Plasma Androgen Response to hCG Stimulation in Prepubertal Boys with Hypospadias and Cryptorchidism

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ABSTRACT. Serum levels of testosterone, androstenedione and dehydroepiandrosterone were measured before and after 5 days of treatment with hCG (2000 IU/d) in 36 prepubertal boys with cryptorchidism and 11 with hypospadias in order to determine whether a defect in androgen synthesis could be a common cause for these disorders. Baseline and stimulated levels of testosterone, androstenedione and dehydroepiandrosterone were similar in patients with unilateral cryptorchidism, monorchism and hypospadias; baseline and stimulated levels of testosterone were lower in boys with bilateral cryptorchidism. Testosterone levels did not correlate with either the anatomical location of the testis in patients with unilateral cryptorchidism or with the site of the urethra in boys with hypospadias. Seven of 36 patients with cryptorchidism had a positive family history of a similar disorder; testosterone levels were similar in patients with and without a family history. It is concluded: 1) in all patients studied, the gonadotropin dependent phase of testosterone production is present; 2) hCG stimulation cannot detect unilateral Leydig cell dysfunction; and 3) in familial cases of cryptorchidism, some factor other than an abnormality in androgen synthesis may be responsible for the hereditary tendency. (*J Clin Endocrinol Metab* **42**: 52, 1976)

CRYPTORCHIDISM and hypospadias are the most common disorders of sexual differentiation in the male. The incidence of cryptorchidism, which varies with age, is 3.4% in newborn males, 0.8% by one year of age, and 0.3–0.7% in adults (1). Hypospadias occurs somewhat less frequently with an incidence estimated to be 0.6–0.8% (2,3). Although the etiology of these disorders is obscure, they represent abnormalities in androgen-dependent events that occur relatively late in male sexual differentiation.

At 6–7 weeks of gestation, differentiation of the indifferent gonad into a testis is first apparent (3). Beginning at 8 weeks, müllerian duct regression is initiated, at 9 weeks Leydig cells are identifiable, and by 10 weeks prostatic buds appear in the urogenital sinus. Under the influence of hormones secreted by the fetal testis, the genital folds fuse to form the urethra, and the testes descend. Fusion of the genital folds begins proximally at 8–10 weeks of gestation and progresses toward the glans penis by 14 weeks. During the fourth month, the prepuce is formed, and later, during the seventh month, the testes descend. Although it is clear that testosterone, the principal androgen of the fetal testis, plays a major role in these developmental processes, it is not clear at present whether other hormones are also involved.

As is true for other forms of incomplete virilization, hypospadias and cryptorchidism could be caused by one of several mechanisms: a) delayed onset of androgen secretion by the testis; b) inadequate production of androgen by the testis; and c) target organ insensitivity to the action of androgen. In addition cryptorchidism may be produced by mechanical factors that prevent descent of the testis.

In a few well documented genetic disorders the cause of cryptorchidism and hypospadias has been identified. Deficient gonadotropin production, as in patients with Kallman's syndrome who lack luteinizing hormone releasing hormone, is a know cause

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of cryptorchidism (4,5). Inadequate production of androgen may be caused by a defect in one of five enzymatic steps required for the conversion of cholesterol to testosterone: the 21,22-desmolase (6), 3 beta-hydroxysteroid dehydrogenase (7), 17-hydroxylase (8), 17,20-desmolase (9), and 17 beta-hydroxysteroid dehydrogenase (10) enzymatic reactions; these disorders are commonly associated with hypospadias and with cryptorchidism. Presumably the same would be the case if damage to the testes occurred during embryonic development. Finally, in disorders of androgen action, such as testicular feminization (11), Reifenstein's syndrome (12,13), and pseudovaginal perineoscrotal hypospadias (14), there is frequently failure of fusion of the urogenital folds and descent of the testes. However, in the great majority of patients, the etiology of hypospadias and cryptorchidism is uncertain. Of the various etiologic mechanisms proposed, the one that is most easily examined postnatally is the ability of the testes to synthesize and secrete androgen. In this study, we have evaluated a group of boys with either hypospadias or cryptorchidism, who were otherwise normal, to determine whether a defect in androgen synthesis could be a common cause for these disorders. Serum levels of testosterone, androstenedione, and dehydroepiandrosterone were measured before and after treatment with human chorionic gonadotropin (hCG), and it has been concluded that the enzymatic capacity to form testosterone is normal in these patients.

