been studied. The theories receiving most attention have been those of estrogen excess, progesterone deficiency or withdrawal, and altered ratio of estrogen to progesterone. Investigators of hormone levels in women with PMTS have, for the most part, not demonstrated the postulated abnormality or have found it only in small subgroups of subjects (*17*). Some theories have been supported by the finding of positive responses to treatments aimed at correcting these hormone abnormalities (*21*), but several coded studies have failed to replicate the earlier positive findings (*17, 22*). Theories of estrogen-progesterone imbalance are further weakened by the general absence of mood disorders in the follicular phase of the menstrual cycle, when there is more circulating estrogen than progesterone,

and by the normal occurrence of progesterone withdrawal prior to menses. The relation of oral contraceptives to PMTS also is unclear (*17, 23*). The use of oral contraceptives to treat PMTS is a form of gonadal hormone manipulation, but an understanding of their mode of action and the criteria for identification of likely responders remain to be established.

Sociocultural factors are interrelated to the endocrine changes of PMTS in a complex way. Adverse psychological attitudes toward menses by families and larger social groups are widespread (*16, 18, 24*). Some investigators have proposed that menstrual distress is largely a result of the negative associations that society at large may attach to menses, being an exaggeration of whatever somatic discomfort may occur in relation to menstruation (*25*). Restrictive religious attitudes toward sexual activity during menses also have been cited to support this view (*26*). An occurrence of PMTS primarily in women who "reject their feminine role" has been both claimed and disputed (*27*). Not surprisingly, most of the reports emphasizing the influence of the mother-daughter relationship, particularly with reference to women's menarchal experiences as antecedents to perimenstrual disturbances, suffer from the methodologic defect of retrospective collection of data. Thus, sociocultural and psychological factors, while believed by most investigators to play an important role in PMTS, remain to be clearly delineated and quantified. The alterations in mood and behavior that occur in some women in relation to menses are undoubtedly the result of several interacting hormonal and psychological influences that can vary considerably among individuals and over time. Although it may be advantageous to attempt to isolate the effects of a single variable, women in whom only one factor is responsible for their perimenstrual dysphoria thus far have been found but rarely.

Pubertal Sex Role Reversal in Pseudohermaphrodites

A third important area of research is the psychoendocrinology of shifts in gender identity (subjective belief in oneself as a male or female) and gender role (sex behavior practices) in male pseudohermaphrodites reported to occur at the time of puberty. Imperato-McGinley *et al.* (*28, 29*) described pubertal shifts from female to male gender identity in an interrelated group of male pseudohermaphrodites from two rural communities in the Dominican Republic and inferred that testosterone exposure during the prenatal, perinatal, and, especially, pubertal stages of development is the most significant factor in the normal differentiation of male gender identity. In contrast, to this hormonal theory, the more widely held contemporary view is that the sex of rearing, as established by early parental and social influences, is the primary determinant of gender identity (*2, 30*). Thus, as might be expected, the reports on the Dominican kindred have generated some controversy (*31, 32*), and they serve to highlight some of the difficulties in obtaining and interpreting retrospective psychosocial data.

Individuals born with male pseudohermaphroditism type 2 are characterized at birth by (i) male sex chromosomes (XY); (ii) profound ambiguity of the external genitalia (severe hypospadias with the urogenital sinus opening on the perineum, clitoral-like phallus, bifid scrotum, and some degree of labioscrotal fusion); (iii) normal differentiation of the male internal genitalia; and (iv) testes present in the inguinal canals or labioscrotal folds. Without treatment, these individuals experience partial virilization at puberty, including deepening of the voice; an increase in muscle mass; growth of the phallus with erections and ejaculation from the perineal urethra; enlargement and descent of the testes (if not already present in the scrotum); elongation, rugation, and pigmentation of the scrotum; and lack of breast development. However, several masculine pubertal events do not occur: there is little or no beard growth, no temporal hairline regression or acne, and a small or absent prostate. In summary, on superficial inspection these individuals appear to be females at birth and males subsequent to the hormonal events of puberty.

The endocrinologic basis for this complex of developmental phenomena in pseudohermaphrodites has been elucidated during the last several years (*28, 29, 33–36*). Because of a genetically determined deficiency of the enzyme Δ^4 steroid 5α-reductase, the formation of dihydrotestosterone (DHT) from testosterone is abnormally low. Since DHT is the putative hormonal mediator of the differentiation of the genital tubercle, fold, swelling, and sinus into the male external genitalia, the ambiguity of the external genitalia in these patients suggests that DHT production also had been decreased during embryogenesis.

