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THE EFFECT OF LUTEINIZING HORMONE-RELEASING HORMONE IN HYPOGONADOTROPHIC EUNUCHOIDISM

By

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ABSTRACT

Fourteen patients with hypogonadotrophic eunuchoidism (HE), 10 males and 4 females, received luteinizing hormone-releasing hormone (LH-RH) as 4-h intravenous infusions of 0.2 μg/min or as subcutaneous (sc) injections of 200 μg. Repeated LH-RH administration over 4 days (200 μg sc daily) was undertaken in 8 patients. Eight of the 10 males and all 4 of the females were found to have definite elevations of luteinizing hormone (LH) and follicle stimulating hormone (FSH) following their first exposure to exogenous LH-RH. The patients included 2 males and 1 female with variant forms of HE, all of whom showed responses of both gonadotrophins.

When the first exposure of HE patients to exogenous LH-RH was as a 4-h infusion, the biphasic pattern of LH increase characteristic of normal adults was not found. Instead, a monophasic and qualitatively small LH increase occurred, similar to that found in pre-pubertal children and in anorexia nervosa. In 2 patients with an initially abnormal LH response, a 4-h LH-RH infusion following 4 days of LH-RH injections (200 μg

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sc/day) produced a normal biphasic LH increase. These results imply that maintenance of the two pools of pituitary LH demonstrable in normal adults depends on adequate production of endogenous LH-RH.
Increases in FSH following the initial exposure to LH-RH were generally as great or greater than those of normal adults in spite of the fact that LH responses tended to be smaller than those of adults. Four days of LH-RH administration (200 sc daily) did not lead to consistent increases in gonadotrophin responsiveness. Increases of testosterone or oestradiol production could not be demonstrated, even with 4 to 5 days of LH-RH administration. Exogenous sex hormone therapy markedly inhibited gonadotrophin responsiveness to LH-RH.

Hypogonadotrophic eunuchoidism (HE) is a congenital, often familial defect in gonadotrophin production from the pituitary (*Kallman et al.* 1944; *de Morsier* 1954). Autosomal dominant inheritance of the condition has been demonstrated (*Santen & Paulsen* 1973). It is now generally accepted that a deficiency of endogenous luteinizing hormone-releasing hormone (LH-RH) production explains the gonadotrophin deficiency in most, if not all patients with this syndrome (*Paulsen* 1974). This concept has been derived from post-mortem studies of a few such patients in whom hypothalamic lesions and normal pituitaries were found (*Gauthier* 1960; *de Morsier & Gauthier* 1963) and also from recent studies in which nearly all such patients have been shown to increase their gonadotrophin secretion in response to exogenous LH-RH (*Mortimer et al.* 1974; *Reitano et al.* 1975).

During 4-h. constant infusions of LH-RH, two phases of LH secretion have been described in normal men (*Bremner & Paulsen* 1974; *de Kretser et al.* 1975). women (*de Kretser et al.* 1976; *Wang et al.* 1976) and experimental animals (*Bremner et al.* 1976). These two phases of secretion have been interpreted as evidence for the existence of two pools of pituitary LH. one immediately releasable, the second requiring longer LH-RH stimulation and possibly new protein synthesis for release (*Bremner & Paulsen* 1974). The present paper describes the patterns of gonadotrophin secretion during 4-h LH-RH infusions in HE both before and after several days of exogenous LH-RH administration and also presents data on gonadotrophin responsiveness to single LH-RH injections in this condition.

MATERIALS AND METHODS

Patients and normal subjects

Fourteen patients, aged 20 to 38 years, with HE were studied (Tables 1 and 2). Ten were male. 4 female. Anosmia or hyposmia (*Henkin & Bartter* 1966) was present in 9. Three patients had a family history of hypogonadism or anosmia. All patients were eunuchoidal when first evaluated at age 20 years or older. Growth had been

Table 1.
Clinical and hormonal data for males with hypogonadotrophic eunuchoidism.