Materials and Methods

Forty-seven prepubertal boys, 1–13 years of age, with either hypospadias (11 patients) or cryptorchidism (36 patients) were studied. All boys were in Stage P_1 of puberty as defined by Tanner (15). Family histories were obtained on all patients including documentation of treatment with drugs during pregnancy. The location of each testis was carefully evaluated before and after therapy with hCG and was documented at the time of surgical exploration. Based on these findings, the patients with cryptorchidism were divided into subgroups: unilateral cryptorchidism, monorchism (unilateral absence of the testis), and bilateral cryptorchidism. Each patient received 2000 IU of hCG (Pregnyl-Organon) IM for four consecutive days. Blood was drawn before the first injection and 24 hours after the last injection. Serum was stored at −20 C until assayed.

Androgens were measured by a competitive radioenzyme assay utilizing human placental aromatase and 1,2^{3}H-androstenedione as substrate. The use of this system for the assay of enzyme activity has recently been described (16) and involves 15 min incubation of limiting amounts of placental microsomes, NADPH,

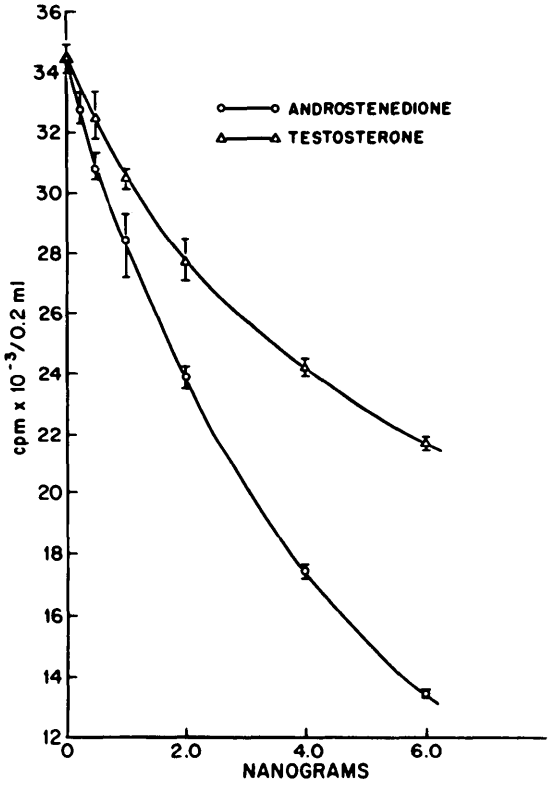

FIG. 1. Replicate standard curves (n = 6) obtained with the aromatase competitive radioenzyme assay for androstenedione and testosterone. Each assay tube contained placental microsomes (100 ng protein) and 2.3 ng of 1,2^{3}H-androstenedione (48 ci/mmole) in 0.5 ml of .05 M Tris buffer (pH 7.4). Incubations were carried out for 15 min at 37 C following the addition of 1 pmole of NADPH in 0.1 ml of buffer. Reactions were terminated by adding 0.1 ml of a 1% charcoal suspension in 5% trichloroacetic acid.

