Effects of Prenatal Sex Hormones on Gender-Related Behavior

Anke A. Ehrhardt and Heino F. L. Meyer-Bahlburg

Summary. *Gender identity depends largely on postnatal environmental influences, while sex-dimorphic behavior and temperamental sex differences appear to be modified by prenatal sex hormones. A role of the prenatal endocrine milieu in the development of erotic partner preference, as in hetero-, homo-, or bisexual orientation, or of cognitive sex differences has not been conclusively demonstrated.*

The basic pattern of mammalian sexual differentiation is illustrated by examination of the reproductive tract. After embryonic differentiation of testis or ovary, the presence of sufficient amounts of androgens (as secreted in the normal course of male development by the testis) largely determines whether sexual differentiation of the sex organs will go along male rather than female lines (*1*).

Androgens also play a critical role for the differentiation of the central nervous system (CNS). This principle has been demonstrated by studies of various species of lower mammals and with different tools of experimental assessment (*2*), one common approach being the manipulation of prenatal or neonatal hormones by castration of the male or by exogenous administration of androgens to the female. Deprivation of the male animal of testosterone during his species-specific critical time of brain differentiation will result in a female pattern of sexually dimorphic behavior (*3*). In contrast, a female mammal exposed to testosterone during pre- or perinatal development will, as an adult, perform similarly to a normal male in tests for male and female sexual behavior. This principle holds true even though mammalian behavior is not completely sexually dimorphic, but rather a matter of degree and relative frequency of behavior components more typical for one sex or the other.

The long-term effects of exposure to sex hormones before or around the animal's birth on postnatal sex-dimorphic behavior have been termed developmental or organizational. Developmental effects are distinguishable from activational or concurrent effects in several ways: (i) Developmental effects typically occur only during a time-limited, sensitive, or critical phase of development, either before or around the time of birth. (ii) Developmental effects tend to be long-term and relatively permanent, although they can be overridden by nonhormonal influences. (iii) Some developmental effects are delayed and become only visible in behavioral manifestations later in life. (iv) The delayed appearance of certain developmental effects may depend on the interaction with sex hormones in puberty or adulthood. By contrast, concurrent or activational effects of hormones are reversible, repeatable, and not limited to a critical phase of development (*3*). Developmental effects are usually tested by manipulating the exposure to sex hormones during the fetal development of the animal, while concurrent effects are usually investigated at the time of puberty or adulthood. This article will focus on developmental effects of sex hormones on sex differences in human behavior.

The classical organization hypothesis of sex-dimorphic behavior has focused on the role of androgens as the enhancer of male behavior (*4*). Recent revisions of this theory include hormones other than androgen (*5*). Progesterone, for instance, is recognized as a hormone that counteracts androgens and thereby may protect the brain of female fetuses in certain species from the effects of available androgens (*6*). Moreover, current theories consider that androgens may have to be converted into estrogens in order to exert their decisive effects on target cell nuclei (*7*); this hypothesis would explain why pharmacologic doses of exogenous estrogens may, in fact, have masculinizing effects in females of various species.

The organizational hypothesis has been supported by many different experimental approaches in lower species, including morphological and physiological studies of the brain (*3, 8*). It has been suggested by Arnold (*9*) that in rodents at least the question of study is no longer whether or not sex differences in neuroorganization exist, but rather what sequence of developmental events leads to the pervasive sex differences observed. By contrast, the evidence in primates and especially in human beings is inferential and much more tentative (*3, 10*).

While the role of social learning is much greater in human behavior than in subhuman mammals, there is sufficient evidence to suggest that biological factors influence psychosexual differentiation in human beings, too. Anatomically and histologically, the subcortical regions of the human brain have a striking similarity to those of subhuman mammals. The timing of peak androgen production by the fetal testes corresponds closely to the timing of hypothalamic differentiation, similarly to the prenatal or perinatal lower mammal (*3, 11*).

Researchers of human behavior must depend on subjects with either spontaneous endocrine abnormalities or a history of prenatal hormone treatment. Available studies can be divided into those where there was an attempt to assess prenatal androgen effects in females and males and those where abnormal levels of progestogens and estrogens could be correlated with postnatal behavior.

Four areas of behavior have been studied in this context. These are (i) gender identity, defined as the primary identification of an individual with one sex or the other; (ii) gender-role or sex-dimorphic behavior, including all those aspects of behavior in which normal boys and girls differ from one another in our culture and at this particular time in history; (iii) sexual orientation, that is, erotic responsiveness to one sex or the other, whether homo-, hetero-, or bisexual; and (iv) intelligence and cognitive sex differences, such as strengths and weaknesses of mental abilities as related to sex in normal subjects.

Both authors are research scientists at the New York State Psychiatric Institute and Pediatric Behavioral Endocrinologists in Psychiatry Service, The Presbyterian Hospital, New York. Dr. Ehrhardt is associate professor of clinical psychology and Dr. Meyer-Bahlburg is associate clinical professor of medical psychology, Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York 10032.

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The measurement of these behavior areas is often complex and difficult. Assessment measures include detailed interviews with the subjects and members of their families, psychometric and projective tests, and direct behavior observation.

Gender Identity

The term "gender identity" describes a specifically human phenomenon. Therefore, there are no experimental analogs in animal research. The development of gender identity depends largely on a process of learning (*12*). Of particular importance have been the studies of children who were born with discrepancies between biological factors of sexual differentiation and their sex of rearing. On the basis of their investigations of such intersex patients, Money, Hampson, and Hampson (*13*) suggested that gender identity is formed in the early postnatal years and that gender identification typically depends on a person's sex of rearing even when this is in contrast to some of the biological factors of sex.