	Age	Ability to smell	Family* history	Gynaeco-mastia	Cryptor-chidism	Testicular biopsy	LH (mIU/ml) normal 5–25	FSH (ng/ml) normal 50–450	Testosterone (μg/100 ml) normal 0.3–1.2	Response to gonadotrophins
1. T. B.	26	Normal	–	–	–	NS	3.1	< 30	0.22	NS
2. D. E.	38	Anosmia	+	–	Bilateral	NS	1.3	< 30	0.08	Poor testosterone-response to HCG
3. G. G.	29	Anosmia	–	–	–	NS	< 1.0	90	0.25	Normal testosterone on HCG
4. L. H.	24	Normal	–	+	Unilateral	NS	< 1.0	< 30	0.10	Normal testosterone on HCG
5. D. L.	34	Anosmia	–	–	–	Pre-pubertal	1.2	77	0.23	NS
6. D. M.	22	Normal	–	+	–	Pre-pubertal	3.4	90	0.13	Normal testosterone on HCG
7. P. N.	26	Hyposmia	–	–	Bilateral	Pre-pubertal	3.0	90	0.15	Poor testosterone-response to HCG
8. J. P.	29	Hyposmia	–	+	–	Pre-pubertal	1.8	40	0.29	Fertility with HCG and HMG
9. D. H.	32	Hyposmia	–	–	–	Sd. spermatids. No Leydig cells	1.6	42	0.19	Normal testosterone on HCG
10. M. S.	25	Normal	–	+	–	Mature spermatozoa. Leydig cells	10.2	240	0.25	Normal testosterone on HCG

–: absent; +: present; NS: not studied; *: history of olfactory deficiency or eunuchoidism; HCG: human chorionic gonadotrophin; HMG: human menopausal gonadotrophin (75 IU LH and 75 IU FSH per ampoule).

Table 2.
Clinical and hormonal data for females with hypogonadotrophic eunuchoidism.

	Age	Ability to smell	Family* history	LH (mIU/ml) normal 5–25 (non-ovulatory)	FSH (ng/ml) normal 50–450 (non-ovulatory)	Oe_2 (pg/ml) normal 30–150 (early follicular)	Response to gonadotrophins
11. L. L.	26	Hyposmia	+	< 2.0	30	17.8	Ovulation on HMG and HCG*
12. D. R.	32	Anosmia	+	2.3	73	12.5	Poor ovulatory response to HMG and HCG
13. L. S.	20	Anosmia	–	2.3	61	14.1	NS
14. H. D.	30	Normal	–	12.6	281	18.6	Ovulation with HMG and HCG

* See legend to Table 1.

normal in all and no endocrine deficiencies other than eunuchoidism were detectable clinically. Gynaecomastia was present in 4 of the 10 males at the time of initial asessment. a frequency that is higher than previously recognized (*Paulsen* 1974). In two of the men (patients 9 and 10), testicular size prior to treatment (2.5 to 3.0 cm in length) was nearly as great as that of normal adults. In both, evidence of endogenous gonadotrophin stimulation was also present in their testicular histology (Table 1). These two men fall within the classification of the "fertile eunuch" syndrome (*Pasqualini & Bur* 1955).

Serum levels of testosterone or oestradiol (Oe_2) were below normal in all subjects, consistent with their eunuchoidism. Serum LH levels were low in all the patients except one of the male fertile eunuchs (patient 10) and one female (patient 14). These 2 patients were unusual in that their serum levels of both LH and FSH were well within the normal adult range. Nevertheless, they otherwise seemed to fit the criteria of HE including eunuchoidism itself, deficiency of gonadal steroid production, lack of responsiveness to clomiphene and normal gonadal function with gonadotrophin therapy. We will refer to patients 9, 10 and 14 as "variant hypogonadotrophic eunuchoidism" (variant HE) (*Paulsen* 1974) and the other patients as "classic hypogonadotrophic eunuchoidism" (classic HE).

