Journal of Steroid Biochemistry, Vol. 11, pp. 637 to 645
Pergamon Press Ltd 1979. Printed in Great Britain

19. Metabolic Defects

MALE PSEUDOHERMAPHRODITISM SECONDARY TO 5α-REDUCTASE DEFICIENCY—A MODEL FOR THE ROLE OF ANDROGENS IN BOTH THE DEVELOPMENT OF THE MALE PHENOTYPE AND THE EVOLUTION OF A MALE GENDER IDENTITY

JULIANNE IMPERATO-MCGINLEY,* RALPH E. PETERSON,
TEOFILO GAUTIER and ERASMO STURLA
Division of Endocrinology, Department of Medicine, Cornell University Medical College, New York, and Universidad Nacional Pedro Henriquez Urena, Department of Pediatrics, Santo Domingo, Dominican Republic

SUMMARY

Male pseudohermaphroditism secondary to 5α-reductase deficiency is reviewed. At birth, the affected males (46 XY) have a clitoral-like phallus, bifid scrotum and urogenital sinus with the testes in the inguinal canals or labial-scrotal folds. At puberty, a muscular male habitus develops with growth of the phallus and without gynecomastia.

When compared to aged matched male controls the mean plasm testosterone (T) levels in affected adults are significantly higher; while the mean plasma 5α-dihydrotestosterone (DHT) levels are significantly lower. The plasma T:DHT ratios range from 24 to 84, compared to a normal range of 8–16. After administration of hCG, the T:DHT ratios in the affected prepubertal male children range from 35 to 172 compared to a range of 3–26 in the controls. The metabolic clearance rates of T and DHT are normal, but the conversion ratio of T to DHT is decreased to less than 1%. The endogenous mean urinary etiocholanolone (5β) to androsterone (5α) ratios, and the urinary 5β to 5α ratios after infusion of radioactive T are significantly higher than in normal males.

Studies with cortisol and corticosterone (11-oxo, C-21) Δ4-11β-hydroxyandrostenedione (11-deoxy, C-19) and testosterone and androstenedione (11-deoxy, C-19) have shown that the fractional conversion of the infused parent steroids to 5α reduced produced products is markedly decreased in individuals with 5α-reductase deficiency and may reflect a generalized defect in steroid metabolism.

Decreased 5α-reductase activity has been demonstrated in fibroblasts cultured from nongenital and genital skin of affected subjects, in cell free extracts from epididymis and fibroblasts cultured from genital skin and in genital skin slices. Characterization of the enzyme activity in four kindreds reveals that 5α-reductase enzyme activity in each kindred has different properties.

Pedigree analysis from the large Dominican kindred reveals inheritance to be autosomal recessive. This model of inheritance is further documented by the fact that some sibling sisters show the same biochemical defect, and obligate carrier parents show an intermediate defect.

The affected subjects provide a clinical model for delineating the roles of T and DHT in sexual differentiation and development.

Because of the appearance of the genitalia at birth, 18 of the affected males from the Dominican kindred were raised as girls. Extensive psychosexual evaluation was conducted by interviewing the affected subjects, parents, siblings and wives, and it was found that in spite of the rearing as female throughout childhood 16 of 18 changed gender identity and role with puberty.

We conclude that in the formation of male gender identity, normal T exposures of the brain in utero and at puberty are major contributing factors. Thus, in normal males the formation of gender identity is at least partially androgen induced.

INTRODUCTION

Male pseudohermaphroditism secondary to steroid 5α-reductase deficiency was first described as a distinct biochemical abnormality in 1974 in 38 affected subjects from 23 families located in the Dominican Republic [1–3], and in two siblings from Dallas [4]. Since that time the enzyme deficiency has been described in two siblings from Los Angeles [5] and two other children from unrelated families [6]. Recently we have diagnosed 5α-reductase deficiency in a 65-year-old male pseudohermaphrodite not related to the Dominican kindred [7]. Neither this subject nor any of the postpubertal affected subjects in the Dominican kindred were castrated, thereby enabling us to follow the natural history of this condition. The diagnosis in the other reported subjects, however, was made either prepubertally or during early puberty [4–6] and the affected subjects were subsequently castrated with the introduction of female hormone therapy at the appropriate time.

* To whom request for reprints should be addressed.