Of particular interest is the example of matched pairs of intersex patients such as two individuals born with the same genetic and gonadal sex, same presumed prenatal hormonal environment, and same degree of ambiguity of the external sex organs (*14*). One child, however, may be assigned to the female sex and the other to the male sex, depending on different medical opinions at different times and at different institutions. The rule has been in this type of case that gender identity agrees with the particular sex of assignment, provided that parental doubts are resolved early, and surgical corrections and postnatal hormonal therapy are in agreement with the assigned sex so that the physical appearance of such a child is unambiguously male or female.

Once gender identity has been established, it cannot be reversed easily. In the first few years of life, a child's gender identity is usually embedded firmly. Money (*15*) has suggested a parallel between the process of gender identity formation and the acquisition of one's native language. By the age of five, most children have an effective grasp of the main linguistic principles that are involved in the use of their native tongues. Analogously, at this same age the primary identification with one sex or the other is irrevocably part of the self-image.

The permanence of gender identification is illustrated by patients who unexpectedly become virilized or feminized at puberty with secondary sex characteristics in contrast to their sex of assignment and their gender identity. For instance, if a person is consistently raised as a girl but suddenly develops a low voice and grows a beard and a clitoris of phallic size, her gender identity typically remains female although the physical changes are disturbing to her and need to be corrected without delay (*16*).

If remaining uncorrected, some few individuals will develop gender identity doubts and may finally change their gender. In our culture, such a gender change of adolescence typically takes years and involves a gradual readjustment to the changing body image and societal reactions. Therefore, it seems unlikely to us that the phenomenon of adolescent gender change in such individuals can be ascribed to direct CNS effects of testosterone. The latter hypothesis seems to be implied in reports by Imperato-McGinley and her colleagues (*17*) who described a group of Central American male pseudohermaphrodites with pubertal masculinization where an adolescent gender identity change appears common. Before their interpretation of a supremacy of hormonal factors over rearing conditions in the development of gender identity can be accepted, the process of change and the particular ontogenetic and cultural background of their patients has to be carefully examined (*18*).

Sex-Dimorphic Behavior

Over the last 15 years or so, several investigators have examined children, adolescents, and adults who presented an unusual prenatal hormonal history. The goal of these studies on behavior has been to ascertain whether unusually high or low levels of prenatal androgens, progestogens, or estrogens may have effects on subsequent behavioral development in human beings, effects that are analogous to modifications of sex-dimorphic behavior in animals. If so, androgenic steroids should produce some masculinization of behavior; progesterone and related compounds would be expected to counteract androgenic effects; and estrogens either might have masculinizing effects or demasculinizing effects, depending on the particular hormone and its dosage.

The aspects of behavior that have been studied in nonhuman primates and in people cluster in a few areas (*19*).

1) *Energy expenditure.* In human beings this has been measured as active outdoor play and athletic skills. In nonhuman primates the comparable behavioral aspect is active play such as in rough-and-tumble play (*20*). Intense physical energy expenditure of this type seems to be an essential aspect of psychosocial development and it appears to be influenced by sex steroid variations before birth.

2) *Social aggression* (*21*). In nonhuman primates, such behavior categories as pursuit, threat behavior in childhood, and fighting are included. For human beings, aggressive behavior includes physical and verbal fighting in childhood and adolescence.

3) *Parenting rehearsal.* In human beings, children engage in doll play (rather than in play with cars and trucks), playing "house," playing "mother" and "father," participating in infant care and fantasizing about having children of their own. Observations of lower mammalian species suggest that the threshold and intensity of parenting is sex dimorphically related to the type and level of prenatal hormones (*22*).

4) *Peer contact, friends, and patterns of group interaction.* In nonhuman primates, dominance behavior and sex segregation of play groups have received special attention (*23*). In human behavior the categories would be preference of playmates by sex.

5) *Gender role labeling.* A given child is labeled by his or her social environment on the basis of play behavior patterns and gender role preference, for example as "tomboy" or "sissy."

6) *Grooming behavior.* Humans adorn themselves as indicated by clothes preference, jewelry, makeup, hairdo, and the like. The analogous behavior aspect in nonhuman primates may be grooming. Since it is doubtful that prenatal hormonal levels have any direct effect on the intensity of this type of grooming behavior in human beings, it may be seen as an aspect of psychosocial development that is interrelated with other temperamental characteristics of a person, such as intensity of physical energy, which itself may be influenced by prenatal hormones.

These behavioral categories of sex-dimorphic behavior have been the focal points of most studies on the role of prenatal sex hormones in the emergence of behavioral sex differences.

Fetal androgenization in genetic females and males. In this context, patients with congenital adrenal hyperplasia (CAH) are of particular interest. The primary defect of CAH is genetic and is transmitted as an autosomal recessive that prevents the adrenal cortices from

synthesizing cortisone. Instead, the cortex releases an excess of adrenal androgens from fetal life onward (*24*). As a result, the external genitalia are masculinized if the fetus is genetically female, while genetic males are born with normal male external genitalia. Postnatally, the condition can usually be corrected by replacement therapy with corticosteroids that suppress the adrenal androgens to normal levels if medical management is optimal. In genetic females, external genitalia can be surgically feminized in the first few weeks of life. If properly regulated on cortisone or prednisone, both females and males experience pubertal development spontaneously at the normal age; and sexual functioning and fertility does not appear to be impaired in adulthood. For the study of the effects of prenatal androgens, those children who were treated with corticosteroids beginning in infancy are the most suitable subjects. If treatment is instituted later in life, androgenization continues with resulting masculinization of the body. In those cases, it becomes difficult to separate prenatal from postnatal hormonal effects.

Over the last decade, several studies have been reported on the behavior of children with CAH who were treated early. Gender identity typically agrees with the sex of rearing of the child: that is, females with CAH firmly identify as girls and women in spite of prenatal androgenization and masculinization of the external genitalia, provided that sex assignment is clearly female from early childhood. Genetic males with CAH are always raised as boys and identify as such.