1,2^{3}H-androstenedione and non-radioactive androstenedione (or other competing substrates, *e.g.*, testosterone). Tritium released as ^3H_2O is measured following termination of the reaction by the addition of an acid suspension of charcoal and centrifugation. The presence of non-radioactive steroid competing with 1,2^{3}H-androstenedione for enzyme depresses the yield of ^3H_2O as shown in Fig. 1. The sensitivity of the assay is readily adjustable by varying the amount of labelled substrate or enzyme and NADPH. Dehydroepiandrosterone (DHEA) is assayed by carrying out a 30 min preincubation in the presence of NAD in order to convert DHEA to androstenedione which then is assayed by the addition of NADPH as usual. Standard curves prepared with DHEA were not significantly different from those obtained with androstenedione under the conditions used. Preliminary separation of androgens was achieved by chromatography on micro celite columns using a slight modification of the method described by Abraham (17) as shown in Fig. 2. A high degree of assay specificity is achieved by combining chromatographic separation with the inherent substrate specificity of the aromatase enzyme. The cross reactivity of a variety of steroids when assayed as androstenedione at the 2 ng level was: androsterone—5%, dihydrotestosterone—20%, DHEA—10%, etiocholanalone, epitestosterone, progesterone and estrone—0%. Small amounts (ca 1000 cpm) of 7α-^{3}H-labeled steroids were added to 1 ml of plasma as internal standards prior to extraction with ether (1 ml, twice) to correct for procedural losses. Replicate assays on pools of male and female plasma yielded the results shown in Table 1. Experiments were carried out with ether-extracted plasma in which the mean recoveries of added androstenedione and testosterone (1 ng) were 100 ± 5.5% and 95.6 ± 8.4%, respectively. Water blanks carried through the entire procedure were not significantly different from zero and were not subtracted from the values presented. Occasional batches of ether gave unacceptable blank values but otherwise solvents were used without purification. All glassware was treated at 430 C for 4 hours prior to use. Statistical significance was analyzed by Student's test.

TABLE 1. Androgens in male and female plasma pools measured by the aromatase radioenzyme assay (ng/ml ± SE, n = 8)

	Androstenedione	Testosterone	Dehydroepiandrosterone
Male	1.05 ± 0.090	6.80 ± 0.18	3.86 ± 0.067
Female	1.48 ± 0.064	0.40 ± 0.006	3.70 ± 0.063

Results

As shown in Fig. 3 baseline levels of testosterone (0.62 ± 0.7 ng/ml, mean ± SE),

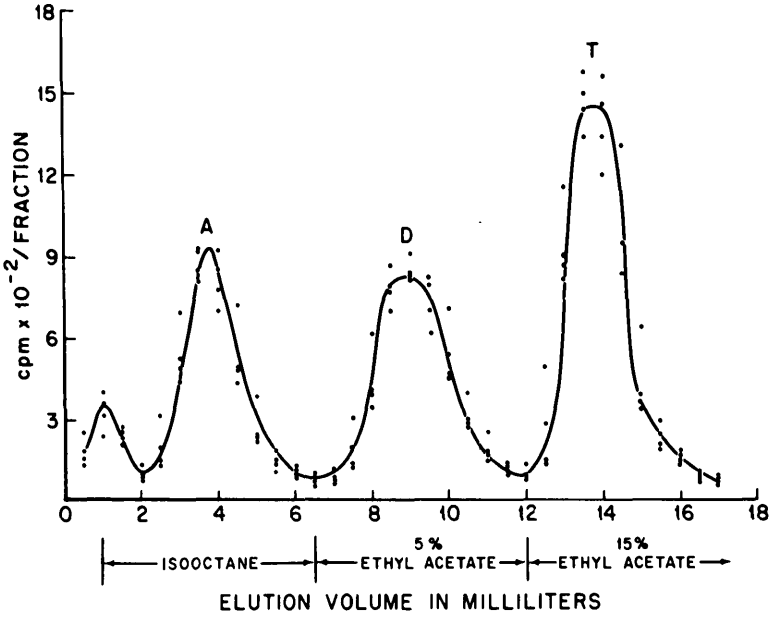

FIG. 2. Chromatographic separation of androstenedione (A), testosterone (T), and dehydroisoandrosterone (D) on micro celite columns. The results of 4 separate runs are plotted.