DESCRIPTION

Male pseudohermaphroditism secondary to 5α-reductase deficiency is characterized biochemically by: (1) normal to elevated levels of plasma testosterone [1–4, 6, 7]; (2) decreased levels of plasma dihydrotestosterone [1–3, 6, 7]; (3) an increased testosterone to dihydrotestosterone ratio after HCG stimulation [3, 5]; (4) decreased conversion of testosterone to dihydrotestosterone *in vivo* [3, 5, 7]; (5) decreased production of urinary 5α-reduced metabolites of testosterone [1–7]; (6) a decrease in urinary 5α-reduced metabolites of C-21 steroids and C-19 steroids other than testosterone, i.e. cortisol, corticosterone, 11β-hydroxy-androstendione and androstendione [6, 8]; and (7) diminished 5α-reductase activity in tissue studies [4–7, 9–14]. Studies of 5α-reductase enzyme activity reveal familial differences and demonstrate genetic heterogeneity [7, 9, 13]. The mode of inheritance of this condition is well documented in the Dominican kindred and appears to be autosomal recessive [2, 3, 12]. In the Dominican pedigree of 23 families from three isolated villages, the genetic defect can be traced back seven generations to one woman. In 11 families one line of descent can be traced to this woman, and in another nine families, lineage can be traced through both parents to the same woman. The pedigree which demonstrates common ancestry and the isolation of the Dominican villages suggest that the increase in the gene frequency within the community is the result of genetic drift—a founder effect.

To date all reported cases with 5α-reductase deficiency have perineal hypospadias, with either separate urethral and vaginal orifaces or with a blind vaginal pouch opening into the urethra. In our most recent case a blind vaginal pouch was not demonstrated [7]. The testes are in the abdomen, inguinal canal or scrotum and there are no Mullerian structures. Wolffian duct differentiation occurs normally and the affected subjects have an epididymis, vas deferens, and seminal vesicles [1–7, 12]. Because of the severe ambiguity of the external genitalia, the affected subjects in the reported cases were thought to be females at birth and raised as females. (Fig. 1, 1a). In the Dominican kindred, the subjects from the older gen-

Fig. 1. An 18-month-old male pseudohermaphrodite with 5α-reductase deficiency.

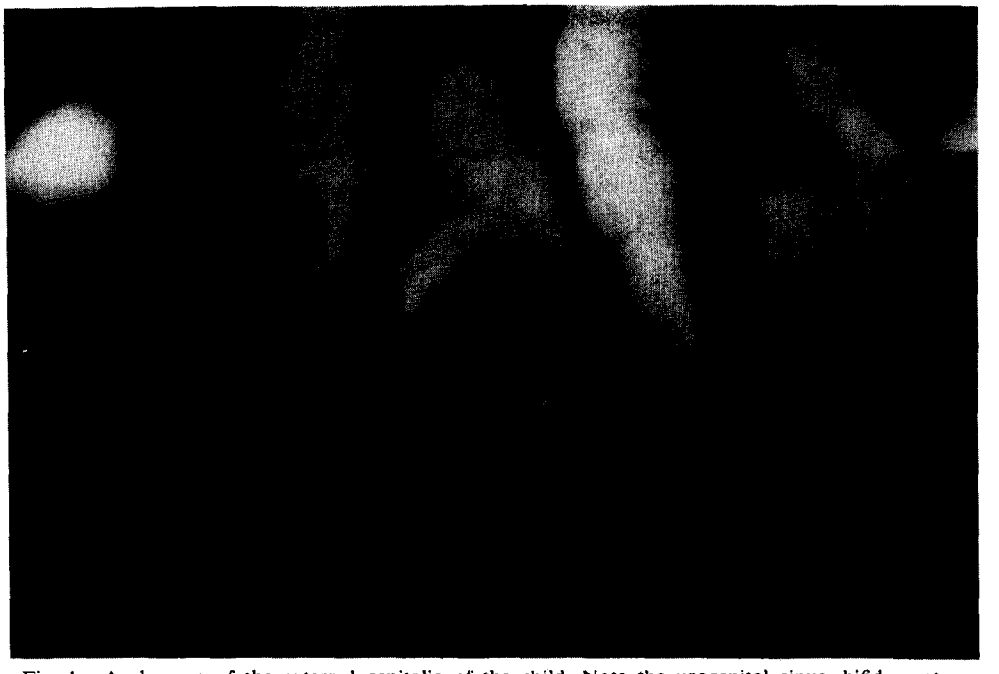

Fig. 1a. A close-up of the external genitalia of the child. Note the urogenital sinus, bifid scrotum, and clitoral-like phallus.