While prenatal androgenization does not appear to affect gender identity formation directly, it seems to influence gender role behavior. Studies with three different designs have been reported: (i) comparison of patients with matched normal controls, (ii) comparison of patients with unaffected siblings, and (iii) comparison of patients with a clinical contrast group. Two studies with a control-group or a sibling-comparison design included genetic females who were surgically corrected and hormonally treated early in postnatal life (*25, 26*). In both samples, the behavior of the prenatally androgenized girls differed significantly from that of the controls in that they typically demonstrated (i) a combination of intense active outdoor play, increased association with male peers, long-term identification as a "tomboy" by self and others, probably all related to high energy expenditure, and (ii) decreased parenting rehearsal such as doll play and baby care, and a low interest in the role rehearsal of wife and mother versus having a career. The characteristic pattern was not transient or limited to a brief phase, but was long-term throughout childhood and was not considered abnormal for female behavior in our culture.

The findings on aggression were less clear-cut. The studies suggested an increase in the initiation of fighting for CAH girls that was not statistically significant (*27*). Money and Schwartz (*28*) published a report specifically devoted to aggression in CAH females. They concluded that participation in body contact sports was increased, but that there was no remarkable increase in aggressive behavior. Whereas the findings are in the expected direction, the assessment methods were relatively crude, and therefore the conclusions have to remain tentative.

Most patients of the studies cited were well-controlled on corticosteroids. Therefore the behavior pattern can be mostly attributed to prenatal effects of excess adrenal androgens, in spite of the fact that it is sometimes difficult to maintain optimal medical regulation. This conclusion is also supported by another report on the effects of androgenizing sex steroids during pregnancy. Ehrhardt and Money (*12, 29*) reported on a group of females whose mothers were treated with masculinizing progestogens during gestation. These fetally androgenized girls were endocrinologically normal after birth and were in no need of medical attention except for surgical correction of an enlarged clitoris in some cases. Most of these girls showed a behavior pattern similar to that of females with CAH as judged by their athletic interests and skills, and preferences for male versus female playmates, for utilitarian and functional rather than traditional feminine clothing, for toy cars and guns rather than dolls, and for career rather than being a mother (*30*).

There always remains the question of whether parental reinforcement patterns were consistently different in these patients and enhanced their specific patterns of psychosocial behavior development. While prenatal hormones must be seen as one factor in a chain of variables that affect psychosocial development in which rearing experiences play a particular role, it seems unlikely that parental reactions are solely responsible for the characteristic behavior pattern described. Ehrhardt (*31*) described parental reactions to the endocrinopathies of their daughters and found that the parents were either not specifically concerned about their behavior, or if concerned, usually about tomboyism, they tended to encourage femininity. That is, they tended to oppose rather than to encourage those temperamental characteristics of their daughters that appeared to be sequelae of their specific prenatal hormone condition. On the basis of these data and our own clinical experience, we do not have any reason to assume that parents of intersexed offspring usually tend to develop ambiguous sex typing and reinforce behavior patterns of the other sex more than they would with endocrinologically normal children provided that sex assignment is done early and handled with assurance by medical personnel.

The behavior of boys with CAH has also been assessed. They differed from a male sibling control group only in that they exhibited higher levels of energy expenditure in play and sports. They also showed a nonsignificant increase in initiating fighting (*26*). This observation strengthens the assumption that prenatal exposure to androgens may be related to the temperamental trait of intense active outdoor play and possibly some aspects of aggressive behavior.

Fetal nonandrogenization in genetic males. The human clinical syndrome that most closely approximates the antithesis of fetal androgenization of the genetic female is a syndrome of androgen insensitivity (testicular feminization) of the genetic male. These individuals have testicular gonads with normal testosterone production, but the tissues of the body are insensitive to androgens, so that the appearance of the external genitalia is female. However, there is no uterus and only a short, blind-ending vagina which often requires surgical lengthening in or after middle teenage to permit satisfactory sexual intercourse. Because of an increased risk of malignancy, gonadectomy is typically performed in childhood or adolescence. Breast development is normal in response to the estrogen produced by the gonads or to estrogen replacement therapy after gonadectomy. Menstruation and fertility are missing. Sex of rearing is female.

Gender identity is typically female in these patients (*32*). Sex-dimorphic behavior has been systematically assessed in adult patients in terms of their current adult and recalled childhood behavior (*33*). In the majority of the cases, the pattern of sex-dimorphic behavior was stereotypically feminine with a preference for being a wife with no outside job, for enjoying homecraft (including having dreams and fantasies of raising a family), for having played primarily with dolls and other girls' toys in childhood, and for having a genuine interest in infant

care. In these cases, the presumptive prenatal hormone influence is nonmasculinizing, which is in agreement with the postnatal behavior pattern of femininity. Since the postnatal rearing history is also typically that of a female, we cannot separate the causative role of endocrine and social factors.

Pregnancy treatment with progestogens and estrogens. The use of sex hormones in the treatment of problem pregnancies was first introduced in the 1940's after it had become known that the successful initiation as well as maintenance of pregnancy depended to a large extent on hormones produced by the mother as well as by the fetoplacental unit. High-risk pregnancies such as those threatened by spontaneous abortions, premature birth, stillbirth, or congenital abnormalities often in conjunction with pathologic states of the pregnant mother, such as diabetes or toxemia of pregnancy, were thought to be linked to deficiencies of hormone production, and supplementation seemed to be the logical approach to treatment. Since most steroid hormones have some progestational properties, a variety of hormone preparations were tried, especially progestogens and estrogens.