Serum FSH levels (Tables 1 and 2) ranged from below the detectability of the assay to well within the normal range. Many of the patients with classic HE had normal levels of serum FSH (e. g. males 3, 5, 6 and 7 and females 12 and 13). One of the

males with the fertile eunuch variant (patient 9) showed low serum FSH levels and the other two subjects with variant HE exhibited normal levels of both LH and FSH. These observations are in contrast to the commonly held view that the fertile eunuch syndrome is due to low serum levels of LH and normal levels of FSH (*Faiman et al.* 1968) while classic HE is associated with low serum levels of both hormones.

All forms of hormonal therapy were omitted for at least 6 weeks prior to the present study.

Ten normal male subjects between 20 and 30 years of age were studied. Normality was confirmed by medical history and physical examination as well as basal LH, FSH and testosterone values.

LH-RH studies

Synthetic LH-RH (supplied by courtesy of Dr. J. G. Rochefort, Ayerst Laboratories, Montreal) was administered either as subcutaneous (sc) injections of 200 μg or as intravenous (iv) infusions of 0.2 μg/min for 4 h (Harvard pump). Five normal men underwent 4-h infusions (*Bremner & Paulsen* 1974) and 5 other normal men were studied with 200 μg sc injections. Six males with classic HE were studied with 4-h infusions as their first exposure to exogenous LH-RH. Three such patients were studied with 4-h infusions following 4 days of exogenous LH-RH administration (200 μg sc daily). Eight HE males and 4 females received sc injections of 200 μg LH-RH. In 4 males and 3 females these injections were repeated daily for 3 to 4 days. Two male and 3 female HE patients received a last 200 μg sc injection following approximately 2 months of sex hormone replacement therapy (testosterone oenanthate, 200 mg intramuscularly (im) each 2 weeks in the males and a cyclic combination of ethynodiol diacetate, 1 mg and mestranol, 100 μg, Ovulen® in the females). All studies were begun between 07.00 and 10.00 h. Subjects were allowed to eat as they wished and to move from a bed to a chair at will during the studies.

Blood sampling was from an indwelling catheter in an arm vein. Two samples separated by 15 min were taken prior to each study. Following the single LH-RH injection, samples were generally taken at 15, 30, 45, 60, 90, 120 and in some cases, 240 min. During the 4-h LH-RH infusions, sampling occurred at 15 min intervals until 90 min, then at 30 min intervals until the end of the infusion. Blood was allowed to clot, then centrifuged and the serum stored at –20°C until assay.

LH, FSH, testosterone (*Capell et al.* 1973) and Oe_2 (*Abraham* 1969) were measured in duplicate by specific radioimmunoassays. All samples from each subject were measured in one assay.

RESULTS

1. *Single administration of LH-RH as a 4-h intravenous infusion or as a subcutaneous injection*

A. *Four hour iv infusion*

Six HE males received 4-h iv infusions as their first exposure to LH-RH (Fig. 1). Serum LH values in 4 patients (1, 3, 5 and 6) showed definite increases while in the other 2 patients (2 and 4) little change in LH occurred. During the first 90 min of the infusions, LH increases in the 4 patients who

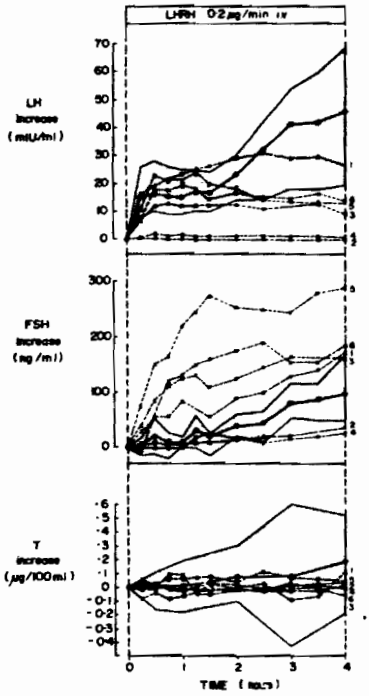

Fig. 1.