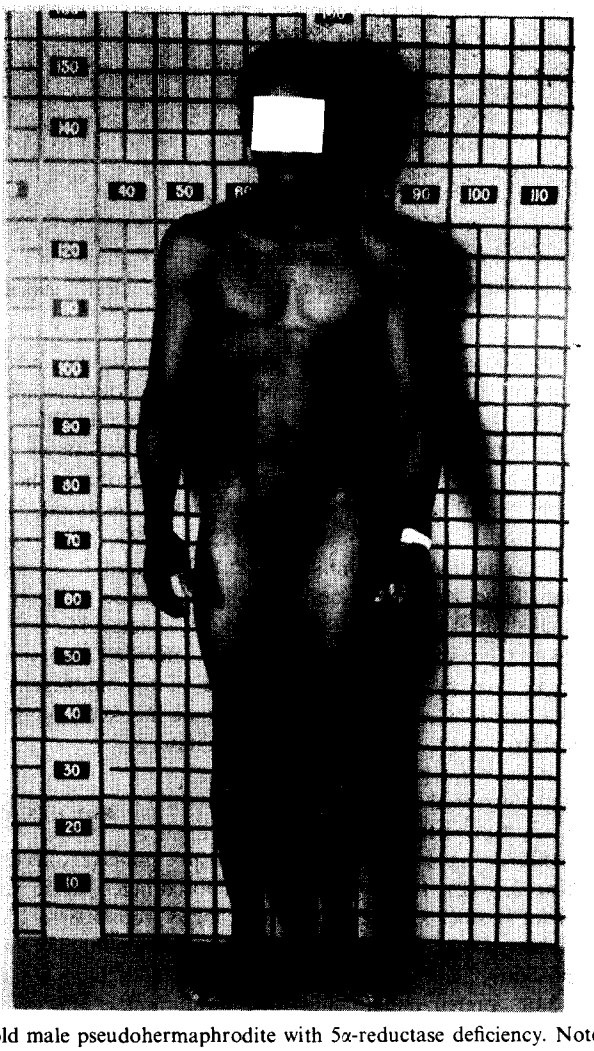

Fig. 2. A 26-year-old male pseudohermaphrodite with 5α-reductase deficiency. Note the android build.

Fig. 2a. The external genitalia of the 26-year-old affected subject.

erations were raised as females. The villagers are now able to recognize this condition at birth however, and are raising the affected subjects as boys. The villagers having realized that despite the female sex of rearing, the affected subjects will change to a male gender identity and male gender role with the onset of puberty.

Puberty in subjects with this condition is unambiguously male with deepening of the voice, development of a muscular habitus, substantial growth of the phallus, and rugation and hyperpigmentation of the scrotum [1–3, 7, 12]. There is no gynaecomastia (Fig. 2, 2a). The subjects have erections and there is an ejaculate from the perineal urethra [2, 3, 7, 12].

The postpubertal affected subjects have a reduced amount or no facial hair and decreased body hair. Two subjects of the 23 post-pubertal affected males from the Dominican kindred have facial hair (slight on upper lip and chin) [2, 3, 12]. However, a 65-year-old affected subject from another kindred has a moderate growth of facial hair which necessitates daily shaving, but is significantly less than the amount of facial and body hair compared with his father and younger brother [7]. The variation in the amount of facial hair and the slight variations in the phenotype described in affected subjects from the different families could either reflect heterogeneity of the enzyme deficiency, or as yet undefined ethnic differences [7, 14]. None of the postpubertal affected subjects have temporal hair line recession or acne [2, 3, 7, 12]. The prostates are small or absent [2–7] and it is interesting that even in the 65-year-old male subject the prostate is not palpated or visualized [7]. Either the prostate did not develop during embryogenesis or there is an absence of the androgens normally present in the adult male necessary for maintenance and growth of the prostate.

BIOCHEMICAL DATA

In 11 postpubertal affected males from the Dominican kindred (aged 18–55 years) the plasma testosterone ranged from 508 to 1550 ng/100 ml with a mean of 989 ng/100 ml ± 376 S.D. (normal male mean 571 ng/100 ml ± 140 S.D.). Plasma dihydrotestosterone levels in the affected males ranged from 9 to 23 ng/100 ml with a mean of 17 ng/100 ml ± 5.0 S.D.

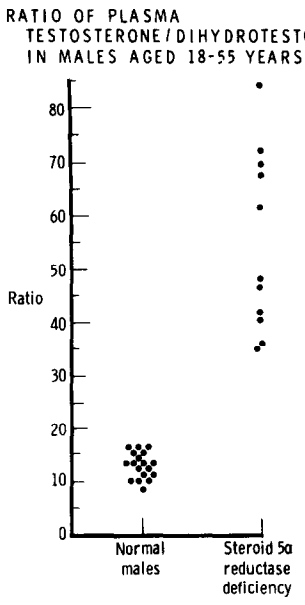

Fig. 3. Plasma concentrations of T and DHT in normal and affected adult males, 18–55 years.