Subsumed under the category "progestogens" are both naturally occurring and synthetic progestational agents that are chemically closely related to either progesterone or to androgenic steroids. Genital masculinization of female fetuses has been found after treatment with either class of hormones. However, such cases are very rare after treatment with progesterone or its derivatives (*34*), and a causal relation has not been unequivocally established. The only study available on behavioral sequelae of prenatal exposure to androgen-derived progestogens in human beings (*12, 29*) demonstrated masculinizing effects in girls and has been referred to earlier. Particularly widespread has been the pregnancy treatment with progesterone-related progestogens. For these types of progestogens, Dorfman and Kincl (*35*) originally suggested that progesterone may protect the developing hypothalamic-pituitary-gonadal system of the fetus against possibly damaging effects of increases in androgen (or estrogen, or both) concentrations. The findings that female rhesus monkeys and rats have higher levels of fetal progesterone led to a general model of an interaction between progesterone and other sex steroids in both male and female fetuses (*6, 36*). According to this theory, progesterone protects the brain from the masculinizing effects of androgens and estrogens.

There are only three studies that concern such effects in humans. In all three, the underlying hypothesis is that males and females who are exposed to an increased level of progestogens during fetal development will be demasculinized or feminized in some aspects of their behavior after birth. All three studies share the problem of inadequate control groups, albeit to different degrees. The first one (*37*) was an interview study of adolescents whose mothers were treated during pregnancy with progesterone for the relief of precursor symptoms of preeclamptic toxemia. It was found that progesterone exposure in boys correlated negatively with physical activity level in childhood and also with (hetero-)sexual activity in adolescence. In girls, progesterone exposure was negatively correlated with reports of tomboyism and positively with traditionally feminine activities in childhood. In a second study (*38*) personality questionnaires were used with a similar sample of adolescents; neither boys nor girls differed from controls on a masculinity-femininity scale.

In a third study (*39, 40*) of males and females in middle childhood and early adolescence, the long-term effects of prenatal treatment with medroxyprogesterone acetate (MPA) were assessed. In this case, MPA-exposed and control subjects were closely matched for background variables and, whenever possible, to maternal pregnancy state. Children and their mothers underwent separate interviews. The hormone-exposed males did not differ consistently from controls (*27, 39*). More consistent differences emerged for the females. Fewer hormone-exposed girls than controls labeled themselves a tomboy during childhood, and more of them showed a consistent preference for feminine clothing styles (*39*); they also scored lower than the controls on several aggression measures (*27*). Further data analysis (*41, 42*) showed that, by their mothers' reports, hormone-exposed girls were lower than controls ($P \leq .05$) in physical activity and athletic ability and slightly higher ($P \leq .10$) in their interests in girls' toys, such as dolls.

Taken together, the available data on sex-dimorphic behavior are compatible with the theory that prenatal progesterone and related compounds act as androgen antagonists. Yet, the effects seem subtle and, even in our own relatively well-controlled study, we cannot exclude the possibility that the differences found were due to factors other than hormones, such as pregnancy conditions.

Estrogens, when administered prenatally or perinatally, exert seemingly paradoxical effects on genital morphology and sex-dimorphic behavior in subhuman mammals; that is, they tend to masculinize females and to demasculinize males. For the treatment of human problem pregnancies estrogens are rarely used alone, and behavioral studies of offspring from pregnant women treated solely with estrogens are not available. Usually, estrogens are given in combination with progestogens. Since little is known about the behavioral effects of the individual estrogens and progestogens, it is impossible to predict with any certainty their interactive effects on sex-dimorphic behavior. The available data point toward demasculinizing effects in both sexes. One study (*43*) dealt with two samples of boys whose mothers had been treated during pregnancy with combinations of various estrogens and progestogens because of diabetes. The mid-adolescent sample showed decreased aggression or assertion (as judged by interview) and decreased athletic coordination (as judged by observation) along with tendencies to overall lowered masculine interests and heterosexual experience; increased gender identity problems or homosexuality were not noted. The other sample, consisting of 6-year-old boys, also showed decreased assertion and decreased athletic ability (according to teacher ratings).

Additional evidence comes from our analysis (*42*) of a sample of children exposed to estrogen and progestogen and who were similar in age and socioeconomic background to our MPA sample described earlier; the same assessment methods were used. The results are somewhat similar to those for the MPA samples. Differences between hormone-exposed males and controls were slight and inconsistent. By contrast, the girls' data showed demasculinization; their mothers rated them significantly lower than controls ($P < .05$) in athletic ability and higher in preference for mother versus father and preference for children over career; there were also slight ($P < .10$) increases in their interest in cosmetics and hairdo, the expressed preference to join female rather than male peers, the expression of affection, and a slight decrease in verbal aggression toward peers. The girls themselves indicated an increased ($P < .05$) preference for mother over father but also slight decreases ($P < .10$) for interest in jewelry and indirect aggression against same-sex peers (*44*).

Summarizing the available data, the behavioral effects of prenatal estrogen-progestogen combinations appear to be

quite similar to those of exposure to progestogen only; that is, in both cases there are effects in the direction of demasculinization or increased feminization. The methodological caveats mentioned before apply here also.

Sexual Orientation

Sexual responsiveness to the same or other sex, as indicated by erotic attractions, sexual fantasies and dreams, and sociosexual experiences, constitute the definition of sexual orientation used here. How a lasting sexual orientation develops is not well understood. With regard to biological factors, the gonads, sex chromosomes, and sex hormones have all been suspected of playing a causal role. With the recent advances in psychoneuroendocrine research, prenatal hormones have also been implicated. If early androgenization or deandrogenization can determine male and female patterns of mating behavior in lower mammals, it is tempting to extrapolate from these findings to the human situation as suggested by Dörner (*45*). The prenatal hormone theory of human sexual orientation has been criticized on theoretical and empirical grounds (*46*). Major difficulties arise from the fact that, in contrast to situational homosexual behavior, a homosexual orientation has not been observed in untreated subhuman mammals except in a few questionable cases of captive subhuman primates (*47*). Most of the pertinent animal research is done in terms of lordosis and mounting behavior for which homologous human behaviors are hard to define. More similar to the concept of sexual orientation in humans is the recently described sexually motivated approach behavior in choice situations (*48*). The effects of pre- and perinatal hormone manipulations on this type of behavior are only partially known. There is empirical evidence that mating behavior in subhuman mammals can be profoundly affected by social learning during childhood (*49*) but this avenue of research has not been pursued for the development of a social learning–based animal model of sexual orientation.

