# Luteinizing Hormone and Follicle Stimulating Hormone-Releasing Hormone Test in Patients with Hypothalamic-Pituitary-Gonadal Dysfunction

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## Summary

**A standard intravenous 100 μg luteinizing hormone/follicle stimulating hormone-releasing hormone (LH/FSH-RH) test was used to assess the pituitary gonadotrophin responses in 155 patients with a variety of diseases of the hypothalamic-pituitary-gonadal axis. In all but nine patients there was an increase in circulating levels of either LH or FSH in response to the releasing hormone though 137 (88%) were clinically hypogonadal. It was not possible with this test to distinguish between hypothalamic and pituitary causes of hypogonadotrophic hypogonadism, since a variety of LH and FSH responses emerged within the disease groups. However, primary gonadal failure characteristically resulted in exaggerated gonadotrophin response. The potential therapeutic use of the gonadotrophin releasing decapeptide is suggested in certain patients with hypogonadotrophic hypogonadism.**

## Introduction

In 1971, Schally and his co-workers isolated a single polypeptide with gonadotrophin releasing activity from porcine hypothalamic extracts (Schally *et al.*, 1971 a, 1971 b). Early work with this synthetic decapeptide showed that in animals it released both LH (luteinizing hormone) and FSH (follicle stimulating hormone) in a manner that was indistinguishable from that of the natural material isolated from porcine hypothalami (Matsuo *et al.*, 1971, Schally *et al.*, 1971 c). In man there were similar dose-related LH and FSH responses when doses between 25 and 100 μg of the decapeptide were given intravenously with a peak occurring between 20 and 30 minutes after the dose (Besser *et al.*, 1972 a). The FSH responses were smaller than the LH responses. The actions of the releasing hormone (LH/FSH-RH) were otherwise specific with no resulting changes in growth hormone (GH), thyroid stimulating hormone (TSH), or adrenocorticotrophic hormone (ACTH), and there were no side effects after administration of the synthetic material. It is also now established that there is no interaction between LH and FSH secretion in response to LH/FSH-RH, and either the TSH or prolactin responses to thyrotrophin releasing hormone (TRH) or the ACTH, GH, or prolactin responses to hypoglycaemia when these stimuli are given together (Mortimer *et al.*, 1973). We have therefore suggested that this material can be used in a simple test procedure to assess the reserve capacity of the hypothalamic-pituitary-gonadal axis for LH and FSH secretion. The results of this test are now reported in 155 patients with a variety of disorders of this system.

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## Patients and Methods

The details of the diagnosis in the patients studied, together with the incidence of clinical and biochemical deficiencies of GH, ACTH, TSH, and the gonadotrophins, are shown in table I. The criteria of Hall *et al.* (1972) were used to define the presence of endocrine deficiency of GH, ACTH, and TSH, and in females hypogonadism was considered to be present if puberty was delayed beyond 19 years of age or if amenorrhoea (in the absence of pregnancy) persisted for longer than three months. This was often accompanied by loss of libido, body hair, and involutional changes of the breasts and genitalia. In males a loss of potency, reduction in beard growth or body hair, and oligospermia or azoospermia were taken as an indication of hypogonadism. In 21 out of 63 male patients regarded as hypogonadal on clinical grounds basal 17β-hydroxyandrogens (17-OHA) were measured and in 17 cases the levels were notably below the normal range, while in the remainder levels were at the lower limit.

"Isolated gonadotrophin deficiency" was accepted as a diagnosis in patients with partial or absent puberty and low or undetectable basal serum gonadotrophin levels which failed to respond to clomiphene administration; there was no evidence of deficiency of other pituitary hormones in these patients except for occasionally impaired GH responses to hypoglycaemia (Marshall *et al.*, 1972). "Delayed puberty" was accepted as the diagnosis in patients with a similar clinical picture, but in whom basal serum gonadotrophin levels or clomiphene responsiveness were normal.

### LH/FSH-RH TEST

In order to study the hypothalamic-pituitary-gonadal axis a standard test was devised (Besser *et al.*, 1972 a) similar to the TRH test in assessing hypothalamic-pituitary-thyroidal function (Ormston *et al.*, 1971). A 100 μg dose of the synthetic LH and FSH releasing hormone (LH/FSH-RH, Hoechst) was given intravenously as a bolus between 8 and 10 a.m. and blood samples were withdrawn before and 20 and 60 minutes after the injection for measurement of LH and FSH. Specimens were rapidly separated and stored at −20°C until assayed. The responses in a group of 39 *normal male volunteers* and seven *normal females* in the follicular phase of their menstrual cycles were determined to establish a provisional normal range of responses at each sampling time (table II). An *absent* response was defined as one in which the administration of LH/FSH-RH failed to produce a rise greater than three times the within-assay coefficient of variation in the basal levels of the gonadotrophins. This was a change of 15% for LH and 18% for FSH. If there was a change in gonadotrophin level but not into the normal