(x- - - -x). Serum LH, FSH and testosterone increases above basal values in 6 males with classic HE during their first exposure to exogenous LH-RH (0.2 μg/min for 4 h iv). Numbers on right-hand margin refer to patient descriptions in Table 1. Shaded areas and solid lines represent ranges and means of hormone increases during similar infusions in 5 normal men.

responded were similar to those of normal subjects. A rapid early rise occurred, reaching a peak by approximately 30 min (except in one patient who exhibited a further gradual increase until 150 min), followed by stable or slightly decreasing LH levels until approximately 90 min. Between 90 min and the end of the infusions at 240 min, a divergence between the values of the normal subjects and the HE patients occurred. LH levels in normal subjects exhibited a second phase of progressive increase beginning at approximately 90 min and lasting until the infusions were stopped. This second phase of LH increase was not found in the HE patients; instead, stable or gradually decreasing levels occurred in spite of continued LH-RH administration. Two HE patients (2 and 4) exhibited only very minimal increases in serum levels (never more than 2 mIU/ml greater than basal values) in spite of 4 h of LH-RH stimulation. For purposes of discussion and further analysis, these 2 patients have arbitrarily been called "low responders" and the 4 subjects described previously have been called "intermediate responders".

In the group of patients classified as intermediate responders on the basis of their LH responses, serum FSH levels revealed larger increases above basal values than those of normal subjects (Fig. 1). In both normal subjects and HE patients, the pattern of increase was progressive throughout the infusions, with no evidence of a biphasic pattern. In the 2 patients classified as low responders on the basis of their LH responses (2 and 4), increases in serum FSH levels were also small (never exceeding 35 ng/ml).

No increase was found in serum levels of testosterone in the HE patients during the 4-h LH-RH infusions (Fig. 1). Only 2 of the 5 normal subjects showed increases in serum testosterone (sustained increase greater than 50 % above basal values). Testosterone values in the other 3 normal men remained stable or decreased.

B. *Single sc injections*

(I) *Males.* – Six males with classic HE received sc injections of 200 μg of LH-RH. In 2 (patients 7 and 8), this injection was their first exposure to exogenous LH-RH and in 4 (patients 4, 5, 6 and 2) the sc injection followed a 4-h LH-RH infusion by 1 day, 1 day, 1 day and 3 months, respectively. In 4 of the patients (5, 6, 7 and 8), the LH increase was within or just below the range seen in normal subjects (Table 3). Patients 7 and 8 were added to the category of "intermediate responders". In the other 2 patients (2 and 4) the LH response was again minimal as it had been during the 4-h infusions.

Increases in serum FSH in the intermediate responder group were within or above the range found in normal subjects (Table 3). Increases in FSH in the pair of low responders were again very slight. Serum testosterone levels failed to reveal definite increases in either the normal subjects or the patients with HE.

(II) *Females.* – Three females with classic HE received a sc injection as their first exposure to exogenous LH-RH. LH increases in all three were definite, but considerably smaller than those of normal subjects (Table 3). Increases in FSH were uniformly greater than those of normal subjects (Fig. 3). No increase was found in serum Oe_2 levels in these 3 patients following sc LH-RH.

(III) *Studies in variant HE.* – In the 3 patients classified clinically as variant HE, a spectrum of gonadotrophin responses was found following the sc LH-RH injection (Table 3). One male (patient 10) exhibited greater responses of both LH and FSH than those found in normal subjects, while the other male (patient 9) showed LH and FSH responses slightly less than those of normal adult males. The female (patient 14) exhibited normal increases in both LH and FHS.

Table 3.