To test the validity of the prenatal hormone theory, we need to examine human subjects with endocrine disorders that involve prenatal sex-hormone abnormalities. The theory predicts that the effective presence of androgens in prenatal life contributes to the development of a sexual orientation toward females, and that a deficiency of prenatal androgens or tissue insensitivity to androgens leads to a sexual orientation toward males, regardless of the genetic sex of the individual.

Therefore, CAH women with their history of prenatal androgen exposure can be expected to show increased homosexuality in adolescence and adulthood. Of the available pertinent studies, two (*28, 49a*) concern girls and women whose hormonal treatment had started in infancy or early childhood so that they did not have a prolonged history of virilization after birth. The majority of these patients were heterosexual although several bisexual or homosexual individuals were also identified. The human analog closest to Dörner's rat model are CAH women whose treatment did not start before late adolescence or adulthood, and who, therefore, experienced high androgen levels with resulting severe virilization for many years after birth. Ehrhardt and co-workers (*50*) examined such a sample and found that, on the basis of overt sociosexual behavior, the majority of these patients were heterosexual, some were bisexual, and none were exclusively homosexual. If classified by erotic dreams and fantasies, at least half of them were heterosexual, the other half were bisexual, and none were exclusively homosexual. Of a similar sample of CAH women from the Soviet Union (*51*), none reported homosexual experiences or dreams. Thus, even late-treated CAH women do not seem to show a clear-cut predominance of homosexuality. Since none of the four studies mentioned contained a control group, we cannot evaluate whether there was any increase at all in the prevalence of bisexuality or homosexuality in CAH women compared to normal controls. Yet, a rigidly deterministic effect of prenatal androgens on sexual orientation appears to have been ruled out.

There are only very limited data available on prenatally hypoandrogenized genetic males. Many of these individuals are reared female from birth onward. If, in adolescence or adulthood, they are sexually attracted to males, as has been demonstrated for patients with complete or partial androgen insensitivity (*32, 52*), their sexual orientation can be ascribed to the prenatal hormone deficiency as well as to rearing factors (*53*). Those individuals that are reared unambiguously as male also usually develop a heterosexual orientation relative to their sex of rearing and identity (*12, 52*). A study (*54*) on adolescent patients with bilateral cryptorchidism, a syndrome in which both a gonadotropin deficiency (*55*) and a secondary partial androgen deficiency during early infancy (*56*) have been demonstrated, showed heterosexuality in all patients. Thus, the available data on genetic male intersexes suggest that sexual orientation mainly follows the sex of rearing and identity and, therefore, is based on social learning rather than on hormones, but the number of male intersexes studied in detail and long enough is too small to exclude the possibility of some hormonal influences.

A second approach to testing the validity of the prenatal hormone theory is the examination of homosexual adults for any neuroendocrine indication of prenatal sex hormone abnormalities. There are certain characteristics of the neuroendocrine regulation of pituitary function in which males and females differ (*57*). Recent studies have demonstrated that homosexual men show regulation patterns that are intermediate between those of normal males and females (*58*). Similarly, more male-like than female-like characteristics of these regulatory mechanisms have been described for female-to-male transsexuals (*59*), that is, genetic females in whom a gender identity conflict is usually combined with a homosexual orientation. The crucial question for this discussion is whether the abnormalities of regulatory characteristics in these cases really reflect a prenatal hormone effect. Recent research has demonstrated that, in primates, the sex-dimorphic neuroendocrine characteristics depend on the sex hormone levels both during the early sensitive period of hypothalamic differentiation as well as during the functional phase after puberty (*60*). This fact makes the interpretation of the data more complicated. Also, the assumption that the prenatal hormone situation generally has parallel effects on the pattern of gonadotropin regulation and on sexual orientation is hard to accept in light of recent data (*61*) that show a masculine pattern of gonadotropin regulation in genetic males with the syndrome of androgen insensitivity, of whom we generally know that their external appearance, their gender identity, and their sexual orientation is comparable to those of genetically normal females.

In summary, the available prenatal hormone data on homosexuality are limited and permit, therefore, only preliminary conclusions. In the majority of intersex patients with known prenatal hormone abnormalities, the sexual orientation follows the sex of rearing. Consequently, we have to assume that prenatal hormone conditions by themselves do not rigidly determine sexual orientation. It seems possible that prenatal hormone abnormalities contribute to

the development of sexual orientation, at least in a minority of homosexual subjects, but this has not been sufficiently documented so far.

Cognition

Prenatal sex hormones have been thought to affect two aspects of cognitive development, general level of intelligence and sex-dimorphic cognitive abilities. That elevated intelligence has repeatedly been found in samples of female and male patients with CAH (*62–65*) suggests a prenatal hormonal basis, especially since the elevations did not seem to be attributable to the patient's socioeconomic status. Yet the demonstration (*63*) that also siblings and parents of CAH patients show elevated intelligence suggests either that there operates a subtle intellectual selection bias in families of CAH patients attending specialty clinics or that the recessive gene underlying the CAH syndrome is somehow linked to another trait favoring postnatal intellectual development. Enhanced mental functioning has also been described in early studies of offspring from hormone-treated pregnancies (*29, 66*). These findings, however, are likely to have resulted from methodological inadequacies (*40, 67*), especially socioeconomic selection bias. Recent studies involving adequate control groups (*44, 68*) did not show any favorable effects of prenatal hormone treatment on general intelligence, which is in line with the now well-established inefficacy of sex hormone treatment for most types of pregnancy abnormalities (*40*).

