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STEROID 17β-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY IN MAN: AN INHERITED FORM OF MALE PSEUDOHERMAPHRODITISM

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Summary—Sixty-eight males with testicular 17β-hydroxysteroid dehydrogenase deficiency (17β-HSD) were identified among a highly inbred Arab population in Israel, and 45 studied over the last 15 years. The founders of this defect originated in the mountainous region of present Lebanon and Syria, but most of the families now live in Jerusalem, Hebron, the Tel-Aviv area, and in particular Gaza, where the frequency of affected males is estimated at 1 in 100 to 150. Affected individuals (46,XY) are born with ambiguity of the genitalia and reared as females until puberty. Thereafter marked virilization occurs, leading in many cases to the spontaneous adoption of a male gender role. Adults develop a male habitus with abundant body hair and beard, and the phallus and testes enlarge to adult proportions. Gender reassignment was possible only when enough erectile tissue was present at birth and developed into a normal size penis with systemic testosterone. Male genitoplasty was performed in 15 children and 8 post-pubertal patients, and female genitoplasty in 2 children and 4 post-pubertal patients. In adults the defect is characterized by markedly increased concentrations of 4-androstendione (4-A) with borderline low to normal testosterone (T) levels, and a high 4-A/T ratio. Dihydrotestosterone (DHT) concentrations were either moderately decreased, normal, or high, and dehydroepiandrosterone levels were high. The estrogen pathway was also impaired, even though both estrone and estradiol-17β levels were elevated. Children had low basal levels of all androgens, but the defect could be demonstrated after prolonged stimulation with human chorionic gonadotropin. LH and FSH levels were very high after puberty, and normal in childhood. However, an over-response to gonadotropin-releasing hormone was found at all ages.

Studies in testicular tissue revealed various abnormalities in steroid metabolism. Tissue from pre-pubertal patients metabolized progesterone (P) only to 4-A, while tissue from post-pubertal patients metabolized P to 16α- and 16β-hydroxyprogesterone (5.4- to 10.3-fold greater production), 17α-hydroxyprogesterone (5.4- to 8-fold smaller production), 4-A and T. 4-A was also metabolized to T, indicating that 17β-HSD was no longer deficient. Flow studies with equimolar concentrations of [^{14}C]P and [^{3}H]pregnenolone showed that the 5-ene pathway was the preferential one for androgen biosynthesis. Both *in vivo* and *in vitro* studies indicate that the severity of testicular 17β-HSD deficiency changes with age. Whereas the enzyme activity is absent in childhood, there is a progressive restoration after puberty. Androgen production increases progressively to normal so that T and DHT concentrations are sufficiently high to gradually induce somatic and genital virilization, thus enabling an adequate male gender function.

"Hermaphroditos [Greek]:
A son of Hermes and Aphrodite
who became joined in one body
with a nymph while bathing."

INTRODUCTION

Ambiguity of the internal and/or external genitalia in individuals with a male karyotype (46,XY) and testicular tissue only is a clinical condition known as male pseudohermaphroditism (MPH). The causes of MPH may be grouped into three categories; (1) defective testicular differentiation and development, (2) defective testosterone (T) metabolism, due to 5α-reductase deficiency, and (3) defective androgen action at the target tissues, due to insensitivity to androgens [1]. Testosterone biosynthetic defects comprise only a minor fraction of all disorders [2], particularly deficiency of testicular 17β-hydroxysteroid dehydrogenase (also termed 17-ketoreductase, 17β-HSD) [3, 4], an enzyme that catalyses the last step of T and estradiol-17β (E-2) biosynthesis [5–7].

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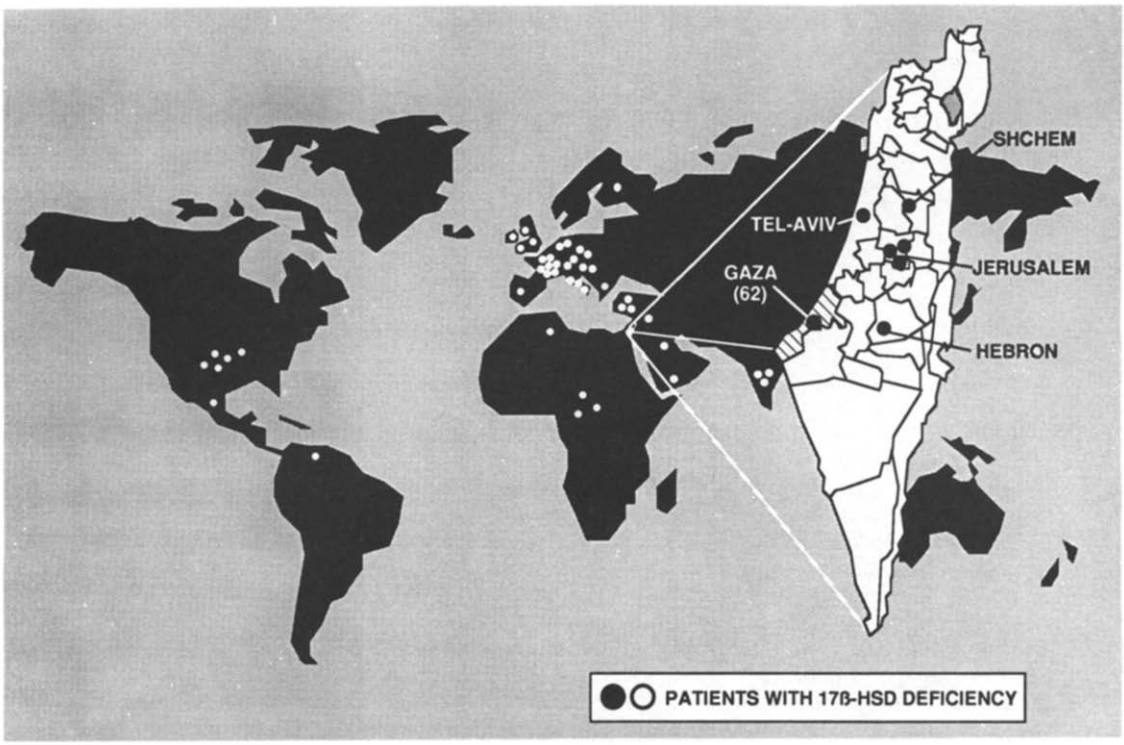

Fig. 1. Country of origin of 112 males with 17β-HSD deficiency described in the world literature. This information was obtained from the data published and/or from the authors response to a written questionnaire.