androstenedione (0.57 ± 0.03 ng/ml) and dehydroepiandrosterone (0.9 ± 0.18 ng/ml) were low in all boys, and there was no correlations between individual levels and age of the patient. Following treatment with hCG, mean serum levels of androstenedione increased 16% ($P < 0.025$), dehydroepiandrosterone increased 45% ($P < 0.01$), and testosterone increased 400% ($P < 0.001$) (Fig. 3). Again, there was no correlation between the age of the patient and androgen levels following treatment with hCG.

When these data are analyzed by individual groups, baseline and hCG stimulated levels of testosterone are similar in patients with unilateral cryptorchidism, monorchism, and hypospadias (Table 2). However, baseline and stimulated levels of testosterone are significantly lower in boys with bilateral cryptorchidism. Baseline and hCG stimulated serum levels of androstenedione and dehydroepiandrosterone were not significantly different in patients with unilateral or bilateral cryptorchidism, monorchism, or hypospadias. The changes in androstenedione and dehydroepiandrosterone are much less than the change in testosterone and are similar to what is known to occur at the time of puberty (18). The physiological significance of these small elevations is uncertain.

The change in testosterone concentrations after four days of treatment with hCG is not as great as has been published after longer treatment periods (19) but the findings are compatible with other reported values (20–23). The actual increase in circulating concentrations of testosterone varied from 1.8 to 3.2 ng/ml. Although baseline and stimulated levels of testosterone were lower in the patients with bilateral cryptorchidism than in the other three groups, the percentage increase of 700%

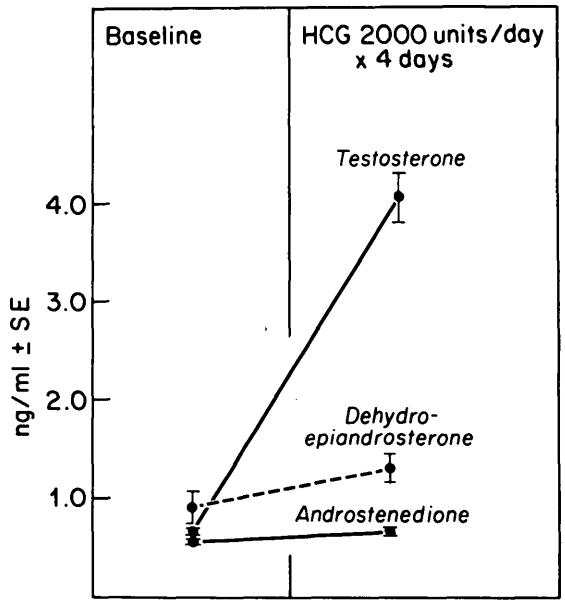

FIG. 3. Mean serum levels of testosterone, dehydroepiandrosterone, and androstenedione in 47 prepubertal boys before and after stimulation with HCG.

TABLE 2. Serum androgen levels in prepubertal boys with cryptorchidism, monorchism and hypospadias before and after treatment with HCG

Group	Number	Mean age years (range)	Androstenedione (ng/ml)		Dehydroepiandrosterone (ng/ml)		Testosterone (ng/ml)		
			Before	After	Before	After	Before	After	Increment
Unilateral cryptorchidism	24	6.3 (1½–13)	0.55 ± 0.04[1]	0.60 ± 0.05	0.95 ± 0.15	1.3 ± 0.17	0.71 ± 0.10	3.15 ± 0.28	2.34 ± 0.28
Bilateral cryptorchidism	8	8.1 (1½–13)	0.64 ± 0.07	0.71 ± 0.04	1.7 ± 0.61	2.12 ± 0.75	0.29 ± 0.05*	2.06 ± 0.37	1.76 ± 0.50†
Monorchism	4	4.4 (1¾–9)	0.59 ± 0.09	0.63 ± 0.11	0.65 ± 0.21	1.35 ± 0.36	0.74 ± 0.36	2.93 ± 0.81	2.19 ± 0.88
Hypospadias	11	3.5 (1¹¹/₁₂–12)	0.59 ± 0.07	0.79 ± 0.13	0.83 ± 0.11	1.26 ± 0.17	0.60 ± 0.07	3.92 ± 0.44	3.22 ± 0.45