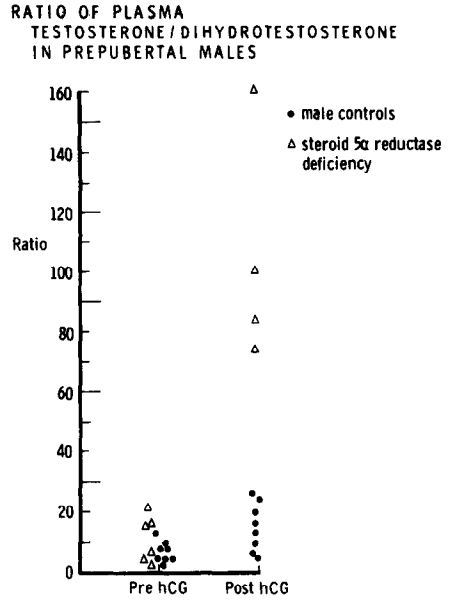

Fig. 4. Ratio of plasma T:DHT in prepubertal male controls and prepubertal affected males before and after HCG stimulation.

(normal male mean 46 ng/100 ml ± 12 S.D.). The testosterone/dihydrotestosterone ratios ranged from 35 to 84 in the affected males compared to a range of 8–16 in normal males (Fig. 3)[3]. The pubertal affected subjects described by Fisher *et al.*[6] had testosterone/dihydrotestosterone ratios of 29–30 and in the 65-year-old affected subject[7] the average ratio was 45.

In 10 affected adult males from the Dominican kindred, the mean plasma LH level was elevated to 8.1 μg/100 ml ± 1.4 S.D. (normal male mean 2.8 μg/100 ml ± 1.4 S.D.[3]. The mean plasma FSH level in the affected subjects was also elevated at 40.9 μg/100 ml ± 15.8 S.D. (normal male mean value 16.6 μg/100 ml ± 14.4 S.D.[3].

In four prepubertal and two early pubertal affected males from the Dominican Republic the baseline plasma levels of testosterone and dihydrotestosterone and the baseline testosterone/dihydrotestosterone ratios were not significantly different from the values in the five prepubertal and three pubertal male controls[3]. After administration of HCG, however, the testosterone/dihydrotestosterone ratios in the control males ranged from 3 to 26, whereas in the four prepubertal affected males they ranged from 74 to 162 (Fig. 4)[3]. In the prepubertal and pubertal cases reported by Saenger *et al.*[5] and Fisher *et al.*[6], the testosterone/dihydrotestosterone ratios ranged from 35 to 81 after administration of HCG.

The metabolic clearance rates of testosterone and dihydrotestosterone in six affected postpubertal adult males from the Dominican kindred were within the normal male range, as were the blood production rates for testosterone. The dihydrotestosterone blood production rates, however, were abnormally low for males and were only slightly higher than those reported for normal adult females[3]. In the six affected postpubertal Dominican subjects the conversion ratios were less than 1% (normal males 2.5–7.07%, normal females 2–4.0%)[3]. The 65-year-old affected subject we previously described[7] had a conversion ratio of 0.45%. The two prepubertal patients described by Saenger *et al.*[5] had conversion ratios which were less than 0.5% with an average prepubertal patient control value of 5.3 ± 3.0%.

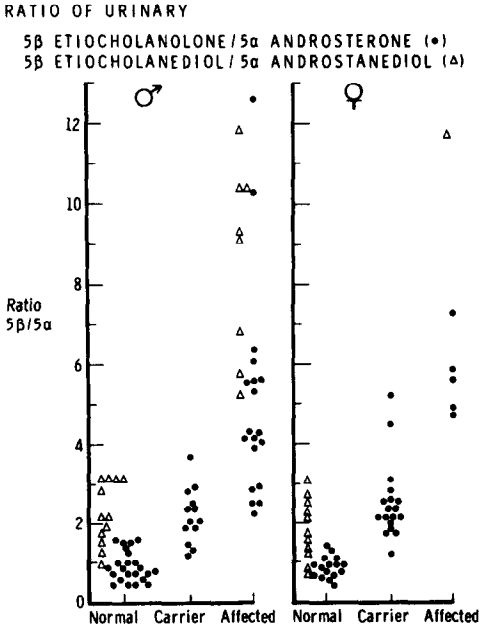

Fig. 5. Ratio of endogenous urinary steroid aetiocholanolone:androsterone (O) and aetiocholanediol:androstanediol (Δ) in normals, obligate carriers, and affected adults.

In 19 affected postpubertal males from the Dominican Republic the aetiocholanolone:androsterone ratios were elevated and ranged from 2.20 to 6.30 with a mean of 5.02 ± 2.62 S.D. (normal male mean 0.88 ± 0.37 S.D.) [3]. The 65-year-old affected male we previously described [7] had an urinary ratio of 4.9. In 13 obligate carrier fathers from the Dominican kindred, the mean aetiocholanolone:androsterone ratio was 2.20 ± 0.68 S.D., with a range of 1.24–3.65 and was intermediate between normal and affected males (Fig. 5) [3]. In 17 obligate carrier mothers, from the Dominican kindred the mean ratio was 2.42 ± 0.99 S.D. with a range of 1.15–5.14 (normal female mean, 0.87 ± 0.25 S.D.). Two obligate carrier mothers had ratios within the 95% confidence limits for affected males and are probably homozygous for the condition. Also, five female siblings of affected males had ratios in the affected male range and are presumably homozygous for the condition (Fig. 5) [3]. Six prepubertal affected males from the Dominican kindred had ratios from 2.62 to 5.37, which were significantly higher than the ratios in normal prepubertal males (normal range, 0.88–1.43) and females (normal range, 0.50–1.18). In the two affected prepubertal subjects described by Saenger *et al.* [5] the urinary aetiocholanolone:androsterone ratios following infusion of [^{3}H]-testosterone were elevated at 8.1 and 6.0, and in the two pubertal affected siblings described by Fisher *et al.* [6] the endogenous ratios were also elevated at 5.2 and 5.0.

In 11 prepubertal males with ambiguous genitalia of unknown etiology the aetiocholanolone:androsterone ratios were similar to those for normal prepubertal males [3]. None of the urinary aetiocholanolone:androsterone ratios in adult males and females with primary or secondary gonadal or adrenal dysfunction were within the range for affected males, with the exception of six patients with Cushing's syndrome [3].

In eight affected males from the Dominican kindred the mean urinary aetiocholanediol:androstanediol ratio was elevated at 8.61 ± 2.29 S.D. with a range of 2.80–11.8 (normal male mean 2.29 ± 0.08 S.D.) Fig. 5 [3].

The urinary ratios of the 5β:5α metabolites formed after administering tracer amounts of tritiated testosterone, androstenedione 11β-hydroxy-androstenedione, cortisol and corticosterone were all elevated when compared to the normal controls [8]. This suggests that a single enzyme is responsible for the 5α-reduction of both C-19 and C-21 steroids. These findings are compatible with the findings of Fisher *et al.* [6], using concentrated preparations of epididymal microsomes from an affected subject. When compared to control epididymal microsomes, the mutant epididymal microsomes demonstrated a lack of production of the 5α-reduced metabolites of both testosterone and cortisol.

Decreased 5α-reductase activity has been demonstrated in fibroblasts cultured from nongenital [5, 12] and genital skin of affected subjects [7, 9, 10, 13, 14], in cell free extracts obtained from epididymis [6] and fibroblasts cultured from genital skin [11] and in genital skin slices [4, 5].

Characterization of the enzyme activity in four kindreds reveals that 5α-reductase enzyme activity in each kindred had different properties [7, 9, 13]. The Dallas and Los Angeles mutants are clearly distinct from one another [13]. In the Dallas mutant the residual enzyme has markedly decreased affinity for the steroid substrates, whereas in the Los Angeles mutant the enzyme has essentially normal affinity for the steroid but was unstable and demonstrated a diminished affinity for NADPH. The Dominican Republic mutant however, was similar to the Dallas mutant, except for the demonstration of slight heat instability and normal activity in the monolayer assay [9]. The New York mutant resembles both the Dallas and Los Angeles mutant with decreased affinity for the steroid substrate as well as heat instability and decreased affinity for NADPH [7]. It appears therefore that the enzyme in each affected family is distinctive and such genetic heterogeneity is similar to that found in other hereditary enzyme deficiencies [15, 16].

Binding studies using fibroblasts cultured from genital skin revealed no abnormality in binding of dihydrotestosterone to the cytosol receptor [5, 17]. The binding studies are compatible with the clinical data. Dihydrotestosterone proprionate was administered 100 mg twice weekly for approx. 1 year to two affected subjects. Both subjects had significant growth of hair on the legs, arms, and along the linea alba. One subject grew a moustache and the size of his prostate increased [3].

PSYCHOSEXUAL DATA

Interviews concerning the psychosexual development of the affected subjects from the Dominican Republic were carried out in two villages [18]. From the interview data, 19 of 34 affected subjects from these villages were unambiguously raised as females and all are now postpubertal. Postpubertal psychosexual data were obtained from 18 of the 19 subjects. Sixteen of the 18 subjects, successfully changed to a male gender identity and a male gender role with puberty. Only one subject from either village is known to have maintained a female gender identity and a female gender role postpubertally. Another subject has a male gender identity, but continues to dress as a female.

Those raised unambiguously as girls began to notice they were different from other girls between 7 and 12 years of age. Testes were noted in the inguinal canal or scrotum, they did not develop breasts and their bodies began to become masculinized. They became concerned over their true gender as they began to "feel like men". A male gender identity slowly evolved as they passed through stages of no

longer feeling like girls, to "feeling like men" and finally to the self realization that they were indeed men. In all instances, there was a lag period from the time they began to realize differences from other girls of their age, until the time they finally changed gender role from female to male. The change in gender role occurred either during mid-puberty or in the post-pubertal period, only after they were convinced they were men. By this time they had experienced sexual interest in girls, were having morning erections and were masturbating. In some instances, the change to a male gender role was further delayed until the affected subjects felt strong enough to defend themselves. Seventeen years was the average age of gender role change; although in three patients, the change did not occur until they were in their twenties [18].

When the age of initiation of morning erections, wet dreams, masturbation and first sexual intercourse were compared, there was no significant difference between those subjects raised as girls or boys. The time of first sexual intercourse was 15–18 years for those raised as girls, 15–17 years for those raised as boys and 14–16 years for 10 normal male controls in the village [18].

Although these subjects who have changed to a male gender identity behaved unequivocally as males, they experienced certain insecurities because of the abnormal appearance of their genitalia. They feared ridicule by members of the opposite sex and initially felt quite anxious about forming sexual relationships. They wondered why God made them this way, but state that He did it and "what is done is done". They saw themselves as incomplete and this saddened them [18].

Psychosexual evaluation of a 65-year-old affected subject from another kindred was also carried out [7]. The data showed that prior to puberty, the patient though regarded as a "tomboy" was confident of a feminine gender identity and anticipated breast development at puberty. However, concomitant with the development of puberty, a male gender identity emerged and this subject has been confirmed in his masculine identity since approx. 16 years of age. However, he continues to present himself as female due to the absence of any hope of medical clarification or resolution of his situation. Since undergoing evaluation for his condition, he is now considering a change to a male gender role and has just completed surgery for correction of an undescended testes and chordee.

DISCUSSION

These male pseudohermaphrodites with 5α-reductase deficiency represent a unique clinical model for discerning the major actions of testosterone and dihydrotestosterone during male sexual differentiation and development. They also elucidate a role for testosterone in the evolution of a male gender identity.

At birth, the defect is limited to the external genitalia and thus, differentiation of the male external genitalia appears to be mainly effected through the actions of dihydrotestosterone. In contrast, in the Wolffian ducts the capacity to form dihydrotestosterone is not present until differentiation is completed suggesting that this is a testosterone mediated function (Fig. 6).

At puberty, the affected males develop an increase in muscle mass, deepening of the voice, skeletal growth, rugation and hyperpigmentation of the scrotum and growth of the phallus. Thus, male puberty is effected through the actions of testosterone. Therefore, conversion of testosterone to dihydrotestosterone, and the nuclear binding of the cytosol receptor–dihydrotestosterone complex may not be a characteristic of all androgen responsive tissues [1–3, 12].

If dihydrotestosterone effects differentiation and growth of the male external genitalia in utero, why at puberty, does genital growth appear to be mainly

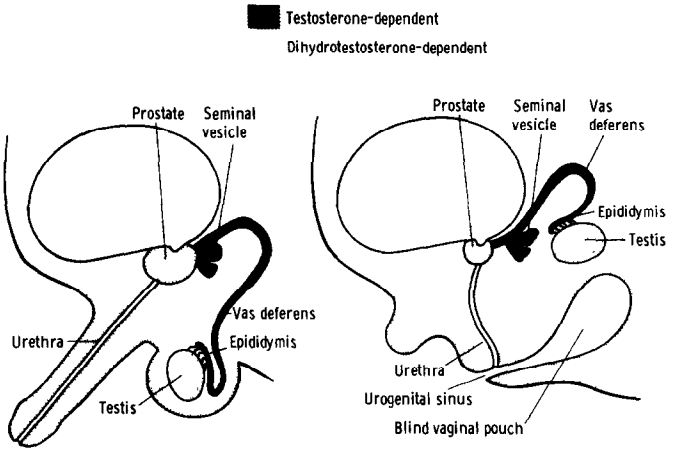

Fig. 6. Illustration of the hypothesis for the role of testosterone and dihydrotestosterone in male sexual differentiation *in utero*.

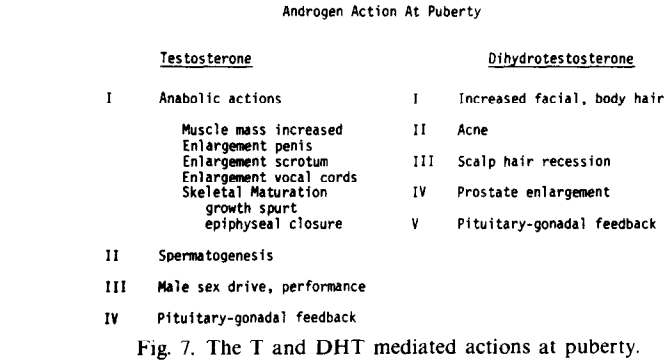

Fig. 7. The T and DHT mediated actions at puberty.

testosterone mediated? It can be postulated that either the receptor affinity of the tissues of the external genitalia changes with age, with testosterone having a greater affinity at puberty, or alternatively, that tissue levels of dihydrotestosterone are higher during sexual differentiation than at puberty.

Prostatic enlargement, acne, normal male facial and body hair, and temporal recession of the hairline did not occur in the affected males, and appears to be effected mainly through the actions of dihydrotestosterone (Fig. 7) [1, 2, 2, 12].

Gynaecomastia does not develop post pubertally and suggests that in utero, testosterone is the androgen that suppresses the breast anlage, so that at puberty gynaecomastia will not occur [2, 3, 12].

Complete spermatogenesis was present on testicular biopsy in one affected subject, and thus testosterone may be more important in the regulation of spermatogenesis than dihydrotestosterone (Fig. 7).

LH and FSH levels are elevated together with elevated plasma levels of testosterone suggesting a role for dihydrotestosterone in the negative feedback control of LH and possibly FSH secretion (Fig. 7) [3].

The affected males have erections and ejaculations and this also appears to be testosterone dependent. Conversely, in two subjects, administration of pharmacologic amounts of dihydrotestosterone caused loss of libido and impotence (Fig. 7) [3].

From the data, it appears that testosterone exposure of the brain *in utero*, the early postnatal period, and at puberty, has more impact in determining male gender identity than the sex of rearing. Theoretically, under the influence of testosterone "masculinization" of the brain occurs, and together with a testosterone mediated male puberty, a male gender identity develops despite a female upbringing. This experiment of nature emphasizes the importance of androgens which act as inducers in the evolution of a male gender identity. Normally, the sex of rearing and testosterone imprinting of the brain are in unison and together with the activation of a testosterone mediated male puberty determine the complete expression of the male gender. However, these subjects demonstrate that in an environment, when the sex of rearing is discordant, the testosterone mediated biologic sex will prevail if the complete events of puberty are permitted to occur [18].

The age at, during, or following puberty when successful interruption (i.e. castration, sociocultural factors, etc.) can be initiated to prevent evolution of a male gender identity will undoubtedly differ for each affected subject, since the time for the complete evolution of a male gender identity with puberty is unique for each individual. However, since male gender identity evolution in this condition appears to be initiated with puberty it is not surprising that either pre-pubertal or even pubertal castration with the initiation of female hormone therapy might abort its development [4–6].

These data indicate that just as the development of the male phenotype is induced by androgens at a critical period *in utero*, the formation of a male gender identity is also an induced state with androgens acting on the brain at critical periods (in utero, neonatally, and puberty)[18].

Acknowledgements—This work was supported by U.S. Public Health Service Career Research Award (R.E.P.) K6-AM 14, 241-15, Clinical Research Center Grant RR-47, Research Grant HD 09421, National Foundation Research Grant 6-52, Shorr Fellowship fund, and a grant from Gulf and Western (Dominican Republic).