Maximal increases above basal values in serum LH and FSH concentrations following 200 μg LH-RH subcutaneous injections. Blank space denotes that study not performed in that patient. The numbers in the first column refer to patient numbers in Tables 1 and 2. LH in mIU/ml, FSH in ng/ml.

Patient	Repeated LH-RH injections (200 μg sc daily) for 4 days				During sex hormone replacement therapy	
	1st day		4th day			
	LH	FSH	LH	FSH	LH	FSH
Classic HE – males						
2	0.4	18				
4	3.4	21	4.7	35		
5	21.1	184	27.1	141		
6	20.5	110				
7	34.0	65	25.0	56	0.0	0.0
8	22.1	110	16.5	75	12.5	110.0
Classic HE – females						
11	4.0	119	13.1	125	0.2	0.0
12	3.5	144	8.1	136	0.0	7.0
13	5.7	167	7.0	135	0.5	0.0
Variant HE						
9	14.8	35				
10	97.8	225				
14	37.5	65				
Normal (n = 5)						
Mean	37.6	93				
Range	27–48	50–110				

(IV) *Studies during exogenous sex steroid administration.* – Of the 5 HE patients who were given sc LH-RH injections while receiving exogenous sex steroid therapy, all 3 females and 1 of the males exhibited marked suppression of their LH and FSH responsiveness (Table 3). Only slight suppression of LH and little change in FSH responsiveness occurred in the other male. This variability in suppression of pituitary responsiveness in the males apparently was not due to irregularities in administration of their androgen therapy since both demonstrated serum testosterone levels above the normal adult male range (patient 7 – 1.8 μg/100 ml; patient 8 – 2.03 μg/100 ml).

2. *Repeated administration of LH-RH over 3 to 5 days*

A. *Four hour infusions following 4 days of LH-RH administration*

Three HE males were treated for 4 days with LH-RH injections (200 μg sc daily) followed by a 4-h iv infusion. Two (patients 1 and 7) had previously been classified as intermediate responders as described above. The pattern of LH increase in these two patients during the 4-h LH-RH infusion following 4 days of LH-RH pre-treatment was indistinguishable from that of normal subjects (Fig. 2). A definite second phase of LH increase beginning at 75 to 90 min was found in each case. Similarly, the FSH increase in these two studies was normal (Fig. 2). Basal values of testosterone were not changed following 4 days of LH-RH administration and no increase was found during the 4-h infusion.

One patient (4). classified originally as a low responder. subsequently under-

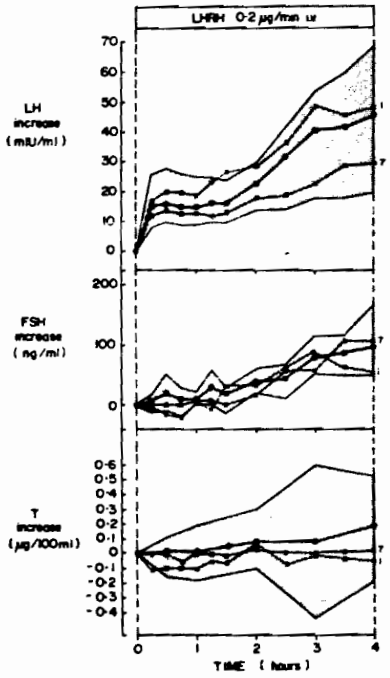

Fig. 2.

(x- - - -x). Serum LH. FSH and testosterone increases above basal values in 2 males with classic HE during 4-h infusions of LH-RH (0.2 μg/min iv) following 4 days of LH-RH injections (200 μg sc daily). Numbers on right-hand margin refer to patient dscriptions in Tabl 1. Shaded areas and solid lines represent ranges and means of hormone increases during similar infusions in 5 normal men.