As a consequence of their genital appearance, male pseudohermaphrodites with a 5α-reductase deficiency are usually assigned at birth and raised either unequivocally or ambiguously as female. The psychoendocrinologic importance of this syndrome lies in the characteristic sequence of events beginning with presumably normal male prenatal and perinatal exposure of the CNS to testosterone, followed by a more-or-less consistent sex of rearing as female, and culminating in hormonally induced virilization at puberty. The circumstances provide an "experiment of nature" in which the influence of factors that contribute to the differentiation of male gender identity in humans may be observed.

With reference to the Dominican kindred (*28, 29*), as of 1979 there were 38 affected subjects identified from 23 interrelated families spanning four generations. Of the 33 living subjects, 25 were postpubertal, 3 peripubertal, and 5 prepubertal. It was reported that 19 of the 33 pseudohermaphrodites had been unambiguously raised as girls, and of the 18 about whom postpubertal information was obtained, 17 had successfully changed to a male gender identity and 16 to a male gender role (*29*). The subjects who differentiated a male gender identity were described as realizing they were different from other girls sometime between the ages of 7 and 12, when they began questioning their true gender. Over a period of several years they passed " . . . through stages of no longer feeling like girls, to feeling like men, and finally to conscious awareness that they were indeed men" (*29*). These subjects apparently first experienced morning erections and nocturnal emissions and initiated masturbation and sexual intercourse at ages not significantly different from males raised as boys. Further, of the 16 subjects who adopted both a male gender identity and a male gender role, 15 had lived or were living with women. Now that the inhabitants of the villages are aware of the developmental course of this disorder, affected individuals are raised either as boys or ambiguously as girls and are sometimes referred to by a characteristic name.

A description of the sociocultural conditions of the Dominican kindred, with particular attention to socialization practices by sex, provides a background upon which to evaluate these behavioral data: (i) The sexes are clearly distinguished and dressed differently from the age of toilet training. (ii) From age 6, children are encouraged to segregate by sex for play. (iii) Girls are encouraged to stay close to home and help their mothers, whereas boys are given more freedom to roam and play. (iv) Girls remain close to home until they marry, which is at an earlier age than boys, and marital

fidelity is expected of women but not of men. (v) Males go to bars and cockfights starting at age 12, and at age 14 they begin to visit prostitutes. (vi) There is a strict division of labor, with women tending home and children, while men farm, mine, or chop wood.

Imperato-McGinley *et al.* (*29*) stated that adequate postpubertal psychosexual data were obtained from 18 of the 19 subjects unambiguously raised as girls, and of these 18 subjects, 17 had successfully changed to a male gender identity and 16 to a male gender role. However, two of the 18 subjects were dead at the time of the reports (*29*), and, of the 16 living subjects, 1 maintained a female gender identity and role despite a masculinized phenotype, enlarged phallus, and inadequate vagina; a second continued to dress as a woman although the investigators regarded his gender identity as unambiguously male; and a third lived alone in the hills, even though he was reported to have assumed an unambiguous male role. Therefore, it appears that 13, rather than 16, of the original 19 subjects had a clearly masculine postpubertal gender identity and role.

Perhaps the most difficult methodologic problem that Imperato-McGinley *et al.* (*29*) faced was determining that 19 of their 33 subjects had been unambiguously raised as girls. It is not clear whether all the living subjects (three of the original 19 are now dead), as well as others who could report on their early development, were personally interviewed, and whether both parents were questioned in each case. It is important to contact all possible sources of information in this kind of retrospective psychoendocrine research, because the opinions of the mothers and fathers of some hermaphroditic children differ on the subject of their children's correct sex (*32*).

The appearance of the genitalia is a potent influence on gender identity, both for the individual and those around that individual. On full body view, the Dominican pseudohermaphrodites do have a female phenotypic appearance. However, their genitalia, while distinctly not masculine, are certainly not normally female. Although it was reported that there is only slight posterior fusion of the labioscrotal folds present in most of the Dominican kindred, photographs of the external genitalia of three of the prepubertal subjects reveal almost complete labioscrotal fusion in one case and marked fusion in another case; absent labia minora in all three cases; and phalluses ranging from an enlarged, abnormal clitoris to a small penis with hypospadias (*28*). Even cursory inspection of the genitalia should have revealed the abnormal configuration of these organs to any observer, especially to the mother. Unfortunately, no data have been provided about the responses of mothers and other family members to these abnormal genitalia; did they notice that the children's genitals were not like those of other females, and, if so, what did they think the abnormality meant? In this regard, it is important to emphasize that sex of rearing is influenced not only by the responses of both parents to the child as a member of one or the other sex, but also by the responses of all members of the family and the community who come in contact with the individual. The inhabitants of the Dominican villages, both adults and children, bathe in the river, and the houses contain only one or two bedrooms, making it necessary for the entire family, or at least all the offspring, to sleep together. Thus, there is little individual privacy, and any physical abnormality of a hermaphroditic individual most likely would be noticed by many people.

As mentioned earlier, prenatal exposure of humans to gonadal steroids, whether of internal or external origin, appears to have an appreciable influence on behavioral development. In particular, exposure of the female to androgens or androgen-based progestins increases the frequency of tomboyish behavior during childhood. Thus, the subjects with 5α-reductase deficiency, even when raised unambiguously as female, would be likely to evidence a high degree of tomboyish behavior, considering that they were exposed to normal male levels of testosterone during early fetal development. In fact, Imperato-McGinley *et al.* described a 65-year-old patient with 5α-reductase deficiency, who was raised in southern Italy until the age of 16 and never hormonally treated or surgically repaired, with the statement that "Throughout childhood, the subject was considered to be a tomboy, as she liked to play ball, pitch pennies, and ride burros with the boys. Only rarely would she play with dolls" (*33*).

Unfortunately, there was no mention of the presence or absence of tomboyish behavior in the Dominican kindred (*28, 29*). All the individuals with a 5α-reductase deficiency whose gender identity has been reported to have changed from female to male at puberty spent the years well into adolescence in very traditional and conservative cultures where differences between the sexes are emphasized and sex role definitions are narrow. These include rural Dominican Republic (*28, 29*), southern Italy (*33*), Arab Algeria (*36*), and Cyprus (*37*). In a conservative, traditional culture, tomboyish behavior would be difficult to express freely and probably would be more disapproved of than in a society with more flexible social standards. This, in concert with ambiguous genitalia, might very well provoke gender confusion and doubt in the mind of an affected individual.

It is of interest that the pseudohermaphrodites from the Dominican Republic apparently began feeling different from other girls between the ages of 7 and 12 when, in their society, children are encouraged to segregate by sex in their play. For tomboyish girls who often prefer male playmates, this could be a real hardship. Thus, individuals with 5α-reductase deficiency who are from cultures with fairly rigid sex role stereotypes, and who have had no opportunity for surgical repair of their abnormal genitalia to be consonant with their sex of assignment, are likely to grow up with ambivalent feelings about their assigned gender. As Money stated, "... if you're a girl who is not sure that you're supposed to be a girl because of your funny-looking genitals, you have an alternate choice. It's a simple law of binary logic that, if you feel everything is wrong the way you are, maybe the correct way is the other way" (*38*).

The major conclusion reached by Imperato-McGinley *et al.* regarding the relative influence of hormones and rearing in the Dominican kindred was that when the sex of rearing is contrary to the testosterone-mediated biologic sex, the biologic sex prevails if the normal testosterone-induced activation of puberty is permitted to occur (*29*). In contrast, eight subjects in the United States who were diagnosed as 5α-reductase deficient, who were raised as females and who experienced testosterone-induced activation of puberty prior to medical intervention, apparently maintained their female gender identity of rearing despite disfiguring pubertal virilization (*39, 40*). One additional 5α-reductase deficient patient who was treated at 12 years of age (*35*) and three who were treated before puberty (*40, 41*) also were described as maintaining clearly differentiated female gender identities through follow-up examinations. Therefore, some individuals with 5α-reductase deficiency, who have been raised as female but not identified and not surgically or hormonally feminized even well beyond puberty, apparently do maintain a female gender identity and role. It may be that these subjects were reared truly unam-

biguously as females, and therefore their postpubertal gender identity remained consistent with their sex of rearing. In contrast, the majority of Dominican subjects, perhaps due to such conditions as lack of privacy and the rigidity and narrow definition of sex roles in a traditional society, may have experienced gender identity confusion during childhood which fostered their masculine gender emergence at puberty.