REFERENCES

1. Imperato-McGinley J., Guerrero L., Gautier T. and Peterson R. E.: An unusual form of male pseudohermaphroditism. A model of 5α-reductase deficiency in man. *J. clin. Invest.* **53** (1974) Abstract 132.
2. Imperato-McGinley J., Guerrero L., Gautier T. and Peterson R. E.: Steroid 5α-reductase deficiency in man: An inherited form of male pseudohermaphroditism. *Science* **186** (1974) 1213.
3. Peterson R. E., Imperato-McGinley J., Gautier T. and Sturla E.: Male pseudohermaphroditism due to steroid 5α-reductase deficiency. *Am. J. Med.* **62** (1977) 1970.
4. Walsh P. C., Madden J. D., Harrod M. J., Goldstein J. L., MacDonald P. C. and Wilson J. D.: Familial incomplete male pseudohermaphroditism, type 2: decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. *New Engl. J. Med.* **291** (1974) 944.
5. Saenger P., Goldman A. S., Levine L. S., Korth-Schutz S., Muecke E. D., Katsumata M., Doberne Y. and New M. I.: Prepubertal diagnosis of steroid 5α-reductase deficiency. *J. clin. Endocr. Metab.* **46** (1978) 628.
6. Fisher L. K., Kogut M. D., Moore R. J., Goebelsmann U., Weitzman J. J., Isaacs H., Jr., Griffin J. E. and Wilson J. D.: Clinical endocrinological and enzymatic characterization of two patients with 5α-reductase deficiency evidence that a single enzyme is responsible for the 5α-reductase of cortisol and testosterone. *J. clin. Endocr. Metab.* **47** (1978) 653.
7. Imperato-McGinley J., Peterson R. E., Leshin M., Griffin J. E., Cooper E., Draghi S., Berenyi, M. and Wilson J. D.: Steroid 5α-reductase deficiency in an adult male pseudo-hermaphrodite. The natural history, ultrastructure of the testes and evidence for inherited enzyme heterogeneity. (In preparation.)
8. Peterson R. E., Imperato-McGinley J., Sturla E., and Gautier T.: Diminished urinary excretion of 5α-reduced metabolites of intravenous or orally administered steroids in subjects with male pseudohermaph-

roditism due to 5α-reductase deficiency. (In preparation).
9. Leshin M., Griffin J. E. and Wilson J. D.: Hereditary male pseudohermaphroditism associated with an unstable form of 5α-reductase. *J. clin. Invest.* **62** (1978) 685.
10. Wilson J. D.: Dihydrotestosterone formation in cultured human fibroblasts. Comparison of cells from normal subjects and patients with familial incomplete male pseudohermaphroditism, type 2. *J. biol. Chem.* **250** (1975) 3498.
11. Moore R. J., Griffin J. E. and Wilson J. D.: Diminished 5α-reductase activity in extracts of fibroblasts cultured with familial incomplete male pseudohermaphroditis, type 2. *J. biol. Chem.* **250** (1975) 7168.
12. Imperato-McGinley J., Guerrero L., Gautier T. and Peterson R. E.: Steroid 5α-reductase deficiency in man: An inherited form of male pseudohermaphroditism. In *Birth Defects: Original Article Series*, (Edited by D. Bergsma). Stratton Intercontinental Medical Book Corporation, New York, Vol. 4 (1975) p. 91.
13. Moore R. J. and Wilson J. D.: Steroid 5α-reductase in cultured human fibroblasts: Biochemical and genetic evidence for two enzyme activities. *J. biol. Chem.* **251** (1976) 5895.
14. Pinsky D. M., Straisfeld D., Zilahi B. and St.-G. Hall C.: 5α-Reductase activity of genital and non-genital skin fibroblasts from patients with 5α-reductase deficiency, androgen insensitivity, or unknown forms of male pseudohermaphroditism. *Am. J. med. Genet.* **1** (1978) 407.
15. Harris H.: Enzyme and protein polymorphism in human populations. *Brit. Med. Bulletin* **25** (1969) 5.
16. Yoshida E., Beutler E. and Motulsky A. G. Human glucose-6-phosphate dehydrogenase variants. *Bull. Wld Hlth Org.* **45** (1971) 244.
17. Griffin J. E., Punyashthiti K. and Wilson J. D.: Dihydrotestosterone binding by cultured human fibroblasts. Comparison of cells from control subjects and from patient with hereditary male pseudohermaphroditism due to androgen resistance. *J. clin. Invest.* **56** (1976) 1342.
18. Imperato-McGinley J., Peterson R. E., Gautier T. and Sturla E.: The impact of androgens on the evolution of male gender identity. *New Engl. J. Med.* (1979). In press.
19. Diamond M.: Human sexual development: biological foundations for social development. In *Sex: Nine Expert Views* (Edited by F. A. Beach). Hopkins Press, New York (1977)