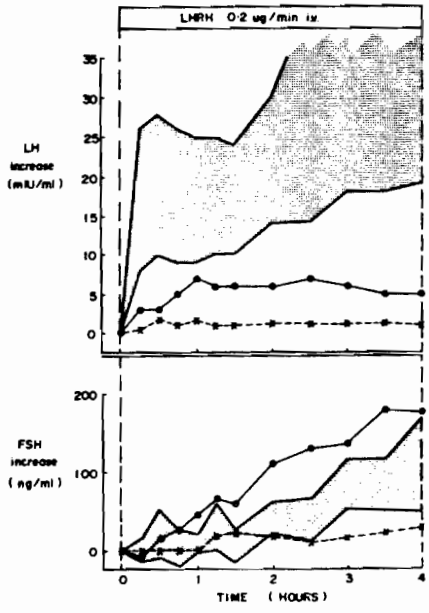

Fig. 3.

Serum LH and FSH increases in one male with classic HE during 2 infusions of LH-RH (0.2 μg/min for 4 h). (x- - - -x) first exposure to exogenous LH-RH. (●- - - -●) second infusion following 4 days of LH-RH injections (200 μg sc daily). Shaded area is range of gonadotrophin increases in 5 normal men during similar infusions.

went 200 μg LH-RH sc injection daily for 4 days. then a second 4-h LH-RH infusion (Fig. 3). The pattern of LH increase in this subject during his second infusion was similar to that of the intermediate responder group during their first infusion (Fig. 1). There was a rapid, early increase, reaching peak values by 60 min, after which LH levels were essentially stable until the end of the infusion, with no evidence of a second phase of increase. The pattern of FSH increase in this patient (Fig. 3) during his second infusion was also similar to that of intermediate responder group during their first infusion (Fig. 1). The FSH increase was large, being greater than that found in normal subjects.

B. *Repeated sc injections over 3 to 4 days*

Four males and 3 females received daily sc injections of 200 μg LH-RH for 3 to 4 days. The maximal increase in LH and FSH induced by LH-RH did not change in a uniform way between the first and last day (Table 3). No change was found in basal or stimulated values of testosterone or Oe_2 after 3 to 4 days of LH-RH exposure.

DISCUSSION

The results of the present study demonstrate that 8 of 10 male and all of 4 female patients with HE exhibited definite increases in serum levels of both LH and FSH during their first exposure to exogenous LH-RH. These results included 2 males and 1 female with variant HE, all of whom showed responses of both gonadotrophins. Two males with classic HE showed very small or absent responses for both LH and FSH. Of the patients with classic HE who showed gonadotrophin responses, LH increases above basal values were equal to or less than those of normal adult males; FSH increases above basal values in these patients were equal to or greater than those of normal adults.

When the first exposure of males with classic HE to exogenous LH-RH was as a 4-h infusion (Fig. 1), serum LH values failed to reveal the two phases of increase found in normal adults. In 4 of the 6 patients, an elevation of serum LH values occurred in the first 30 min of the LH-RH infusions, but no second phase of increase occurred. These results resemble those that we (*Bremner et al.* 1975; *Baker et al.* 1976) and others (*Reiter et al.* 1976) have reported for pre-pubertal children, in whom LH responses during prolonged LH-RH infusions are monophasic and quantitatively smaller than those of adults. A similar monophasic pattern of LH response is found in another form of sexual immaturity, anorexia nervosa (*Bremner et al.* 1977). Pre-pubertal children (*Boyar et al.* 1972). and patients with anorexia nervosa (*Boyar et al.* 1974) and with HE (*Santen & Bardin* 1973) exhibit very small or absent episodic LH secretion, *i. e.* LH "spikes". Recent evidence implies that LH spikes are caused by LH-RH spikes (*Carmel et al.* 1976). It may be speculated that these three types of sexual immaturity are deficient in endogenous LH-RH production. particularly in the spiking pattern of LH-RH secretion. As described, these three groups have deficient LH responses to LH-RH infusions, lacking at least the second phase of LH secretion. These observations suggest that normal adult levels of endogenous LH-RH production, particularly in a spiking pattern, are necessary to maintain the two pools of pituitary LH which are thought to be responsible for the two phases of LH secretion found during LH-RH infusions in normal adults (*Bremner & Paulsen* 1974).