TABLE I—*Clinical and Biochemical Endocrine Assessment in 155 Patients with Hypothalamic-Pituitary-Gonadal Dysfunction*

| Disease | Total | Females | No. of Patients with Clinical Deficiencies | | | | No. of Patients with Biochemical Deficiencies | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | GH | † | ACTH† | | Thyroid‡ | | TSH/TRH† | | | | |
| | | | Hypo-gonad | GH | ACTH | TSH | Tested | Defic. | Tested | Defic. | Tested | Defic. | Tested | N. | A. | D. | I. | E. |
| Hypothalamic disease: | | | | | | | | | | | | | | | | | | |
| Isolated gonadotrophin deficiency | 15 | 4 | 15 | | | | 15 | 2 | 15 | | 15 | | 1 | 1 | | | | |
| Craniopharyngioma | 10 | 6 | 7 | 4 | | 3 | 6 | 4 | 8 | 3 | 10 | 5 | 5 | 2 | | 2 | 1 | |
| Isolated TRH deficiency | 1 | 1 | | | | 1 | 1 | | 1 | | 1 | 1 | 1 | 1 | | | | |
| Tumours | 2 | 1 | 2 | | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | | | 1 | 1 | |
| Pituitary disease: | | | | | | | | | | | | | | | | | | |
| Functionless tumours* | 31 | 22 | 25 | | | 5 | 23 | 15 | 22 | 9 | 31 | 9 | 14 | 5 | | 4 | 4 | 1 |
| Acromegaly | 27 | 15 | 25 | | | | 27 | | 18 | 8 | 27 | 1 | 15 | 9 | | 3 | 3 | |
| Cushing's disease | 3 | 2 | 2 | | | | 3 | 3 | 3 | | 3 | | 3 | | 1 | 1 | 1 | |
| Sheehan's syndrome | 2 | 2 | 2 | | | | 1 | 1 | 1 | 1 | 2 | | | | | | | |
| Idiopathic hypopituitarism | 6 | 1 | 4 | | | | 3 | 2 | 5 | 2 | 6 | | 3 | 2 | | | | 1 |
| Amenorrhoea syndromes: | | | | | | | | | | | | | | | | | | |
| Delayed puberty—primary amenorrhoea | 4 | 4 | 4 | | | | 4 | | 4 | | 4 | | 4 | 4 | | | | |
| Anorexia nervosa | 13 | 13 | 13 | | | | 3 | | 5 | | 13 | | 3 | 2 | | 1 | | |
| Secondary amenorrhoea and galactorrhoea | 15 | 15 | 15 | | | | 11 | 3 | 11 | 1 | 15 | | 8 | 7 | | 1 | | |
| Polycystic ovary syndrome | 3 | 3 | 3 | | | | 1 | | 1 | | 3 | | 1 | 1 | | | | |
| Turner's syndrome | 2 | 2 | 2 | | | | 1 | | 1 | | 2 | | 1 | 1 | | | | |
| Male syndromes: | | | | | | | | | | | | | | | | | | |
| Delayed puberty | 3 | | 3 | | | | 3 | | 2 | | 3 | | 0 | | | | | |
| Precocious puberty | 1 | | | | | | 0 | | 1 | | 1 | | 0 | | | | | |
| Testicular feminization | 1 | | 1 | | | | 1 | | 1 | | 1 | | 1 | 1 | | | | |
| Primary gonadal failure (3 Klinefelter, 4 idiopathic) | 7 | | 7 | | | | 0 | | 0 | | 7 | | 1 | 1 | | | | |
| Anorexia nervosa | 1 | | 1 | | | | 1 | | 1 | | 1 | | 1 | 1 | | | | |
| Galactorrhoea | 3 | | 3 | | | | 2 | 2 | 2 | 2 | 3 | | 3 | 3 | | | | |
| Gynaecomastia | 2 | | | | | | | | | | 2 | | | | | | | |
| Miscellaneous: | | | | | | | | | | | | | | | | | | |
| Internal hydrocephaly | 2 | 1 | 2 | | | | 1 | 1 | 2 | 1 | 2 | | 0 | | | | | |
| Werner's syndrome | 1 | | 1 | | | | 1 | | 1 | 1 | 1 | | 1 | 1 | | | | |
| Total | 155 | 92 (60%) | 137 (88%) | 4 (3%) | 1 | 10 (6%) | 110 | 35 (32%) | 107 | 30 (28%) | 155 | 17 (11%) | 68 | 42 (62%) | 1 | 13 (19%) | 10 (15%) | 2 |

* No clinical or biochemical evidence of excess hormone secretion but hyperprolactinaemia not excluded in all.
† Tested with insulin induced hypoglycaemia and TRH according to the criteria of Hall *et al.* (1972) and Ormston *et al.* (1971).
‡ Circulating thyroid hormone status based on protein bound iodine, resin uptake, free thyroxine index.
GH = Growth hormone. ACTH = Adrenocorticotrophic hormone. TSH = Thyroid stimulating hormone. TRH = Thyrotrophin releasing hormone. Defic. = Deficient. For TRH test N. = Normal. A. = Absent. D. = Delayed. I. = Impaired. E. = Exaggerated.