Sex differences in certain cognitive abilities are well known; for instance, verbal ability tends to be higher in females and spatial perception in males (*21*). With appropriate tests, these differences can already be shown in elementary school age and they become even more marked in puberty (*69*). This raises the question whether the biological factors that influence gender-role behavior also affect sex-dimorphic cognition. The CAH samples studied to date have not shown a particular cognitive profile, except for low number ability, that is, arithmetic skill, relative to the overall level of mental functioning (*63, 65, 70*) which is not a sex-dimorphic ability. Thus, these studies do not provide evidence of prenatal hormone effect on sex-dimorphic cognitive abilities. Scattered cognitive data available on other pertinent endocrine syndromes (*71*) or on offspring from sex-hormone treated pregnancies (*37, 38, 43, 68*) also offer no (*37, 38, 68*) or only tentative (*43, 71*) support for prenatal hormone effects on sex-dimorphic cognitive abilities.

Conclusions

The evidence accumulated so far suggests that human psychosexual differentiation is influenced by prenatal hormones, albeit to a limited degree. Where there are effects, they are compatible with animal experimental data on the role of prenatal androgens, progestogens, and estrogens in the expression of sex-dimorphic behavior. Best established are the effects of prenatal androgens on physical energy expenditure and play rehearsal of parenting behavior; effects on peer preferences and grooming behavior may be related to the former. The evidence for antiandrogenic action of prenatal progesterone and related compounds seems insufficient as yet; observations from various independent studies are in agreement concerning a slight demasculinizing effect of progestogens, but confounding variables such as pregnancy pathology have not been adequately controlled. Any conclusions drawn on the basis of human research studies have to remain tentative, but it is already obvious that prenatal hormones have to be considered along with other factors that interact in exerting their influence on the expression of sex-dimorphic behavior.

The development of gender identity seems to depend largely on the sex of rearing; in intersex patients, identity may become ambiguous if there are inconsistencies in parental sex-typing.

The evidence for the role of prenatal hormones in the development of sexual orientation is inconclusive. The data available on intersex patients indicate that prenatal hormones do not rigidly determine sexual orientation. More subtle contributions cannot be ruled out, however, and this possibility is strengthened by recent findings of differences between heterosexual and homosexual individuals in neuroendocrine regulatory characteristics.

The results of studies on the effects of prenatal sex hormones on general intelligence are fairly negative. Especially the relatively well-controlled studies seem to indicate a lack of any positive effect of prenatal androgens, progestogens, and estrogens on postnatal mental functioning. Effects of prenatal sex hormones on sex-dimorphic cognitive abilities have usually not been demonstrated in those few studies in which this issue has been investigated.

References and Notes

1. D. D. Federman, *Abnormal Sexual Development* (Saunders, Philadelphia, 1967); F. P. Haseltine and S. Ohno, *Science* **211**, 1272 (1981); J. D. Wilson, F. W. George, J. E. Griffin, *ibid.*, p. 1278.
2. B. S. McEwen, *Sci. Am.* **235**, 48 (July 1976).
3. F. A. Beach, in *Human Sexuality in Four Perspectives*, F. A. Beach, Ed. (Johns Hopkins Press, Baltimore, 1976), pp. 247–267; A. Jost, *Johns Hopkins Med. J.* **130**, 38 (1972); N. MacLusky and F. Naftolin, *Science* **211**, 1294 (1981).
4. C. H. Phoenix, R. W. Goy, A. A. Gerall, W. C. Young, *Endocrinology* **65**, 369 (1959).
5. R. W. Goy and D. A. Goldfoot, *Arch. Sex. Behav.* **4**, 405 (1975).
6. J. A. Resko, in *The Relationship Between Fetal Hormones and the Differentiation of the Central Nervous System in Primates*, W. Montagna and W. A. Sadler, Eds. (Plenum, New York, 1974), pp. 211–222.
7. B. S. McEwen, J. Lieberburg, N. MacLusky, L. Plapinger, *Ann. Biol. Anim. Biochim. Biophys.* **16**, 471 (1976); F. Naftolin *et al.*, *Recent Prog. Horm. Res.* **31**, 295 (1975).
8. R. A. Gorski, J. H. Gordon, J. E. Shryne, A. M. Southam, *Brain Res.* **148**, 333 (1978); G. Raisman and P. M. Field, *ibid.* **54**, 1 (1973); C. D. Toran-Allerand, *ibid.* **189**, 413 (1980).
9. A. P. Arnold, *Am. Sci.* **68**, 165 (1980).
10. R. W. Goy, in *Endocrinology and Human Behaviour*, R. P. Michael, Ed. (Oxford Univ. Press, London, 1968), pp. 12–31.
11. G. Dörner and J. Staudt, *Endokrinologie* **59**, 152 (1972); S. L. Kaplan, M. M. Grumbach, M. L. Aubert, *Recent Prog. Horm. Res.* **32**, 161 (1976).
12. J. Money and A. A. Ehrhardt, *Man and Woman, Boy and Girl: The Differentiation and Dimorphism of Gender Identity from Conception to Maturity* (Johns Hopkins Press, Baltimore, 1972).
13. J. Money, J. J. Hampson, I. L. Hampson, *Bull. Johns Hopkins Hosp.* **97**, 301 (1955).
14. J. Money and A. A. Ehrhardt, in *Endocrinology and Human Behaviour*, R. P. Michael, Ed. (Oxford Univ. Press, London, 1968), pp. 32–48.
15. J. Money, in *Hormonal Correlates of Behavior*, B. E. Eleftheriou and R. C. Spratt, Eds. (Plenum, New York, 1975), pp. 325–340.
16. A. A. Ehrhardt, in *Genetic Mechanisms of Sexual Development*, H. L. Vallet and I. H. Porter, Eds. (Academic Press, New York, 1979), pp. 473–483.
17. J. Imperato-McGinley, L. Guerrero, T. Gautier, R. E. Peterson, *Science* **186**, 1213 (1974); J. Imperato-McGinley, R. E. Peterson, T. Gautier, E. Sturla, *N. Engl. J. Med.* **300**, 1233 (1979).
18. R. T. Rubin, J. M. Reinisch, R. F. Haskett [*Science* **211**, 1318 (1981)] provide a detailed discussion of the problematic evidence on which Imperato-McGinley and colleagues base their theory.
19. A. A. Ehrhardt and H. F. L. Meyer-Bahlburg, *Ciba Found. Symp.* **62**, 41 (1979).
20. R. W. Goy, *Philos. Trans. R. Soc. London Ser. B* **259**, 149 (1970).
21. E. E. Maccoby and C. N. Jacklin, *The Psychology of Sex Differences* (Stanford Univ. Press, Stanford, Calif., 1974).
22. J. S. Rosenblatt, *Science* **156**, 1512 (1967); M. X. Zarrow, A. Farouq, V. H. Denenberg, P. B. Sawin, S. Ross, *J. Reprod. Fertil.* **6**, 375 (1963).
23. D. A. Goldfoot, in *Behavioral Primatology: Advances in Research and Theory*, A. S. Schrier, Ed. (Erlbaum, Hillsdale, N.J., 1977), vol. 1, pp. 139–184.
24. P. A. Lee, L. P. Plotnick, A. A. Kowarski, C. J. Migeon, Eds., *Congenital Adrenal Hyperplasia* (University Park Press, Baltimore, 1977).
25. A. A. Ehrhardt, R. Epstein, J. Money, *Johns Hopkins Med. J.* **122**, 160 (1968).
26. A. A. Ehrhardt and S. W. Baker, in *Sex Differences in Behavior*, R. C. Friedman, R. M. Richart, R. L. Vandewiele, Eds. (Wiley, New York, 1974), pp. 33–51.
27. H. F. L. Meyer-Bahlburg and A. A. Ehrhardt, *Aggressive Behav.*, in press.
28. J. Money and M. Schwartz, in (*24*), pp. 419–431.
29. A. A. Ehrhardt and J. Money, *J. Sex Res.* **3**, 83 (1967).
30. L. S. McGuire, K. O. Ryan, G. S. Omenn, *Behav. Genet.* **5**, 175 (1975).
31. A. A. Ehrhardt, thesis, University of Düsseldorf, Düsseldorf (1969).
32. D. N. Masica, J. Money, A. A. Ehrhardt, *Arch. Sex. Behav.* **1**, 131 (1971).
33. J. Money, A. A. Ehrhardt, D. N. Masica, *Johns Hopkins Med. J.* **123**, 105 (1968).
34. For example, L. Wilkins [*J. Am. Med. Assoc.* **172**, 1028 (1960)] and R. Burstein and H. C.