It is now generally agreed that the majority of patients with HE have a defect in endogenous LH-RH production. We have not yet found a patient for whom it was necessary to postulate a primary pituitary defect. Although two males initially exhibited very small or absent gonadotrophin responses. 4 days of exogenous LH-RH administration to one of them led to a pattern of pituitary responsiveness similar to that of the rest of the patients in their first study (Fig. 3). Also, 4 days of exogenous LH-RH administration to 2 patients classified originally as intermediate responders led to a pattern of responsiveness similar to that of normal adults (Fig. 2). Variability in endogenous

LH-RH production is the most likely explanation of the difference in pituitary responsiveness in HE; patients with the lowest responses may be the most deficient in endogenous LH-RH production. Congenital HE, however, may be a heterogenous disease and it is possible that a minority of such patients may be shown to have primary pituitary disease.

In the group classified as intermediate responders on the basis of LH increase during their first 4-h LH-RH infusion, FSH increases were equal to or greater than those of normal subjects (Fig. 1). Similar patterns for FSH increase during prolonged LH-RH infusions have been found in pre-pubertal children (*Bremner et al.* 1975; *Baker et al.* 1976; *Reiter et al.* 1976) and in some patients with anorexia nervosa (*Bremner et al.* 1977). The reason for the relative hyper-responsiveness of FSH in these sexually-immature groups is not known but could be due to a change in their gonadotrophs associated with their presumed deficiency of endogenous LH-RH or due to a deficiency of inhibin production from their immature gonads. That at least a minimal exposure of the pituitary to LH-RH is necessary to produce FSH hyper-responsiveness is suggested by the data from patient 4 (Fig. 3). His FSH responsiveness changed from being very low to being greater than normal during 4 days of LH-RH treatment.

The 3 patients classified as variant HE all showed definite increases in both LH and FSH following LH-RH administration (Table 3). The female and one of the males exhibited normal or slightly less than normal increases of both LH and FSH. The other male, however, showed excessive responses of both hormones. This may imply adequate releasing hormone production in this subject to maintain pituitary hormone stores but inadequate gonadal maturation to exert a normal negative feedback effect on pituitary responsiveness. The one previous patient (a male) with variant HE who has had an LH-RH study reported also showed large responses of both LH and FSH (*Williams et al.* 1975). It is possible that some patients with variant forms of HE, particularly those with normal serum gonadotrophin levels by radioimmunoassay and gonadal deficiency may produce abnormal forms of the gonadotrophins.

A marked inhibitory effect of sex steroid administration on pituitary responsiveness to LH-RH in HE was demonstrated in 3 females and 2 males. No evidence for a positive feedback effect of steroids on pituitary responsiveness was found. In 4 HE male patients, *Isurugi et al.* (1973) found that testosterone therapy completely suppressed both LH and FSH responsiveness to LH-RH. These data emphasize the importance of stopping steroid administration well before LH-RH testing.

The precise mechanisms underlying the two phases of LH secretion in adults are unknown. We have previously suggested the existence of two pools of pituitary LH, one requiring longer stimulation for release than the other (*Bremner & Paulsen* 1974). The first pool could represent previously synthe-

sized hormone and the second may require new synthesis of LH or of a protein necessary for its release. The concept of two pools of LH has been supported by the finding that the steroid hormone milieu may affect one pool differently from the other (*Wang et al.* 1976) and that the ratio of bio- to immunoactivity may be greater in hormone released from the second pool than in that from the first pool (*Dufau et al.* 1976). The results of the present study give further support to the concept of two pools of pituitary LH. Our results imply that the ability to secrete hormone from the second or "later" pool of LH is impaired by mild deficiencies of endogenous LH-RH and that secretion from both pools may be decreased by more severe LH-RH deficiency.

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