TABLE II—*Absolute Range of Responses in Normal Subjects given 100 μg LH/FSH-RH as an Intravenous Bolus*

| Time (min) | Male (n = 39) | | Female (n = 7)* | |
|---|---|---|---|---|
| | LH mU/ml | FSH mU/ml | LH mU/ml | FSH mU/ml |
| 0 | 3·2-8·6 | 1·4-7·8 | 3·2-5·6 | 3·8-8·3 |
| 20 | 8·4-34·0 | 1·6-10·5 | 9·0-22·0 | 4·3-10·0 |
| 60 | 5·8-34·0 | 1·2-11·0 | 6·0-18·4 | 6·0-12·0 |

* The females were in the follicular phase of the menstrual cycle.

range at 20 and 60 minutes this was regarded as an *impaired response.* When the 60-minute value was the same or exceeded that at 20 minutes the response was defined as *delayed.* If values were outside the normal range at 20 or 60 minutes or at both times they were considered to be *exaggerated.*

### DETAILS OF ASSAYS

*Serum LH and FSH* were measured in duplicate by double antibody radioimmunoassays as described previously (Besser *et al.*, 1972 a) and results were all expressed in mU/ml of LH and FSH of standard LER 907. The normal ranges for serum LH and FSH under basal conditions are shown in table II.

*Serum TSH* was measured by a double antibody immunoassay (Hall *et al.*, 1971) and the results were expressed in μU/ml of M.R.C. Standard 68/38. *Serum GH* was measured by the method of Hartog *et al.* (1964) and expressed in ng/ml of M.R.C. Standard A. *Serum prolactin* was assayed using a specific double antibody technique and an anti-human prolactin antiserum raised in rabbits (McNeilly, 1973). Results were expressed as ng/ml of a standard human pituitary prolactin which was also used for iodination (kindly provided by Dr. H. Friesen). There was no cross-reactivity between any of the radioimmunoassays at levels many times greater than those encountered in these tests. In the insulin-induced hypoglycaemia tests plasma fluorogenic *corticosteroids* were measured by the method of Mattingly (1962) and blood sugar by a ferroferricyanide method (Technicon). *Plasma testosterone* and related *17-OHA* were measured by the method of Anderson (1970); this measures predominantly testosterone and dihydrotestosterone (normal male range at 9 a.m. for plasma 17-OHA, 5-22·5 ng/ml).

## Results

"Delayed" responses were seen in six normal male subjects for LH and 18 for FSH (table II); each of the females showed a delayed FSH response.

### HYPOTHALAMIC DISEASE

*Isolated Gonadotrophin Deficiency.*—We have previously reported the results of the investigation of 14 patients with isolated gonadotrophin deficiency (Marshall *et al.*, 1972). For completeness these are again included in Tables I and III of this report, together with a further 24-year-old man in whom there was an impaired LH but normal FSH response to 100 μg LH/FSH-RH. Of the total 15 patients 12 showed some LH and 12 some FSH secretion after 100 μg LH/FSH-RH. Of the non-responders two were retested with 500 μg LH/FSH-RH and each showed an impaired LH but no FSH response.

*Craniopharyngiomas.*—There were six females and four males with suprasellar craniopharyngiomas, though the degree of anatomical involvement of the pituitary within the fossa was uncertain. Eight patients had undergone surgical decompression with or without irradiation, and two were untreated. Of the seven adults three women had normal LH and FSH responses, and the other three had absent LH and FSH responses. The only man showed an impaired and delayed LH but absent FSH response. Each of the four adult patients with absent or impaired responses were clinically hypogonadal. Of the five patients in this group with absent gonadotrophin responses to LH/FSH-RH integrity of at least part of the pituitary function was found in two who had normal GH and corticosteroid responses to hypoglycaemia and TSH responses to TRH. Three other males were prepubertal, two aged 13 and one 15 years. Two had an absent LH response and one an absent FSH response; nevertheless, ACTH reserve was normal in these patients and one was euthyroid.

*Isolated TRH Deficiency.*—This female patient had thyroid insufficiency with a normal response to exogenous thyrotrophin, a normal TSH response to TRH, and no evidence of pituitary insufficiency other than of TSH—that is, isolated TRH deficiency or "tertiary" hypothyroidism. She had undetectable basal gonadotrophin levels with impaired LH and FSH release.

TABLE III—*Serum LH and FSH Responses to LH/FSH-RH in 155 Patients with Hypothalamic-Pituitary-Gonadal Dysfunction*

| | Total | LH | | | | FSH | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Normal | Absent | Impaired | Exaggerated | Normal | Absent | Impaired | Exaggerated |
| Hypothalamic disease: | | | | | | | | | |
| Isolated gonadotrophin deficiency | 15 | 4 | 3 | 8 | | 9 | 3 | 3 | |
| Craniopharyngioma | 10 | 4 | 5 | 1 | | 2 | 5 | 3 | |
| Isolated TRH deficiency | 1 | | | 1 | | | | 1 | |
| Tumours | 2 | | 1 | 1 | | 1 | | 1 | |
| Pituitary disease: | | | | | | | | | |
| Functionless pituitary tumours | 31 | 11 | 1 | 19 | | 28 | | 3 | |
| