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ANDROGENS AND THE EVOLUTION OF MALE-GENDER IDENTITY AMONG MALE PSEUDOHERMAPHRODITES WITH 5α -REDUCTASE DEFICIENCY

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Abstract To determine the contribution of androgens to the formation of male-gender identity, we studied male pseudohermaphrodites who had decreased dihydrotestosterone production due to 5α -reductase deficiency. These subjects were born with female-appearing external genitalia and were raised as girls. They have plasma testosterone levels in the high normal range, show an excellent response to testosterone and are unique models for evaluating the effect of testosterone, as compared with a female upbringing, in determining gender identity. Eighteen of 38 af-

ected subjects were unambiguously raised as girls, yet during or after puberty, 17 of 18 changed to a male-gender identity and 16 of 18 to a male-gender role. Thus, exposure of the brain to normal levels of testosterone in utero, neonatally and at puberty appears to contribute substantially to the formation of male-gender identity. These subjects demonstrate that in the absence of sociocultural factors that could interrupt the natural sequence of events, the effect of testosterone predominates, over-riding the effect of rearing as girls. (N Engl J Med 300:1233-1237, 1979)

MALE pseudohermaphrodites with a deficiency of the enzyme 5α -reductase^{1,2} raised as girls provide a unique opportunity for evaluation of the effects of testosterone and the sex of rearing in the determination of gender identity in man. Because of a deficiency in the activity of this enzyme, there is decreased in utero production of dihydrotestosterone, which results in severe ambiguity of the external genitalia of the affected male fetus. Thus, at birth, many affected infants were thought to be girls and were raised accordingly. However, since the biosynthesis and peripheral action of testosterone are normal, prenatal, neonatal and pubertal exposure to testosterone in affected subjects proceeds normally.

At birth, the subjects have a markedly bifid scrotum that appears labia-like. There is a clitoris-like phallus and a urogenital sinus with a blind vaginal pouch. The testes are in the abdomen, inguinal canal or scrotum.^{1,2} However, during puberty, under the influence

of normal plasma testosterone levels, definite virilization occurs. The voice deepens, and affected subjects develop a muscular habitus. There is substantial growth of the phallus, and the scrotum becomes rugated and hyperpigmented. In most subjects, the testes descend into the scrotum if they have not already done so. There is no gynecomastia. The subjects have erections, and there is an ejaculate from the urethral orifice on the perineum. They are capable of intromission but, because of the position of the urethra, are incapable of insemination.^{1,2} These subjects are therefore testosterone-exposed and testosterone-responsive boys born with female-appearing external genitalia and raised as girls.

MATERIALS AND METHODS

There are 38 known male pseudohermaphrodites with 5α -reductase deficiency from 23 inter-related families spanning four generations in three rural villages in the southwestern region of the Dominican Republic. The condition is inherited as an autosomal recessive trait.^{1,2} Five of these 38 subjects have died, two in infancy and three in adulthood. Of the remaining 33 pseudohermaphrodites, 25 are postpubertal, three pubertal and five prepubertal.

Historical data were obtained by interviewing affected subjects in villages A and B. Other men and boys in the villages were interviewed as controls. Parents, siblings, wives, girl friends and neighbors of the affected subjects were interviewed when possible. The interviews were conducted in Spanish by members of our research group who were known to the community since 1972 and were independently translated into English by another member of the group. The interviews were designed to discern any sexual ambiguity in the rearing of subjects raised as girls and to determine in

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these subjects the validity of the change to a male-gender identity and male-gender role.* In subjects who appeared to change to a male-gender identity and male-gender role, the manifestations of male sexual behavior were evaluated according to four patterns of sexual behavior differentiation described by Diamond¹: sexual gender identity, sexual patterns (sex-related behavior, which for men includes direct aggressiveness, assertiveness, large motor activity and occupation), sexual object of choice (the sex of the person chosen as an erotically interesting partner) and sexual mechanisms (the features of sexual expression over which an individual has little control, which for men include the ability to obtain and maintain an erection and to achieve orgasm).

Six subjects work in a hospital in Santo Domingo where a member of the research team is affiliated. Members of the team have made numerous trips to the community since 1972, and the villagers are familiar with them. Six subjects and a father and sister of one of them have been hospitalized at New York Hospital for six to eight weeks. Two subjects now reside in New York. Thus, we have observed the subjects during formal interview sessions and for long periods thereafter and have become involved with them and their families.

Data on social practices within the villages were obtained to discern possible effects on the change in gender identity of the subjects.

RESULTS

The interview data showed that 19 of 33 subjects from villages A and B had been unambiguously raised as girls (Fig. 1). Adequate postpubertal psychosexual data were obtained from 18 of these 19 subjects. Of the 18 subjects, 17 had successfully changed to a male-gender identity and 16 to a male-gender role. The 17 subjects who changed to a male-gender identity began to realize that they were different from other girls in the village between seven and 12 years of age, when they did not develop breasts, when their bodies began to change in a masculine direction and when masses were noted in the inguinal canal or scrotum. These subjects showed self-concern over their true gender. A male-gender identity gradually evolved over several years as the subjects passed through stages of no longer feeling like girls, to feeling like men and, finally, to the conscious awareness that they were indeed men. The change to a male-gender role occurred either during puberty or in the post-pubertal period, after the subjects were convinced that they were men (male-gender identity) and were experiencing sexual interest in women. The gender-role change took place at 16 years of age, on the average, with a range of 14 to 24 years.

The ages at which the subjects first experienced morning erections, nocturnal emissions, masturbation and sexual intercourse were not appreciably dif-

ferent between those raised as girls who changed to a male-gender identity and those raised as boys. The time of first sexual intercourse was 15 to 18 years of age for subjects raised as girls, 15 to 17 years for those raised as boys and 14 to 16 years for 20 normal male controls in the village. The adequacy of sexual intercourse depends on the size of the phallus and the severity of the chordee.

Although these subjects behave unequivocally as males, they experience certain insecurities because of the appearance of their genitalia. They view themselves as incomplete persons, and this attitude burdens them. They fear ridicule by members of the opposite sex and initially feel anxious about forming equal relations. However, 15 of 16 subjects who changed to a male-gender role are either living with women in common-law marriages or have lived with women in a common-law relation. The one exception is subject 1 from village B who lives alone in the hills, where he works as a farmer since changing to a male-gender role at 20 years of age (Fig. 1). Three subjects are presently living with women who have children from previous unions. In a domestic setting, the women take care of the household activities, while the affected subjects work as farmers, miners or woodsmen, as do the normal males in the town. They enjoy their role as head of the household (see Appendix).

Subject 4 (Fig. 1) from village A changed to a male-gender identity but continues to dress as a woman (female-gender role). This subject has the affective mannerisms of a man and engages in sexual activity with village women.

Subject 25 (Fig. 1) from village B is the only subject affected after puberty who has maintained a female-gender identity and female-gender role. At 16 years of age, she "married" a man in village B who left after one year. She left the village, has been living alone and working as a domestic and has not been sexually involved with other men. She wears no breasts, yet her build and mannerisms are masculine. She denies any attraction to women and desires surgical correction of the genitalia so that she can be a normal woman.

In village A, postpubertal subjects 12 and 13 (Fig. 1), initially raised as girls, were reared as boys later in childhood by their parents and have remained men. Subject 19 from village A (Fig. 1) was raised as a girl, despite parental knowledge that an older brother had changed gender identity and gender role at puberty, and despite the fact that two affected young siblings were being raised as boys. Thus, these three subjects were not unambiguously raised as girls. Likewise, subject 33 from village B (Fig. 1) is being raised as a girl, despite family awareness of the situation. Subject 23 (Fig. 1), whose parents are descendants of the inhabitants of village A, was born in Santo Domingo and raised as a girl. When she was hospitalized for a hernia at the age of 18 months, her parents were told of her condition. When the subject

*Gender identity is defined as the sameness, unity and persistence of one's individuality as man, woman or ambivalent, especially as the attitude is experienced in self-awareness and behavior; gender identity is the private experience of gender role.²¹

Gender role is defined as everything that a person says and does, to indicate to others or to the self the degree that one is either man, woman or ambivalent. The term includes, but is not restricted to, sexual arousal and response; gender role is the public expression of gender identity.²²

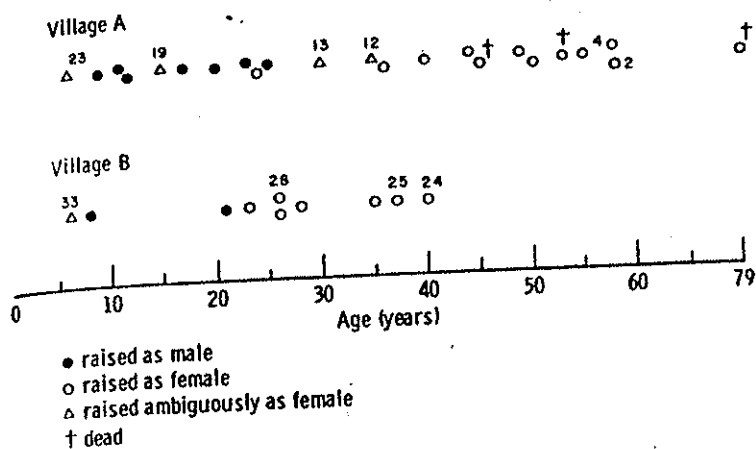


Figure 1. Ages in 1978 and Sex of Rearing in 33 Male Pseudohermaphrodites with 5 α -Reductase Deficiency from Villages A and B.

The numbers indicate the subject numbers mentioned in the text. Note that the condition is now recognized at birth or shortly thereafter in the younger subjects, and most of them are being raised as boys. In the older subjects, however, the condition was unrecognized throughout childhood, and they were raised unambiguously as females.

was 5 1/2 years of age, the girl's father decided to raise her as a boy.

Thus, the subjects in villages A and B were raised as girls, until the townspeople became aware of the problem. The villagers now either raise the subjects as boys from birth, rear them as boys as soon as the problem is recognized in childhood or raise them ambiguously as girls. Now that the villagers are familiar with the condition, the affected children and adults are sometimes objects of ridicule and are referred to as *guevedoce*, *guevotte* (penis at 12 years of age) or *machihembra* (first woman, then man).

DISCUSSION

Androgens given prenatally, postnatally or at both stages to either female animals or male castrate animals can induce both adult male sexual and non-sexual behavior and can inhibit female sexual behavioral responses. Although the amount of androgens given and the critical period for treatment differ among species, similar effects on the development of male sexual behavior have been obtained in the rat,^{5,6} guinea pig,⁷ mouse,⁸ rabbit,⁹ hamster,¹⁰ dog,¹¹ sheep¹² and rhesus monkey.¹³ In addition to behavioral differences, androgen-induced sexual differences in brain morphology and function have been well documented in animals.¹⁴⁻¹⁸ The effects of androgens on the brain that cause sexual dimorphism in animals may be mediated either directly by androgens (i.e., testosterone), by in situ aromatization of androgens to estrogens in the brain¹⁹ or by both mechanisms.

In man, the question of the relative influences of hormonal factors and environmental factors in the determination of gender identity remains unanswered. In 1955, the theory of sexual neutrality at birth was proposed.^{20,21} This theory was later broadened to include knowledge that although infant boys and girls express sexually dimorphic behavior from birth (which may be hormonally mediated), it is not the exclusive property of either sex but may be incor-

porated into either a male-gender or female-gender identity pattern that is acquired during various childhood experiences (i.e., sexual identity of rearing). The theory also stated that gender identity "imprinting" begins by one year of age and is firmly established by three to four years.²²

To test this hypothesis, pseudohermaphrodites were matched so that they were "chromosomally, gonadally and otherwise diagnostically the same" and were said to differ only in their sexual identity of rearing.²² The studies concluded that since the gender identity of the individuals was concordant with the sex of rearing and not with the chromosomal or gonadal sex, the sex of rearing predominated in the formation of gender identity in man. The subjects of these studies may have been matched chromosomally and gonadally, but they were not matched for a similar hormonal milieu, because methods for the measurement of plasma sex steroids were not available when the studies were conducted. Thus, the issue of nature (i.e., androgen) versus nurture (i.e., sex of rearing) in the determination of a male-gender identity cannot be adequately resolved in these cases. Also, in most subjects in whom gender identity was the same as the sex of rearing and contrary to chromosomal and gonadal sex, castration and sex-hormone therapy were usually given to complement the sex of rearing.^{20,22}

This paper demonstrates that in a laissez-faire environment, 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. Eighteen subjects were unambiguously raised as girls, yet despite the female sex of rearing, 17 subjects changed to a male-gender identity and 16 subjects to a male-gender role during or after puberty. Intervention by a physician, namely, reassurance, surgical correction of the external genitalia to agree with the female sex assignment or hormone therapy to coincide with the female sex of rearing, did not occur. Parental attitudes during the

course of the change involved amazement, confusion and, finally, acceptance rather than hostility and prevention. Social pressure, for example, embarrassment and possible harassment afterward by other villagers, were the major anxieties the affected boys experienced and may have caused them to hesitate in making the change. However, the pressures were not strong enough to prevent the change to a male-gender role in 16 of 17 subjects who had adopted a male-gender identity at puberty. The one subject who retained a female-gender identity after puberty is an exception to the phenomenon of pubertal gender-identity change in these subjects.

Thus, it appears that the extent of androgen (i.e., testosterone) exposure of the brain in utero, during the early postnatal period and at puberty has more effect in determining male-gender identity than does sex of rearing. This experiment of nature emphasizes the importance of androgens, which act as inducers (in utero and neonatally) and as activators (at puberty), in the evolution of a male-gender identity. This study also shows that gender identity is not unalterably fixed in early childhood but is continually evolving, becoming fixed with the events of puberty.

Since the evolution of a male-gender identity begins at early puberty in subjects with 5α -reductase deficiency, either prepubertal or pubertal castration with the introduction of female hormone therapy might abort its development.^{2,23,24} Because the time course for the development of a male-gender identity with puberty appears to be unique to each person, the age at which successful interruption (i.e., castration or sociocultural factors) can prevent the complete evolution of this gender identity and the change to a male-gender role or both phenomena will undoubtedly differ for each subject.

We have recently studied a 65-year-old male pseudohermaphrodite with 5α -reductase deficiency who was born in southern Italy and raised as a girl. The subject emigrated to the United States at 16 years of age. Psychosexual evaluation showed that the subject gradually changed to a male-gender identity at puberty. He now has a male-gender identity but because of family pressure has retained a female-gender role. These observations have been reported elsewhere in great detail (Imperato-McGinley J, Peterson RE, Leshin M, et al: unpublished data).

In male pseudohermaphrodites with inadequate testosterone production or action, gender identity may be the same as the sex of rearing, which then becomes the predominant force in this setting. These subjects are a testimonial to the maleability of human beings in the acquisition of gender identity but in no way approximate the normal sequence of events.²⁵

There are many reported male pseudohermaphrodites who successfully changed from female to male gender.²⁶⁻³⁴ In many of these patients, the change oc-

curred during adolescence. Adequate hormonal evaluation would be important in such patients. It also appears to challenge both the theory of the mutability of gender identity after three to four years of age and the sex of rearing as the major factors determining male-gender identity.

Our data show that environmental or sociocultural factors are not solely responsible for the formation of male-gender identity. Androgens make a strong, definite contribution.

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APPENDIX

The Towns and Social Practices

Villages A and B are in a remote and rural area in the southwestern section of Santo Domingo. Both villages were geographic isolates, with access only by dirt roads. However, 20 years ago, the government paved the road to village A. The road to the salt mine from a neighboring village. The road to village B, however, is unchanged. The population of village A is about 5000, and the population of village B is about 2000. Houses on the main street of the villages are constructed with roofs made of woven palm leaves; these houses contain bedrooms and a living area. The other houses in the villages are huts with only two rooms, a community bedroom and a kitchen. They are constructed from sticks and have thatched roofs. In a few houses, the kitchen is separate and located behind the house. The inhabitants of the towns, both adults and children, live near the river.

The family unit consists of a mother and father, who have been married in either a legal or religious ceremony, and children. The men earn a living either farming, mining or logging. The farms are small agricultural plots and are worked individually by the head of the household (the father) or collectively by the male members of the family and other male kin. One of the men of village A, there is a salt and gypsum mine. The men from the village are employed in the mine, but many of the miners are brought in by truck from a larger town.

The women generally do not help in the *carbonero* activities, but they cultivate the agricultural plots. They maintain the house and take care of the children and cultivate small gardens in the back of the house. Female relatives of the mother usually come over the day to participate in such household activities as cooking, washing and babysitting. The children are taken care of by the mother or grandmother, older sisters and other female relatives.

There is definite socialization of the children according to sex. The boys are also allowed to go naked until seven or eight years of age. However, the girls wear underpants from the time they are toilet trained. The boys and girls play together until they are 11 years of age. Between six and 11 years of age, the children are encouraged to play separately according to sex. After about 11 years of age, the girls help their mothers with the household activities, while the boys help their fathers during the planting and harvesting season or with the *carbonero* activities. In general, however, the boys have more freedom to romp and play outside the house, while the girls are encouraged to stay with their mothers or play in the house.

There is a primary school in the town, and the children start their education at seven or eight years of age. Boys and girls attend school together, with no segregation according to sex. Most of the children, however, do not go to school either because the parents don't have the money to buy them books and pencils or because of lack of parental interest. Very few children in the town attend school beyond the third grade.

After 11 or 12 years of age, the boys seek entertainment at the bars and attend cockfights. The girls, on the other hand, stay home and help with household chores and only occasionally go to the local bar to dance and socialize. In general, the girls marry earlier, between 13 and 20 years of age, and the boys between 18 and 25. Fidelity is demanded from the women but not from the men.

There are no laws in the town against homosexuality, but there is strong social pressure against it, and thus it is practiced furtively in both villages. Female prostitution also exists and is accepted as a fact of life. The boys in the town start going to prostitutes at 14 years of age.

REFERENCES

- Imperato-McGinley J, Guerrero L, Gautier T, et al: Steroid 5 α -reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science* 186:1213-1215, 1974
- Walsh PC, Madden JD, Harrod MJ, et al: Familial incomplete male pseudohermaphroditism, Type 2: decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. *N Engl J Med* 291:944-949, 1974
- Peterson RE, Imperato-McGinley J, Gautier T, et al: Male pseudohermaphroditism due to steroid 5 α -reductase deficiency. *Am J Med* 62:170-191, 1977
- Diamond M: Human sexual development: biological foundations for social development, *Human Sexuality in Four Perspectives*. Edited by FA Beach. Baltimore, Johns Hopkins University Press, 1977, pp 22-61
- Harris GW: Sex hormones, brain development and brain function. *Endocrinology* 75:627-648, 1964
- Pfaff DW, Zigmund RE: Neonatal androgen effects on sexual and non-sexual behavior of adult rats tested under various hormone regimens. *Neuroendocrinology* 7:129-145, 1971
- Phoenix CH, Goy RW, Gerall AA, et al: Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology* 65:369-382, 1959
- Edwards DA, Burge KG: Early androgen treatment and male and female sexual behavior in mice. *Horm Behav* 2:49-58, 1971
- Beyer C, de la Torre L, Larsson K, et al: Synergistic actions of estrogen and androgen on the sexual behavior of the castrated male rabbit. *Horm Behav* 6:301-306, 1975
- Paup DC, Coniglio LP, Clemens LG: Masculinization of the female golden hamster by neonatal treatment with androgen or estrogen. *Horm Behav* 3:123-131, 1972
- Beach FA: Hormonal modification of sexually dimorphic behavior. *Psychoneuroendocrinology* 1:3-23, 1975
- Clarke IJ: The sexual behaviour of prenatally androgenized ewes observed in the field. *J Reprod Fertil* 49:311-315, 1977
- Goy RW, Wolf JE, Eisele SG: Experimental female hermaphroditism in rhesus monkeys: anatomical and psychological characteristics. *Handbook of Sexology*. Edited by H Husaph, J Money. Amsterdam, Excerpta Medica, 1976, pp 136-156
- Pfaff DW: Morphological changes in the brains of adult male rats after neonatal castration. *J Endocrinol* 36:415-416, 1966
- Gorski RA, Gordon JH, Shryne JE, et al: Evidence for a morphological sex difference within the medial preoptic area of the rat brain. *Brain Res* 148:333-346, 1978
- Barracrough CA: Modifications in the CNS regulation of reproduction after exposure of prepubertal rats to steroid hormones. *Recent Prog Horm Res* 22:503-539, 1966
- Nottebohm F, Arnold AP: Sexual dimorphism in vocal control areas of the songbird brain. *Science* 194:211-213, 1976
- Bubenik GA, Brown GM: Morphologic sex differences in primate brain areas involved in regulation of reproductive activity. *Experientia* 29:619-621, 1973
- Reddy VVR, Naftolin F, Ryan KJ: Conversion of androstenedione to estrone by neural tissues from fetal and neonatal rats. *Endocrinology* 94:117-121, 1974
- Money J, Hampson JG, Hampson JL: Hermaphroditism: recommendations concerning assignment of sex, change of sex, and psychological management. *Bull Johns Hopkins Hosp* 97:284-300, 1955
- Idem*: An examination of some basic sexual concepts: the evidence of human hermaphroditism. *Bull Johns Hopkins Hosp* 97:301-319, 1955
- Money J, Ehrhardt AA: *Man and Woman, Boy and Girl: The differentiation and dimorphism of gender identity from conception to maturity*. Baltimore, Johns Hopkins University Press, 1972
- Saenger P, Goldman AS, Levine LS, et al: Prepubertal diagnosis of steroid 5 α -reductase deficiency. *J Clin Endocrinol Metab* 46:627-634, 1978
- Fisher LK, Kogut MD, Moore RJ, et al: Clinical, endocrinological and enzymatic characterization of two patients with 5 α -reductase deficiency: evidence that a single enzyme is responsible for the 5 α -reduction of cortisol and testosterone. *J Clin Endocrinol Metab* 47:653-664, 1978
- Diamond M: A critical evaluation of the ontogeny of human sexual behavior. *Q Rev Biol* 40:147-175, 1965
- Chapman AH, Saslow G, Watson F: Pseudohermaphroditism: a medical, social, and psychiatric case study. *Psychosom Med* 13:212-219, 1951
- Burns E, Segaloff A, Carrera GM: Reassignment of sex: report of 3 cases. *J Urol* 84:126-133, 1960
- Ghabrial F, Girgis S: Reorientation of sex: report of two cases. *Int J Fertil* 7:249-258, 1962
- Berg I, Leeds MB: Change of assigned sex at puberty. *Lancet* 2:1216-1217, 1963
- Brown JB, Fryer MP: Plastic surgical correction of hypospadias with mistaken sex identity and transvestism resulting in normal marriage and parenthood. *Surg Gynecol Obstet* 118:45-46, 1964
- Teter J, Boczkowski K: Errors in management and assignment of sex in patients with abnormal sexual differentiation. *Am J Obstet Gynecol* 93:1084-1087, 1965
- Dewhurst CJ, Gordan RR: *The Intersexual Disorders*. London, Bailière, Tindall & Cassell, 1969, pp 124-149
- Stoller RJ: A contribution to the study of gender identity. *Int J Psychoanal* 45:220-226, 1964
- Zuger B: Gender role determination: a critical review of the evidence from hermaphroditism. *Psychosom Med* 32:449-467, 1970