Wasserman [*Obstet. Gynecol.* **23**, 931 (1964)].
35. R. M. Dorfman and F. A. Kincl, Abstract, Reunion Anual, Societat Mexicana Nutricion y Endocrinologia, December 1963, p. 171.
36. B. H. Shapiro, A. S. Goldman, A. M. Bongiovanni, J. M. Marion, *Nature (London)* **264**, 795 (1976).
37. J. U. Zussman, P. P. Zussman, K. Dalton, Abstract, Meeting of the Society for Research in Child Development, Denver, Colo., 1975; J. U. Zussman, P. P. Zussman, K. Dalton, Abstract, Third Annual Meeting of the International Academy of Sex Research, Bloomington, Ind., 1977.
38. A. Lynch, W. Mychalkiw, S. J. Hutt, *Early Hum. Dev.* **2**, 305 (1978). Only results concerning sex-dimorphic behavior are described in the text.
39. H. F. L. Meyer-Bahlburg, G. C. Grisanti, A. A. Ehrhardt, *Psychoneuroendocrinology* **2**, 383 (1977); A. A. Ehrhardt, G. C. Grisanti, H. F. L. Meyer-Bahlburg, *ibid.*, p. 391.
40. H. F. L. Meyer-Bahlburg and A. A. Ehrhardt, in *Drugs and Chemical Risks to the Fetus and Newborn*, R. H. Schwarz and S. J. Yaffe, Eds. (Liss, New York, 1980), pp. 93–107.
41. A. A. Ehrhardt, H. F. L. Meyer-Bahlburg, S. E. Ince, J. F. Feldman, *Progestogens and Estrogens: New Evidence for Long-Term Effects on Sex-Dimorphic Behavior*, in preparation.
42. H. F. L. Meyer-Bahlburg, A. A. Ehrhardt, S. E. Ince, J. F. Feldman, in *Life Span Research on the Prediction of Psychopathology*, L. Erlenmeyer-Kimling, B. S. Dohrenwend, N. Miller, Eds. (Columbia Univ. Press, New York, in press).
43. I. D. Yalom, R. Green, N. Fish, *Arch. Gen. Psychiatry* **28**, 554 (1973).
44. Behavioral estrogen-progestogen effects have also been studied [J. M. Reinisch and W. G. Karow, *Arch. Sex. Behav.* **6**, 257 (1977); J. M. Reinisch, *Nature (London)* **266**, 561 (1977)]. However, the personality questionnaires used do not assess sex-dimorphic behavior.
45. G. Dörner, *J. Endocrinol.* **42**, 163 (1968); ——— and G. Hinz, *ibid.* **40**, 387 (1968); G. Dörner, *Hormones and Brain Differentiation* (Elsevier, Amsterdam, 1976).
46. H. F. L. Meyer-Bahlburg, *Arch. Sex. Behav.* **6**, 297 (1977); *ibid.* **8**, 101 (1979); F. A. Beach, *Ciba Found. Symp.* **62**, 113 (1979).
47. C. S. Ford and F. A. Beach, *Patterns of Sexual Behavior* (Harper & Row, New York, 1951), pp. 141–146; J. Erwin and T. Maple, *Arch. Sex. Behav.* **5**, 9 (1976); T. Maple, D. Bernard, M. McGlynn, *J. Biol. Psychol.* **19**, 25 (1977).
48. B. J. Meyerson and L. H. Lindström, *Acta Physiol. Scand. Suppl.* **389**, 1 (1973); J. Hetta and B. J. Meyerson, *ibid.* **453**, 1 (1978); F. A. Beach, A. I. Johnson, J. J. Anisko, I. F. Dunbar, *J. Comp. Physiol. Psychol.* **91**, 711 (1977); R. P. Michael, D. Zumpe, E. B. Keverne, R. W. Bonsall, *Recent Prog. Horm. Res.* **28**, 665 (1972).
49. J. Kagan and F. A. Beach, *J. Comp. Physiol. Psychol.* **46**, 204 (1953); D. A. Goldfoot and K. Wallen, in *Recent Advances in Primatology*, vol. 1, *Behaviour*, D. J. Chivers and J. Herbert, Eds. (Plenum, New York, 1978), pp. 155–159.
49a. A. A. Ehrhardt and S. W. Baker, paper presented at the International Congress of Sexology, Montreal, Quebec, Canada, 28 to 31 October 1976; data quoted in H. F. L. Meyer-Bahlburg [*Arch. Sex. Behav.* **8**, 101 (1979)].
50. A. A. Ehrhardt, K. Evers, J. Money, *Johns Hopkins Med. J.* **123**, 115 (1968).
51. A. Lev-Ran, *Arch. Sex. Behav.* **3**, 27 (1974).
52. J. Money and C. Ogunro, *ibid.*, p. 181.
53. Similarly inconclusive is the situation of genetic females with CAH who have been reared male. J. Money and J. Daléry [*J. Homosex.* **1**, 357 (1976)] desribe three such cases, all of whom were living as heterosexual well-identified males.
54. H. F. L. Meyer-Bahlburg, E. McCauley, C. Schenck, T. Aceto, Jr., L. Pinch, in *Sex Differences in Behavior*, R. C. Friedman, R. M. Richart, R. L. Vandewiele, Eds. (Wiley, New York, 1974), pp. 281–299.
55. J.-C. Job, D. Gendrel, A. Safar, M. Roger, J.-L. Chaussain, *Acta Endocrinol.* **85**, 644 (1977).
56. D. Gendrel, J.-C. Job, M. Roger, *ibid.* **89**, 372 (1978).
57. This discussion refers to the "positive estrogen feedback effect" on luteinizing hormone and related phenomena.
58. G. Dörner, W. Rohde, L. Krell, *Endokrinologie* **60**, 297 (1972); G. Dörner, W. Rohde, K. Seidel, W. Haas, G. Schott, *ibid.* **67**, 20 (1976); G. Dörner, W. Rohde, F. Stahl, L. Krell, W. G. Masius, *Arch. Sex. Behav.* **4**, 1 (1975).
59. L. E. Seyler, E. Canalis, S. Spare, S. Reichlin, *J. Clin. Endocrinol. Metab.* **47**, 176 (1978).
60. J. A. Resko, S. K. Quadri, H. G. Spies, *Endocrinology* **101**, 215 (1977).
61. T. Aono, A. Miyake, T. Kinugasa, K. Kurachi, K. Matsumoto, *Acta Endocrinol.* **87**, 259 (1978); P. F. A. Van Look, W. M. Hunter, C. S. Corker, D. T. Baird, *Clin. Endocrinol.* **7**, 353 (1977).
62. J. Money and V. Lewis, *Bull. Johns Hopkins Hosp.* **118**, 365 (1966).
63. S. W. Baker and A. A. Ehrhardt, in *Sex Differences in Behavior*, R. C. Friedman, R. M. Richart, R. L. Vandewiele, Eds. (Wiley, New York, 1974), pp. 53–76.
64. L. S. McGuire and G. S. Omenn, *Behav. Genet.* **5**, 165 (1975).
65. S. M. Perlman, *J. Learn. Disabil.* **6**, 26 (1973).
66. K. Dalton, *Br. J. Psychiatry* **114**, 1377 (1968); *ibid.* **129**, 438 (1976).
67. A. Lynch and W. Mychalkiw, *Early Hum. Dev.* **2**, 323 (1978).
68. H. F. L. Meyer-Bahlburg and A. A. Ehrhardt, in *Progress in Sexology*, R. Gemme and C. C. Wheeler, Eds. (Plenum, New York, 1977), pp. 85–92.
69. D. P. Waber, *Science* **192**, 572 (1976); *Dev. Psychol.* **13**, 29 (1977).
70. V. G. Lewis, J. Money, R. Epstein, *Johns Hopkins Med. J.* **122**, 192 (1968).
71. D. N. Masica, J. Money, A. A. Ehrhardt, V. G. Lewis, *ibid.* **124**, 34 (1969).
72. Supported in part by grants from the Spencer Foundation, the Ford Foundation, and the Grant Foundation.

Postnatal Gonadal Steroid Effects on Human Behavior

Robert T. Rubin, June M. Reinisch, Roger F. Haskett

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

Dr. Rubin is a professor of psychiatry, Harbor–U.C.L.A. Medical Center, Torrance, California 90509. Dr. Reinisch is an associate professor of psychology at Rutgers University, Busch Campus, New Brunswick, New Jersey 08903. Dr. Haskett is an assistant professor of psychiatry at the University of Texas Medical Branch, Galveston 77550.

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