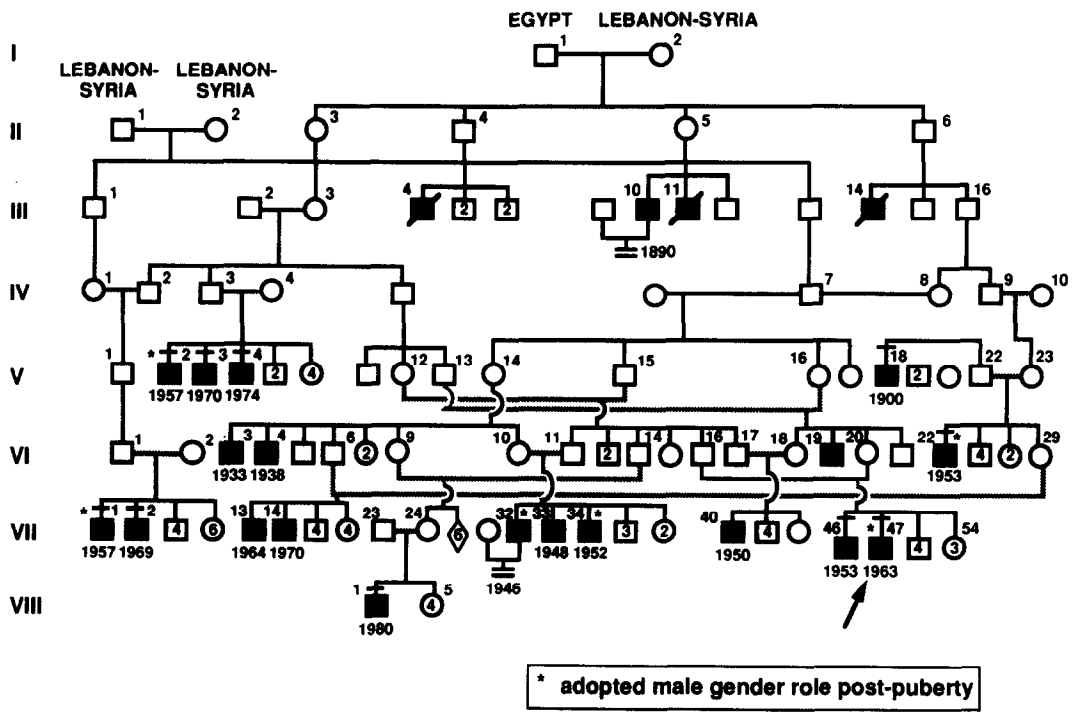

Fig. 2. Pedigree illustrating common ancestry of 14 sibships with MPH due to 17β-HSD deficiency. The families now live in Gaza. Black symbols indicate affected individuals, and the year of birth is shown below. Transmission of the defect can be traced back 8 generations. The arrow indicates the index case.

Table 1. Natural history of Arab males with 17β-HSD deficiency

1. *Phenotypic females from birth until puberty*
   Palpable gonads in the inguinal canals or scrotum and/or ambiguity of the external genitalia.
   Normal karyotype (46,XY).
2. *Progressive virilization from the time of puberty*
   Male body habitus.
   Beard, abundant body, axillary and pubic hair.
   Large testes in inguinal canals or scrotum.
   Enlargement of phallus to adult size.
   Thick chordee.
   Partially fused labial-scrotal folds with mild posterior fusion.
   Two perineal orifices [See Fig. 5(B)]:
   (1) anterior, an urethra at the base of the phallus;
   (2) posterior, a blind vaginal pouch.
   Normal internal male genitalia (vas deferens, epididimis and seminal vesicles).
3. *Spontaneous adoption of a male gender role after puberty*

HISTORY, ORIGIN AND INHERITANCE

More than 25 years ago Neher and Khant [8] reported the biochemical abnormalities in a patient with ambiguous genitalia. His study represented the first description of a deficiency in testicular 17β-HSD [9]. Since then 112 cases of 17β-HSD deficiency have been added to the world literature [3, 4, 10–43] (Fig. 1). A demographic analysis reveals that more than half of these individuals stem from selected regions in the Middle East, particularly Israel, and are ethnically Arabs and Moslems by religion [20–22, 24, 27, 31, 35, 36, 40, 42]. In 1983 we described 25 MPH patients with 17β-HSD deficiency among a highly inbred Arab population of the Gaza strip [27]. Twenty-three of them belong to a very large kinship that extends over 8 generations (Fig. 2). Three of the four earliest ancestors originated from the mountainous region of present day Lebanon and Syria, whereas the fourth came from Egypt. Fourteen separate kinships constitute this large kinship, and in 10 of them parental consanguinity is present. The incidence of affected males in the Gaza strip was estimated between 1 in 100 to 1 in 150 [31]. A total of 68 Arab males with 17β-HSD deficiency have been identified to date [35, 42]. Six of them live in various cities of Israel and the West Bank, whereas 62 belong to several inbred kinships, and live in Gaza (Fig. 1). It is possible however, that some of the patients described in the literature as originally from the Middle East area also belong to this population, and therefore, may carry the same genetic mutation. The majority of the affected families reside in Jabaliya, a town of 25,000 inhabitants located on the coastal plain of the Mediterranean sea. The high incidence of consanguinity makes inheritance most compatible with an autosomal recessive disorder, expressed in males only. Thus, the increased gene frequency in this population is most probably the consequence of genetic drift—a founder affect. The biochemical defect has not been demonstrated in phenotypically normal females, most probably because the methods of hormone determination are not sensitive enough to detect subtle abnormalities when T production is very low. Therefore until this is done, X-linked recessive inheritance cannot be completely ruled out.

During the last 15 years we have studied and treated 45 of the 68 Arab males with 17β-HSD deficiency, and the results are reviewed here. This report also includes new examples of the disorder.

THE CLINICAL EXPRESSION AND NATURAL HISTORY

The clinical manifestations differ according to the pubertal stage of the patient (Table 1). Affected males are born with mild to moderate degrees of ambiguity of an apparently normal-looking female genitalia, and are unequivocally assigned and reared as females [Figs 3(A and B) and 4]. However, careful inspection of the genitalia may reveal a normal or slightly enlarged clitoral-like phallus surrounded by a chordee. The other features are described in Table 1 and shown in Figs 3 and 5. Wolffian structures are entirely normal, and a vas deferens, epididimis and seminal vesicles are found on laparotomy. On the other hand, Müllerian structures are absent.

From the time of puberty progressive virilization occurs in all affected individuals. Patients develop a male habitus with abundant muscle mass and may reach an average height and weight of a normal male [Fig. 4(C)]. Their body hair is ample, and so is the beard, requiring daily shaving in the adult. The voice deepens, and except for one patient (from Hebron) gynecomastia was absent in all others. Marked genital changes become obvious as puberty advances [Fig. 5(A and B)]. The phallus grows to almost adult proportions (length of 5 to 8 cm, and width of 2 to 3 cm). Since the phallus is always surrounded by a thick chordee, only after male genitoplasty (see below) does this organ become a functional penis [Figs 3(C) and 5(C)]. The testes markedly enlarge [to 16 to 30 ml (44)] and are usually found in the inguinal canals. Thus, the external genitalia cannot readily be seen in the standing position, but only on perineal inspection. Although these individ-

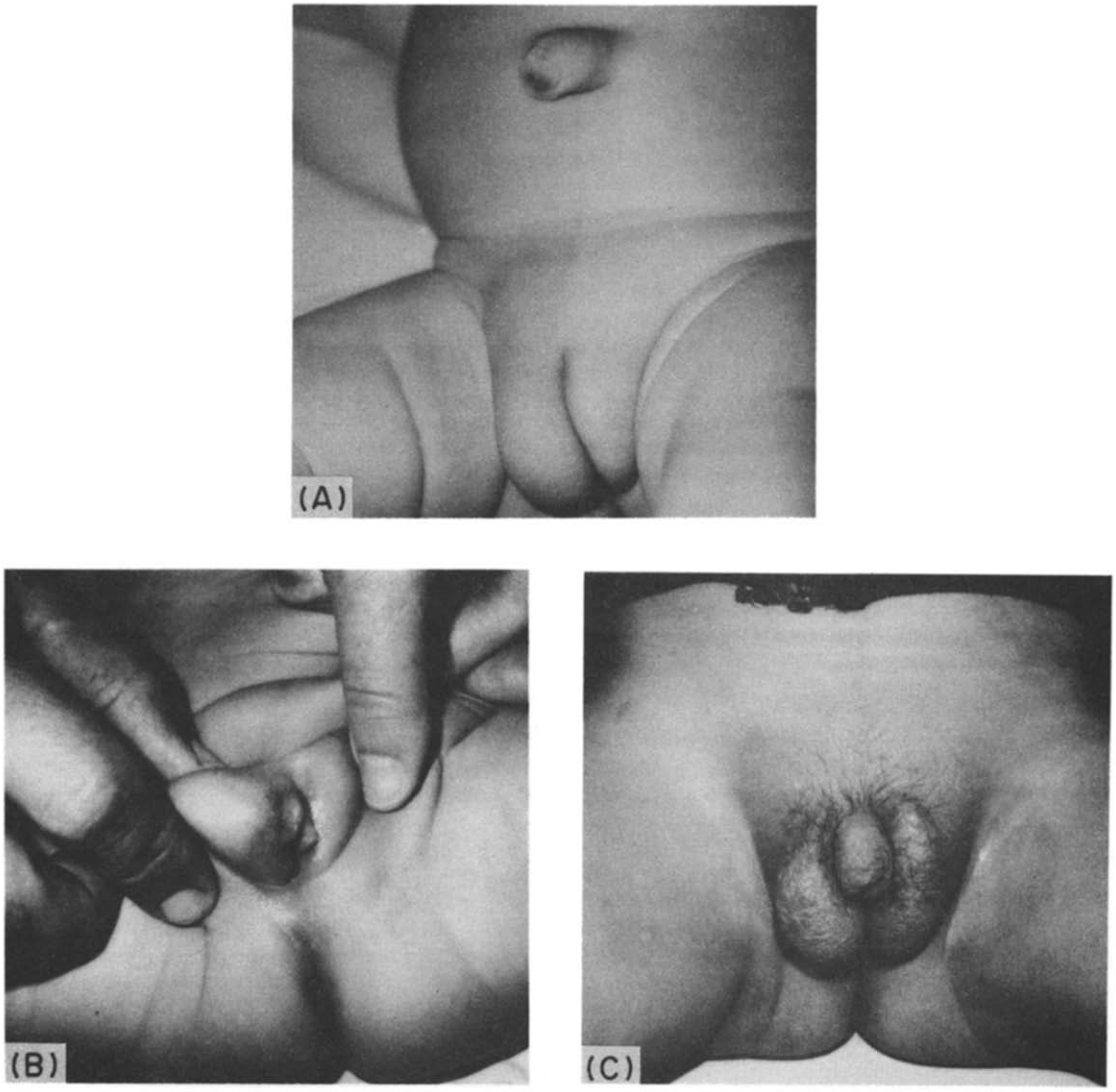

Fig. 3. External genitalia of a MPH patient with 17β-HSD deficiency who underwent gender reassignment in childhood (see also Tables 2 and 7). (A and B) At the time of diagnosis, age 4 months. Except for swollen labia due to the presence of a right descended testes, the infant has normal-looking female external genitalia. Note the slight posterior fusion of the labia. The child was named, dressed and reared as a girl. (C) At the age of 2 years and 9 months, after 3 courses of systemic T therapy and the first stage of male genitoplasty (see Fig. 9). The phallus has reached a normal size (5.5 cm). Both testes have been fixed in the scrotum. Rugation and pubic hair are well noticeable, but progressively disappeared over the following months. The second stage of male genitoplasty was done 1 year later. The child now has a normal male phenotype and behaves accordingly.

uals have erections, they are not capable of intromission and insemination without anatomical correction, because of the retractile chordee and perineal opening of the urethra. A small prostate can be palpated on rectal examination.

As puberty progresses these individuals acquire a normal male physique (Fig. 4). The great majority thus adopt a male gender identity, but not all of them adopt a male gender role. The psychosexual behavior and social history of the Arab males from Gaza with 17β-HSD deficiency has been described in detail [27, 31]. Although the disorder and its course are now well recognized among the extended families, all pre-pubertal affected males are still being reared as females until sex reassignment is completed, usually at the request of the families (Table 2).

Until recently it has been assumed that gender identity is firmly established by the age of 3 to 4 years, regardless of the genetic or phenotypic sex [45]. However, this may not be true among certain societies including the Arab, where the