[1] Mean ± SE

* Significantly different from unilateral cryptorchidism and hypospadias $P < 0.01$.

† Significantly different from hypospadias $P < 0.025$.

TABLE 3. Relationship between the anatomical defect and basal and HCG stimulated testosterone levels in boys with unilateral cryptorchidism or hypospadias

Diagnosis	Anatomical defect	Number	Mean age years (range)	Testosterone (ng/ml) Before	Testosterone (ng/ml) After
Unilateral cryptorchidism	Testis in:				
	Inguinal Canal	10	6.5 (4–13)	0.77 ± 0.2[1]	2.41 ± 0.22
	Denis-Browne pouch	8	6.5 (1½–8)	0.77 ± 0.5	3.26 ± 0.5
	Retractile	2	9.0 (8½–9½)	0.35 ± 0.03	3.18 ± 0.75
	Abdominal	2	5.3 (5–5½)	0.66 ± 0.06	4.71 ± 0.23
	Absent	4	4.4 (1¾–9)	0.74 ± 0.36	2.93 ± 0.81
Hypospadias	Location of urethral meatus:				
	Coronal	3	3.3 (1½–5)	0.41 ± 0.09	3.67 ± 1.23
	Penile	7	4.5 (1½–7)	0.71 ± 0.05	4.11 ± 0.55
	Perineal	1		0.21	3.43

[1] Mean ± SE.

in patients with bilateral cryptorchidism is actually the largest increase demonstrated in any group.

The relationship between the anatomical location of the defect and basal and stimulated testosterone levels was examined in 24 patients with unilateral cryptorchidism or monorchism who underwent surgery and in 11 patients with hypospadias (Table 3). In boys with unilateral cryptorchidism there was no correlation between baseline and stimulated testosterone levels and the anatomical location of the testis. In patients with hypospadias, testosterone levels were similar in patients with coronal, penile, and perineal forms of the disorder. In conclusion, the response of serum testosterone to hCG administration appears to be relatively uniform in these patients who demonstrate a broad spectrum in regard to anatomical and functional severity.

When boys with unilateral cryptorchidism were treated with hCG, the testis descended into the scrotum in 2 boys, descended far enough to become palpable but required surgical correction in 3, and remained unchanged in anatomical location in 19. In the 5 patients in whom the testes descended in response to hCG, testosterone levels after hCG treatment (3.24 ± 0.7 ng/ml) were not significantly different from the levels in boys who failed to respond (2.88 ± 0.3 ng/ml).

Seven of the 36 patients with cryptorchidism had a family history of a similar disorder. In 3 cases the maternal side of the family was affected (mother's cousin; mother's brother and grandmother's nephew; and grandmother's brother), in 3 cases the paternal side was affected (father, grandfather, and great-grandfather; father; and father's brother and grandmother's nephew) and in one case a sibling's brother had cryptorchidism. Serum levels of testosterone after hCG were similar in patients with (3.2 ± 0.6 ng/ml) and without (2.74 ± 0.24) a positive family history. Two of the patients with hypospadias had family histories of relatives with cryptorchidism but the family histories of these patients were otherwise uninformative.

Discussion

Since the abnormality in virilization in these patients involves the last phase of male sexual differentiation and since their basic phenotype is unequivocally male, it is clear that the underlying defect, whether

it involves gonadotropin production, androgen synthesis, or androgen action, must be partial and incomplete.

In this study, hCG administration produced a marked elevation of serum testosterone and minimal but significant increases in serum levels of androstenedione and dehydroepiandrosterone. Androgen levels before and after hCG administration were similar in patients with unilateral cryptorchidism and hypospadias, and these levels were within the broad range of values reported by others using similar treatment protocol (20–23). Although no age matched normal boys were tested in this study, the findings indicate that the enzymatic capacity to synthesize testosterone is present in all three groups. Furthermore, since the stimulated levels of testosterone were similar in the unilateral cryptorchidism and hypospadias groups, it is not likely that any subtle difference exists in the maximal capacity for testosterone synthesis in the two disorders. Insofar as we have been able to define these groups as normal, the findings suggest that the fundamental defect is more likely to be some abnormality in gonadotropin levels or response or a partial defect in androgen action. Clearly the quantitative aspects of LH and FSH regulation and the intracellular events in androgen action should be examined in these patients.

Several important clinical implications of these studies deserve comment. First, because it was not possible to distinguish testosterone responses in patients with unilateral absence of the testis from those in patients with unilateral cryptorchidism or bilateral descent, these data indicate that this test cannot detect unilateral Leydig cell dysfunction. Similar results have previously been reported in adults by Weinstein *et al.* (24), and it is presumed that when unilateral Leydig cell dysfunction is present in either adults or children, hypertrophy of the contralateral scrotal testis takes place so that the baseline and stimulated testosterone production becomes normal (25). Unless a high local concentration of testosterone is necessary for descent to occur, these data suggest furthermore that in unilateral cryptorchidism the failure of descent is not due to an abnormality in androgen production.

Second, on the basis of these studies it is not possible to be certain whether the abnormality of Leydig cell function in bilateral cryptorchidism is the result or the cause of the maldescent. In boys with bilateral cryptorchidism, baseline and hCG stimulated levels of testosterone were lower than in patients with unilateral cryptorchidism and hypospadias. These results are similar to the findings of Rivarola *et al.* (20). However, it is evident that patients with bilateral cryptorchidism can respond to hCG stimulation by producing androgen in significant concentrations, and at the present time there is no way to know whether the slightly impaired response in patients with bilateral cryptorchidism is responsible for the failure of descent or is the result of the ectopic location of the testes. In the rat, experimental cryptorchidism produces both injury to the germinal epithelium and impairs Leydig cell function (26,27). This effect of cryptorchidism on androgen synthesis cannot be demonstrated in immature rats but develops with the onset of sexual maturation (28). In the human, it would be of interest to study groups of boys with bilateral cryptorchidism at various ages, beginning in infancy, to determine whether this defect is present at birth or whether it is acquired with advancing age. It would also be of interest to determine whether androgen dynamics improve following bilateral orchiopexy.

Third, in this study 19% of patients with cryptorchidism had a family history of a similar disorder. Scorer and Farrington reported 14% of 106 cases had a positive family history (29). Klein, Ferrier, and Ammann (30) concluded that cryptorchidism may be inherited as an autosomal domi-

nant trait with variable expressivity, but suggest that only 3.4–5% of all cases arise this way. The findings in this study of similar levels of testosterone in familial and non-familial cases indicates that some factor other than an abnormality in androgen synthesis must be responsible for this hereditary tendency such as delayed or inadequate fetal gonadotropin secretion or inadequate transfer of chorionic gonadotropin to the fetus.

Finally, in a study of 80 patients with hypospadias, Aarskog noted that in 5 cases progestin had been administered during the first trimester of pregnancy (31). In addition, when the position of the urethral meatus was compared to the week of gestation at which progestin treatment was started, there seemed to be a relationship with the more proximal openings in the infants of mothers who had been treated in the first month of pregnancy. In our study, no patient had a history of therapy with progestational agents during pregnancy.

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