Most investigators now regard the factors contributing to the development of gender identity to be neither "nature" nor "nurture" alone, but rather an interaction of hormonal and psychosocial influences. The studies of Imperato-McGinley *et al.* contribute to the growing body of evidence that prenatal and pubertal hormone exposure interacts with environmental factors to influence behavioral development in humans, as has been demonstrated for many species lower on the evolutionary scale. With specific reference to the Dominican kindred, it can be concluded from the available data that, if a child is born with ambiguous genitalia that are not soon repaired and, as a consequence, develops confusion regarding its proper sex, pubertal testosterone activation and virilization in concert with prenatal testosterone exposure can facilitate the solution of the gender question in a masculine direction.

Discussion

The foregoing examples of postnatal gonadal steroid effects on sexually dimorphic behavior in humans highlight the complexity of the interaction between hormonal and psychosocial factors. As is evident from the foregoing presentations, the state of knowledge in each of these three areas is different. With reference to testosterone and aggression in men, measures of aggressive and violent behavior can reliably characterize groups of particularly violent individuals, but these measures have not been consistently related to increased plasma testosterone. One problem has been the blood sampling schedules used in these studies; often, only a single blood sample is taken from each subject, so that an accurate estimate of integrated testosterone concentrations in blood cannot be obtained. Most hormones are secreted in episodic bursts, so that several blood samples must be taken over a relatively short period of time in order to ascertain an average hormone level (*42*). Further, the secretion patterns of testosterone as well as those of several other hormones have a circadian rhythm; thus the time of day of blood sampling must be held constant for all subjects. Future studies must accommodate these methodologic issues if the suggestive elevation of testosterone in subgroups of men with extremely violent behavior is to be confirmed.

With reference to mood and the menstrual cycle in women, there has been a careful elucidation of hormone profiles both in women with normal menstrual cycles and in women with PMTS, but the behavioral disturbances of premenstrual tension are just beginning to be codified. At present, there is not a consistently high correlation between identified hormone abnormalities and disturbances of mood in women with this syndrome. Future research must be directed toward a more specific classification of the various behavioral characteristics of premenstrual tension, which may have different hormonal correlates and, therefore, different effective treatments.

Finally, with reference to testosterone-induced emergence of male gender identity at puberty in male pseudohermaphrodites, while the endocrinopathy underlying this disorder is well understood, there is considerable controversy concerning the actual state of the prepubertal gender identity of these individuals. To resolve this issue, it will be necessary for behavioral scientists to undertake the systematic collection of complete behavioral and psychosocial data from affected individuals, their families, and other social contacts.

Whatever the specific methodologic requirements are for future data gathering and clarification of endocrine and psychosocial factors in these and other areas of research, present-day knowledge indicates that in each area there is a complex interaction between hormonal influences on brain function and psychosocial and environmental forces that results in the expression of sexually dimorphic behavior. Thus, the concept of a "nature versus nurture" dichotomy is anachronistic; the goal of future research should be to delineate the relative contributions of both sets of influences on each specific behavior.

Research in these areas has practical implications, the most important of which relates to the kinds of endocrine treatments that are suggested and implemented for human sexually dimorphic behavior that is judged to be pathological. With specific reference to the three areas of research discussed above, relevant issues include the treatment of violent and aggressive men with androgen antagonists; the treatment of premenstrual mood disturbances with hormone therapy or more classical psychiatric therapies; and the treatment of patients having a gender identity inconsistent with their phenotype by surgical alteration of their phenotype or by psychological and hormonal alteration of their gender identity. At present these questions cannot be answered categorically, but the principle of hormone-environment interaction, with varying contributions of endocrinologic and psychosocial factors in different persons, suggests that approaches to treatment must be individualized. Every patient must be assessed carefully along several psychological and physical dimensions, and only after an in-depth evaluation can an appropriately individualized treatment plan be formulated.

Although we have focused mainly on the androgenic and estrogenic gonadal steroids, these are not the only hormones known to influence sexually dimorphic behavior. For example, luteinizing hormone releasing hormone (LHRH), the decapeptide that stimulates the secretion of luteinizing hormone and follicle-stimulating hormone from the anterior pituitary gland (which in turn promote the secretion of the gonadal steroids), can synergize with estrogen to evoke sexual posturing (lordosis) behavior in female rats (*43*). However, LHRH has been administered to many human subjects, both male and female, and no consistent subjective or objective behavioral effects have been noted (*43*). Thus, the relative potency of gonadal steroids as compared to other classes of hormones that influence sexually dimorphic behavior varies among species, and data from laboratory animals cannot be extrapolated readily to man. Future research efforts, therefore, must be directed toward these other hormones as well.

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