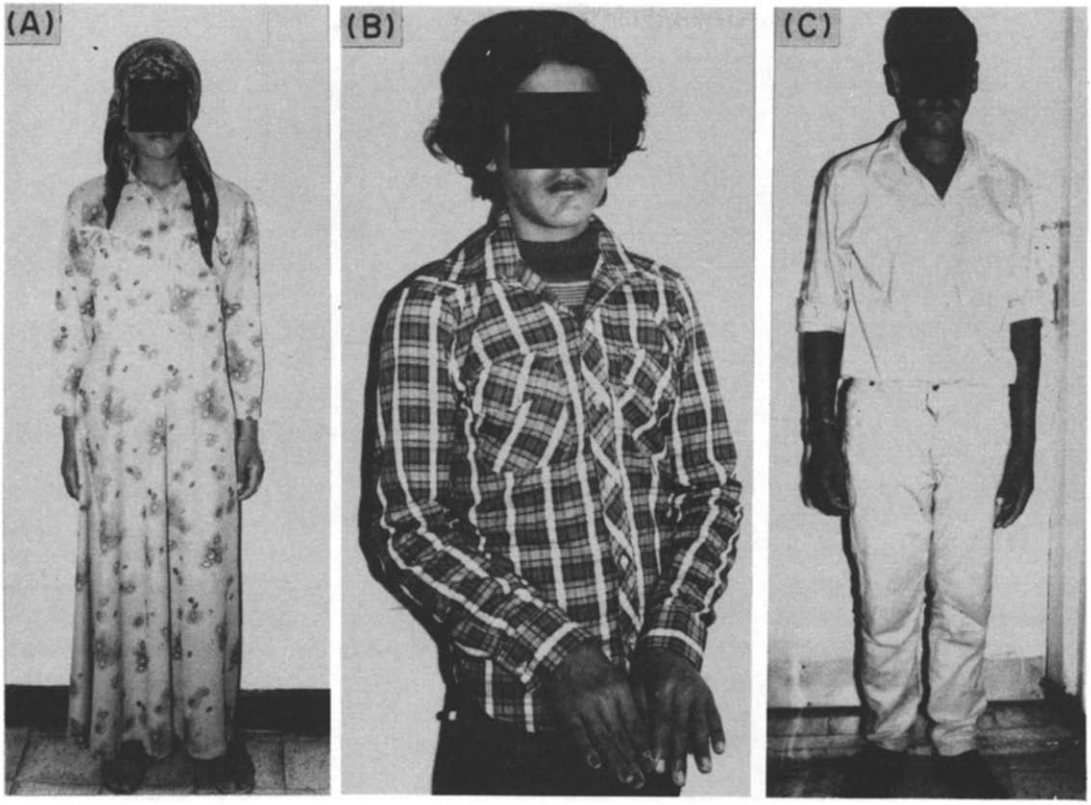

Fig. 4. Spontaneous adoption of male gender role in an MPH patient with 17β-HSD deficiency from Gaza. (A) First examination at age 15 years. The patient was named, dressed and reared as female since birth and requested medical attention because of marked somatic and genital virilization (see Fig. 5), and "strange" feelings (felt as a man with sexual attraction towards females). (B) After completion of genetic, endocrine, urological and psychiatric evaluation (see also Table 4), the patient is spontaneously adopting a male gender role, once he was told that he was a male. In this transitional period he has cut his hair, dressed as a male but still has nail polish on his right hand. (C) At the age of 17 after completion of male genitoplasty this individual is well adjusted in the male gender role, and is now working in a physically demanding job. He has since then married and integrated into the community.

preferred sex is male even if such individuals are sterile for life. In this respect our patients resemble quite closely the males with 5α-reductase in the Dominican Republic [46]. These were also reared as females during childhood, and their society accepted well their post-pubertal gender role change and integration as males in the community.

THE ENZYME DEFICIENCY AND BIOCHEMICAL DIAGNOSIS

17β-HSD catalyses the reversible conversion of 4-androstenedione (4-A) to T, dehydroepiandrosterone (DHEA) to 5-androstenediol (5-diol), androsterone to dihydrotestosterone (DHT), and estrone (E-1) to E-2 [5, 6, 47, 48]. The androgen and estrogen pathways seem to be under a different genetic control [7, 49]. However, affected individuals lack the testicular enzyme for both [3, 4]. The clinical and biochemical heterogeneity of the disorder has been well documented *in vivo* and *in vitro* by us [27, 31, 35, 42], and others [3, 4, 8–26, 28–30, 32–41, 43, 50]. In the adult the defect is characterized by a marked overproduction of 4-A resulting in very high plasma concentrations (range between 12.5 to 43.4 nmol/l, normal males 2.8 ± 0.8 nmol/l) (Fig. 6). T concentrations are moderately decreased or normal (range between 6.6 to 19.4 nmol/l, normal males 18.2 ± 2), and DHT levels are normal or high (range between 0.95 to 6.9 nmol/l, normal males 1.4 ± 1.3) [15, 22, 27, 28, 32, 51]. DHEA is also produced in excess, and the plasma concentrations range between 14.7 to 43.6 nmol/l (normal males 12 ± 1.2 nmol/l) (data not shown). The determination of the androgen (and estrogen) steroid pattern in spermatic vein blood reveals a more severe impairment in 17β-HSD activity than in peripheral blood (Table 3). The

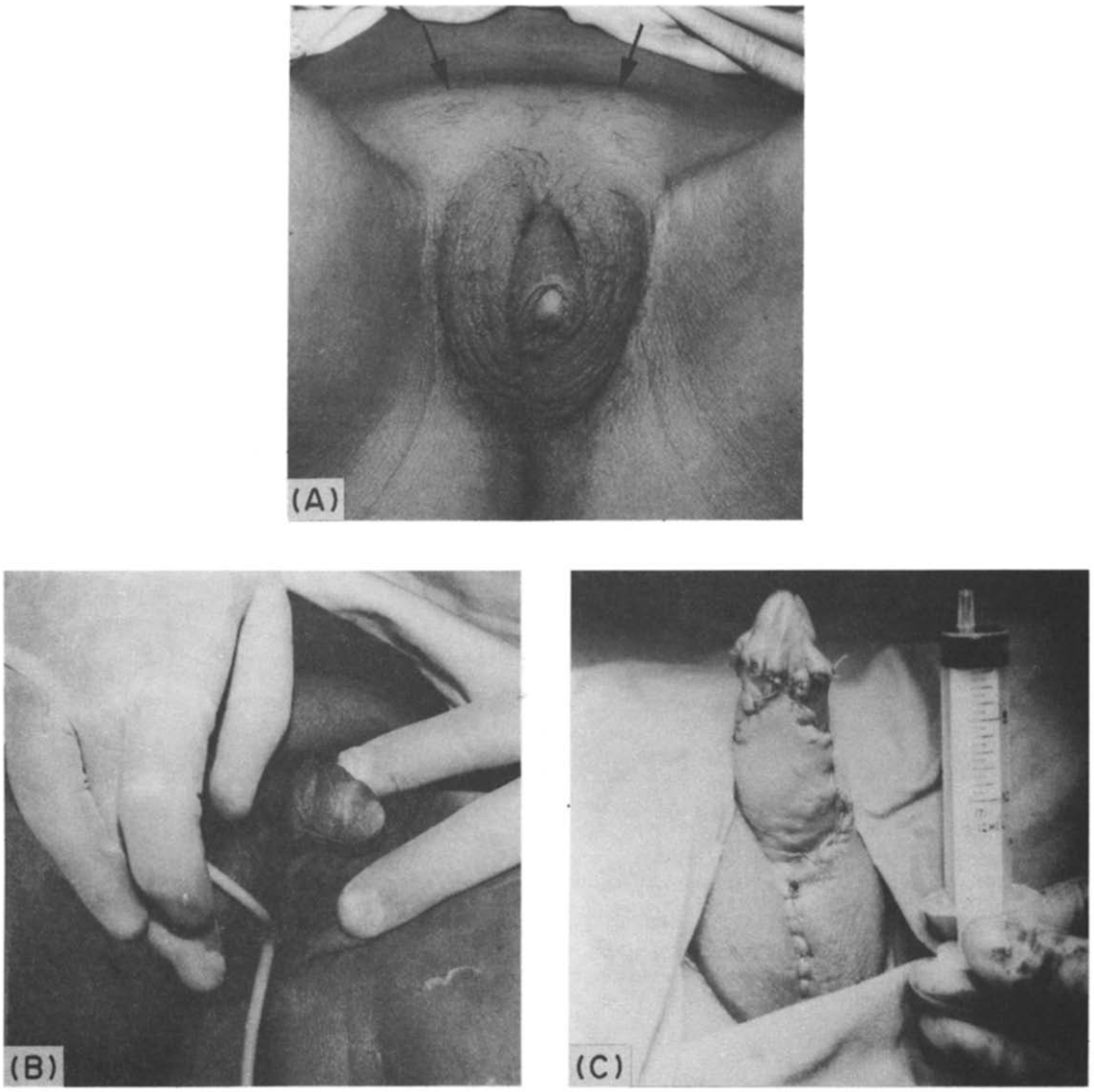

Fig. 5. External genitalia of the MPH patient with 17β-HSD deficiency shown in Fig. 4, before and after the first stage of male genitoplasty (see also Tables 4 and 7). (A and B) First examination at age 15 years. The phallus has enlarged (6.5 cm length) but is retracted dorsally by a thick chordee which partially obstructs the opening of the urogenital sinus. The labial-scrotal folds have developed substantially and become rugose, however the enlarged testes of 25 ml (shown by the arrows) have remained in the inguinal canals. Within the urogenital sinus there are two orifices (shown by the catheters): the anterior represents the urethral opening and is found at the base of the phallus, and the posterior connects to a blind (vaginal) pouch of 5 cm. (C) After stage I of male genitoplasty (see Fig. 9). The phallus has been enlarged to 9 cm long and the chordee completely resected. The prepucial skin has been conserved and the helicoidal shaped incision sutured in place. This procedure prevents the development of fibrotic tissue and fistulas, thus allowing the adequate reconstruction of the external urethra in stage II.

abnormal androgen pattern is clearly evident in the basal state only after puberty, but not in childhood. Affected children have normally low basal levels of 4-A, T and DHT (data not shown), when compared to age-matched controls (Fig. 6). However, infants of 1 year of age or less have relatively higher 4-A, and lower T concentrations than in normal children, who during this period of life experience a temporary increase in T secretion [52]. In childhood the defect becomes overt only after stimulation with human chorionic gonadotropin (hCG) (Fig. 6). Prolonged administration of high doses of hCG (500 to 1000 U twice a week for 6 to 8 weeks [53]) were necessary to produce a significant increase in 4-A [in parallel to marked enlargement in testicular volume; see Fig. 3(C)], whereas T concentrations remained relatively

Table 2. Sex of rearing of males with 17β-HSD deficiency

Country	Period of life/ mode	Sex of rearing		Ratio
		Male[a]	Female	male/female
Israel	Since birth	7	10	
	Reassigned in infancy	15	2	
	Post-pubertal change[b]	11		
		33	12	2.8:1
World literature[c]		15	30	0.5:1

[a] Also includes patients who still need testosterone therapy and/or corrective surgery.
[b] Spontaneously adopted a male gender role between the ages of 12 and 23 years.
[c] The country of origin of this patient population is shown in Fig. 1. Includes all three modes indicated for Israel.

low [35]. In our experience significantly elevated 4-A concentrations together with a high 4-A/T ratio represented the most reliable diagnostic parameters in all age groups (Fig. 6 and Table 4), if the normal changing pattern of these parameters is taken into consideration [54]. In normal individuals the 4-A/T ratio is low in early infancy (0.22 ± 0.40) and after puberty (0.12 ± 0.11), whereas between the age of 1 to 10 years it ranges between 1.27 ± 0.33 and 1.5 ± 0.3. hCG stimulation does not amplify consistently the 4-A/T ratio as anticipated (Table 4), and in early infancy the opposite may occur (Fig. 6).

Some of the hormonal abnormalities, such as high 17α-hydroxyprogesterone (17-OHP) (data not shown) [3, 4, 27], 4-A, and moderately increased T and E-2 levels also occur in virilizing classic and non-classic congenital adrenal hyperplasia [55]. Although on clinical grounds this disorder is very unlikely to be found in our cases, failure of dexamethasone to suppress plasma androgens and estrogens, together with normal glucocorticoid secretion rules out this disorder completely (Table 4).

Indirect evidence for the T biosynthetic defect was also shown by the very high gonadotropin

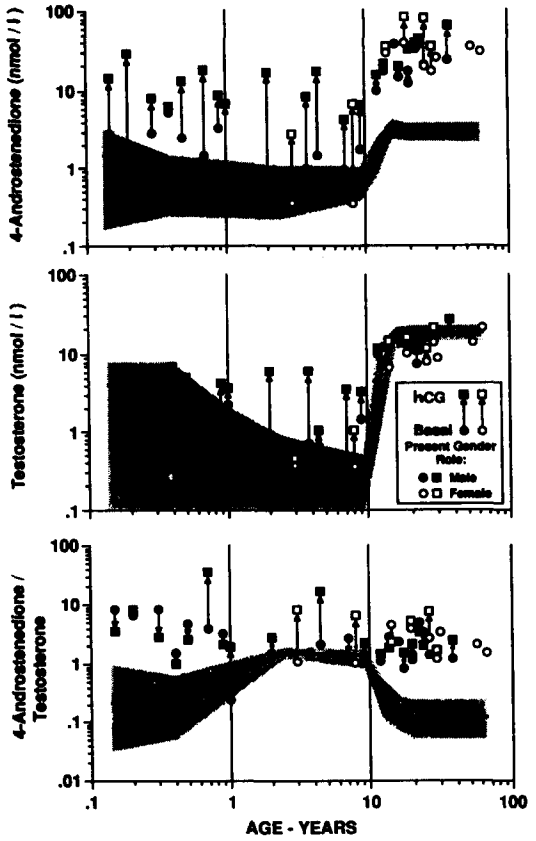

Fig. 6. 4-A and T concentrations, and the 4-A to T ratios before and after hCG stimulation in MPH patients with 17β-HSD deficiency, according to age and present gender role. The shaded area shows the normal basal range for males (mean ± SD). The normative data was kindly provided by Dr Paul Saenger [54].

levels found in all affected individuals after puberty [3, 4, 27, 42]. In childhood basal FSH and LH concentrations are low, as expected [35]. However, the fact that we could document an over-response to gonadotropin-releasing hormone indicates that the defect is present at all ages [27].

Table 3. Steroid pattern in spermatic venous blood from 2 males with 17β-HSD deficiency

Pathway	Hormone (nmol/l)/ ratio	Patient 1 (16 years)	Patient 2 (28 years)	Controls[a] (mean ± SD)
Δ4-				
	4-Androstenedione (4-A)	4004	2897	74.9 ± 9.5
	Testosterone (T)	428	129	1115 ± 186
	Dihydrotestosterone (DHT)	138	30	14.7 ± 2.5
	4-A/T	9.4	22.5	0.007 ± 0.005
	T/DHT	3.1	4.3	75.8 ± 25
Δ5-				
	Dehydroepiandrosterone (DHEA)	3491	5797	135 ± 52
	5-Androstenediol (5-diol)	74.9	62.5	165 ± 58
	DHEA/5-diol	46.5	92.5	0.8 ± 0.9
Estrogen				
	Estrone (E-1)	30	36.8	1.1 ± 0.2
	Estradiol-17β (E-2)	8.7	8.3	2.3 ± 0.4
	E-1/E-2	3.5	4.5	0.48 ± 0.3

[a] Control values correspond to 15 to 24 age-matched healthy males [51].

Table 4. Hormonal data in a 15-year-old male from Gaza with 17β-HSD deficiency[a]

Condition	Estradiol-17β	DHEA	4-androstenedione	Testosterone	4-A/T
Basal	0.30[b]	17.3	21.7	6.6	3.3
ACTH (48 h)	0.38	76.3	22.2	5.6	4.0
Dexamethasone (2 mg/day)	0.45	8.7	18.3	8.3	2.2
Dexamethasone +hCG (5000 U) for 3 days	0.60	21.2	24.8	11.8	2.1
Normal basal values	0.15 ± 0.09	12.1 ± 1.2	2.8 ± 0.8	18.2 ± 1.9	0.12 ± 0.11

[a]This patient spontaneously adopted a male gender role after diagnosis was established, and subsequently underwent male genitoplasty (see Figs 4 and 5).
[b]All values measured in nmol/l.

The enzyme deficiency in the estrogen pathway is more complex to understand. Although it is obvious from our data that both estrogens are produced in great excess by the testes of these patients, the significantly elevated E-1/E-2 ratio unquestionably indicates that 17β-HSD is deficient (Table 3). This ratio is less abnormal than the 4-A/T ratio, supporting the concept that the enzyme activity is less impaired in the estrogen than in the androgen pathway [3, 4]. The high E-2 concentrations in the spermatic effluent cannot be explained solely on the basis of peripheral tissue conversion, which is a major mechanism for E-2 production in males [56]. This could be due to enhanced aromatase activity in the testes, in addition to partial E-1 to E-2 conversion in peripheral tissues [51], an hypothesis that needs to be proved.

If estrogen production is increased in 17β-HSD deficiency, why do only about half of all affected males develop breasts? [4, 9–11, 13, 17, 20, 21, 26, 29, 30, 33, 36, 40, 57, 58]. Although E-2 concentrations were found high in almost all of our post-pubertal patients, only one had breasts (Fig. 7). Androgens normally inhibit the breast anlage of the male fetus [59], and a decrease in T production with a parallel increase in estrogens may alter this process. This hypothesis led Imperato-McGinley *et al.* [22] to emphasize the importance of the T/E-2 ratio, with respect to the presence or absence of gynecomastia. They noted that patients developed breast tissue when the ratio was <40, whereas this did not occur if the ratio was normal (>100). This observation may also explain the simultaneous occurrence of gynecomastia and virilization in some of the patients with 17β-HSD deficiency.

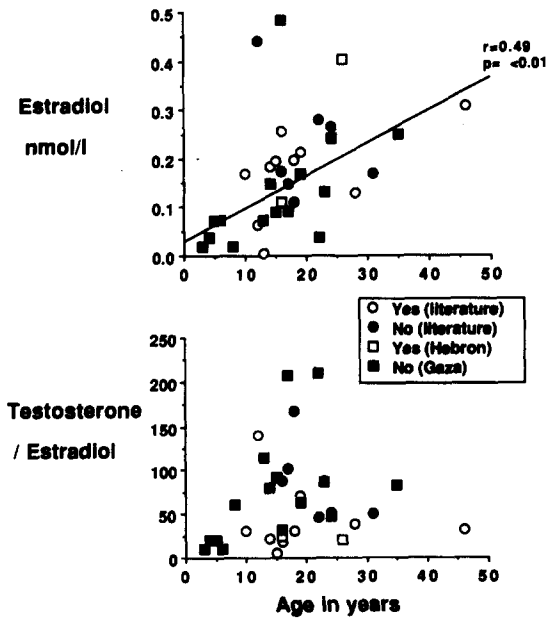

Fig. 7. Gynecomastia in relation to E-2 concentrations and the T to E-2 ratio in MPH patients with 17β-HSD deficiency, according to age. Gynecomastia was more prone to develop if this ratio was <40, whereas this did not occur if the ratio was normal (>100) [22].

ABNORMALITIES IN TESTICULAR STEROID METABOLISM

Post-pubertal masculinization associated with normal T (and DHT) levels implies that there exists an efficient compensatory mechanism in adult males with 17β-HSD deficiency. The elegant studies of Eckstein *et al.* [42] demonstrated that 17β-HSD activity was absent in the testes of affected children, whereas adults produced T

Table 5. Conversion of 4-A to T in testicular tissue of patients with 17β-HSD deficiency

Testicular tissue/ patient	TLC (sp. act.)	HPLC (mass)
MPH $3\frac{3}{4}$ years	0	0
MPH $4\frac{1}{2}$ years	0	0
MPH 13 years	9.1	8.35
MPH 17 years	3.33	3.77
Control 50 years	4.41	3.91
Control 68 years	4.82	5.07

Nanomoles of testosterone produced from 75 μmol/l 4-A per mg tissue during 10 min incubations. Separation and quantification of the steroids were carried out by high performance liquid chromatography (HPLC) according to mass, as well as by thin layer chromatography (TLC) according to the specific activity of the radiometabolites (the disintegrations per minute eluted from the TLC plate divided by the milligrams of cold steroid added), and were also identified on the basis of chemical derivatization methods. Detailed description of these methods and information on the testicular tissue preparation and incubation techniques can be found in Refs [42, 60].

Table 6. Conversion of P to steroid metabolites in testicular tissue of patients with 17β-HSD deficiency

Testicular tissue/ patient	Steroid			
	17-OHP	16-OHP	4-A	T
MPH $3\frac{3}{4}$ years	0	0	3.98	0
MPH 13 years	8.80	7.21	6.60	2.57
MPH 17 years	7.62	7.58	4.46	2.98
Control 50 years	55.15	1.32	5.07	2.47
Control 68 years	58.89	0.80	2.76	2.58

Nanomoles of product produced per mg protein during 10 min incubations. Substrate concentration was 30 μmol/l. For abbreviations see text. Methods are as described in legend to Fig. 5.

in normal amounts from 4-A (Table 5) or progesterone (P) (Table 6). Testicular 17β-HSD is possibly activated by the chronic over-stimulation of LH, as a result of the relatively low T concentrations. These studies revealed several other metabolic aberrations. Testicular tissue of post-pubertal males also metabolized P to 4-A, 17-OHP, and 16α- (16α-OHP) and 16β-hydroxyprogesterone (16β-OHP) [42], whose biological role in this disorder is still unknown. The production of the latter two steroids was 5.4- to 10.3-fold greater than in testes of control individuals. On the other hand, 17-OHP production was 5.8- to 8.1-fold smaller in the testes of the MPH patients than in controls. Formation of 16α-OHP occurs in testicular homogenates of various species of monkeys [61], in normal human testes [62, 63], as well as in human testes with several pathologies [64–66]. When administered to castrated rats 16α-OHP has no virilizing or anabolic properties [67]. *In vitro* however, it competitively inhibits the 17α-hydroxylase activity of cytochrome *P*-450c17 [42, 63]. This explains the great reduction in the production of 17-OHP found in our patients [42], as well as in other males with 17β-HSD deficiency [3, 12, 50]. As a result of this, androgen biosynthesis is impaired through the 4-ene pathway and steroidogenesis is functional mainly through the 5-ene pathway. The preferential pathway for 4-A production was examined in testicular tissue of these patients using equimolar concentrations of [^{14}C]P and [^{3}H]pregnenolone as substrates [42]. While the flow of substrates in the testes of the controls was equal or slightly greater through the 4-ene pathway, the 5-ene pathway predominated in the testes of the males with 17β-HSD deficiency (data not shown, see Ref. [42]). Furthermore, a large quantity of DHEA accumulated when NAD, the cofactor for 3β-hydroxysteroid dehydrogenase was omitted [42], supporting the concept that indeed 4-A was produced mainly

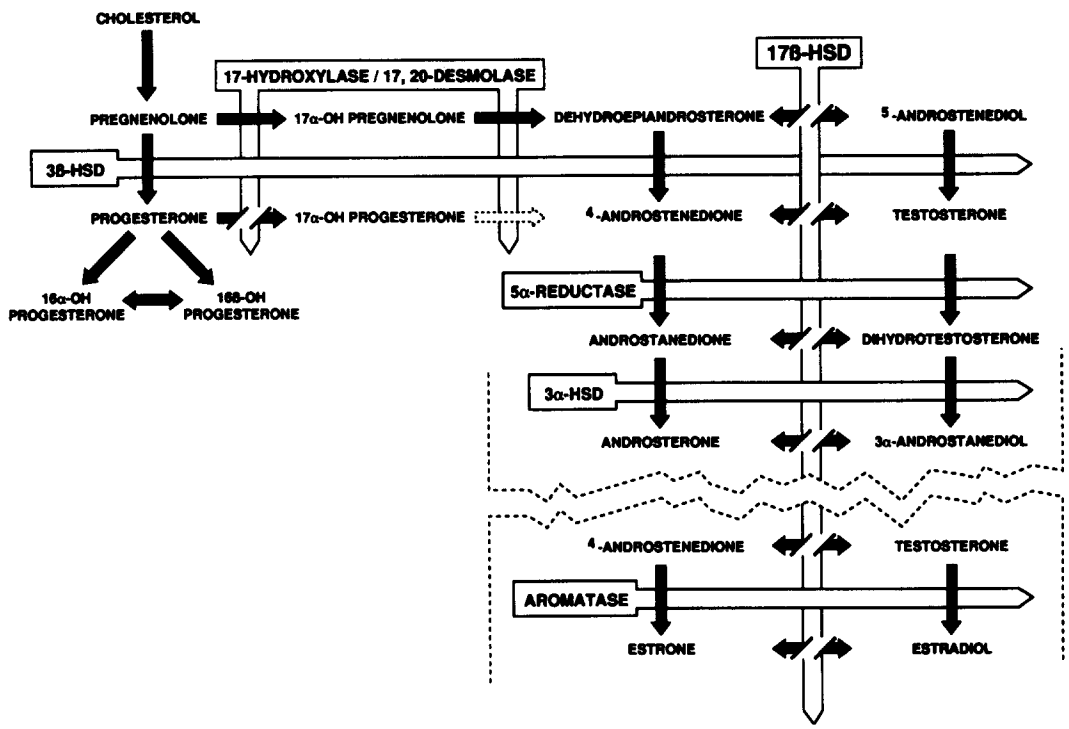

Fig. 8. Schematic overview of androgen and estrogen biosynthesis from cholesterol. 17-Hydroxylase and 17,20-desmolase represent a single protein termed cytochrome *P*-450c17. 17β-HSD: 17β-hydroxysteroid dehydrogenase; 3β-HSD: 3β-hydroxysteroid dehydrogenase-isomerase; 3α-HSD: 3α-hydroxysteroid dehydrogenase. The *full black arrows* indicate the preference of the pathway in the MPH patients with 17β-HSD deficiency. The *outlined and broken arrows* show the sites of inhibition.

Table 7. Male and female genitoplasty in patients with 17β-HSD deficiency

Type of genitoplasty	Surgical procedure	No. of patients
Male[a]		
Stage I	Penile lengthening[b], chordee resection closure of labial-scrotal folds, orchidopexy.	21
Stage II	Reconstruction of urethra to base of phallus.	11
Stage III	Correction of previous surgical procedures (fistulectomy, and other special procedures).	6
Female[c]	Castration and vaginoplasty	6

[a] Fifteen patients were treated with 1 to 6 courses of 3 monthly injections of testosterone enanthate (25 to 125 mg/dose) for penile enlargement, prior to surgery and during the intervals between the different stages. After completion of male genitoplasty T replacement therapy was administered to all post-pubertal patients [27, 35].

[b] By a modification of the technique of Johnston [72].

[c] After female genitoplasty estrogen replacement therapy was administered to all patients.

through the 5-ene pathway, most probably by enhanced 3β-reduction of DHEA [51].

MECHANISM(S) OF T PRODUCTION AND POST-PUBERTAL VIRILIZATION

A hypothesis may be advanced to explain the mechanism of the disorder, particularly in reference to the phenomenon of absence of virilization in fetal life versus the massive masculinization that takes place from puberty to adulthood. Figure 8 summarizes the putative pathways for T production in normal testes, and indicates the principal abnormalities found in the testes of patients with 17β-HSD deficiency. *In utero* the production of T is markedly decreased since the enzyme is deficient in the fetal testes [68]. Although 17β-HSD activity in peripheral tissues may be normal at this age, androgen production is still insufficient. Therefore, normal genital development does not occur at the critical period of life and affected males are born with either female, or ambiguous external genitalia. On the other hand, Müllerian duct inhibition proceeds normally. From infancy until puberty the testes do not function, as expected, so these individuals continue to be reared as females. From the time of puberty gonadotropin secretion progressively increases, and reach very high levels in adults, due to the fact that T production is inappropriately low. Steroidogenesis is functional in the testes, but biosynthesis is abnormal; P is converted to 16α- and 16β-OHP, which accumulates in large amounts and (16α-OHP) competitively inhibits 17α-hydroxylase. Therefore the 4-ene pathway is non-functional and steroidogenesis occurs mainly through the 5-ene pathway. Large quantities of androgen precursors are produced, particularly DHEA, and 4-A, and T production becomes almost normal. Peripheral tissue conversion of androgen precursors into T further increases the production [51, 69]. The deficiency in 17β-HSD is now compensated. Plasma T concentrations fluctuate within the borderline low to normal range. We have recently shown that there is also enhanced 5α-reductase activity in the testes of these patients (Table 3) [51], so that DHT concentrations may also be within normal limits, or even very high. Thus, affected individuals are exposed to normal amounts of androgens and with time markedly virilize, which enables them to spontaneously adopt a male gender role in their particular society [27, 31, 35].

SEX OF REARING, GENDER REASSIGNMENT AND GENITOPLASTY

The sex of rearing of the entire study group compared to similar data from the world literature is shown in Table 2. Because of the natural history of 17β-HSD deficiency among Arabs of Gaza, the preferred sex is male. In children, and at the request of the parents and relatives we have successfully attempted gender reassignment [35]. However, it is recommended to do this procedure in early childhood. To obtain the best results T therapy for penile enlargement must be started immediately after the biochemical diagnosis is established, and before the age of 1 to 2 years. Male genitoplasty may be performed after 2 to 4 courses of 3-monthly injections of T enanthate [70], and as soon as the penile length is within the normal range [71]. We usually administer each course with an interval of 6 months in between, as previously reported [35]. This schedule avoids major side effects such as premature epiphyseal maturation and excessive body growth, although transient pubic hair growth may be found often. The procedure for male genitoplasty is essentially the same for adults and children, and can be performed in 2 to 3 stages (Table 7). Penile lengthening is done by a modification of the technique of Johnson [72]. Briefly, the penile skin is opened with a helicoidal shape incision and is completely detached from the corpus cavernosus. Penile lengthening is achieved by partially detaching the crura from the puboischial rami, thus allowing the corpus cavernosus to be advanced into the shaft (Fig. 9). The

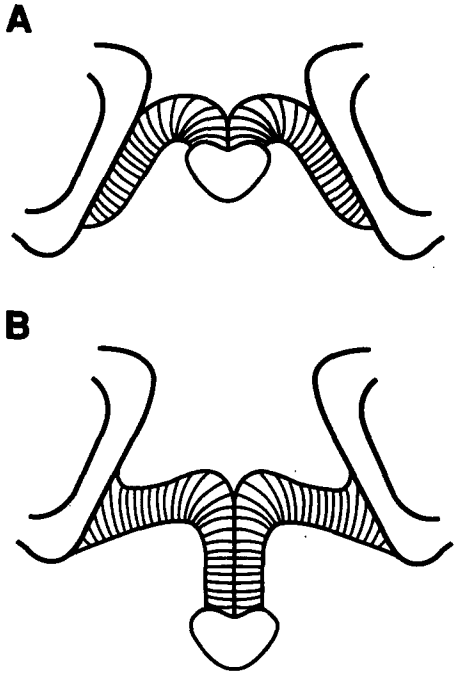

Fig. 9. Schematic view of the technique for lengthening of the penis [72].

chordee is carefully resected, and the result of this step is examined by an artificial erection done with the injection of normal saline into the corpus cavernosus. Thereafter bilateral orchidopexy is performed and the skin is sutured into place [Figs 3(C) and 5(C)]. The blind vaginal pouch is left intact within the (closed) perineum since this apparently causes no problems. Stage II is done approximately 1 year later, if no correction of the previous stage is necessary (e.g. completion of chordee resection), and consists in the reconstruction of the urethra. Utilizing the prepucial skin a tunnel is built so that the urethral opening is brought up to the base of the phallus [Figs 3(C) and 5(C)]. Six out of the 21 patients needed further corrective surgery later on (Stage III) (Table 7). Six of the 12 MPH patients who had a female gender role, or were assigned as such following the advice of their treating physicians, underwent female genitoplasty. This consisted of castration, phallic resection (or recession in young children), and vaginal reconstruction. Although the other 6 patients functioned as females in the society, they retained a male gender identity, even at an advanced age, and denied any form of sex reassignment.

There is no doubt that in children early T therapy and gender reassignment is the treatment of choice. This is justified on anatomical, functional, and particularly psychological grounds, providing a good image for an adequate adjustment in the male gender role after puberty. Nevertheless, the question of infertility in individuals with 17β-HSD deficiency remains unsolved. Adults have normal male internal genitalia and most have normal sexual drive and function. Corrective surgery may permit intromission and vaginal insemination. However, the quality of the ejaculate in several adults examined ranged from severe oligo-astenospermia to complete azoospermia [3, 4, 35]. Histological examination revealed severe Leydig cells hyperplasia, normal Sertoli cells, and signs of early spermatogenesis in some individuals (spermatogonia, a few spermatocytes with no progression to spermatozoa), and absent germ cells in others [35, 73]. The absence of spermatocytes could be attributed to inadequate intratubular T concentrations [74], or to testicular damage caused by long-standing undescended testes. Yet spermatogenesis remains impaired even though the testes are descended in infancy and testosterone replacement is administered in time [36]. It is also possible that certain steroid metabolites produced in excess, such as 16α- and 16β-OHP have a deleterious effect on spermatogenesis [42]. Until this problem is solved, diagnosis, hormonal therapy and early sex reassignment in males with 17β-HSD deficiency is mainly intended to achieve a normal adjustment in the male gender role.

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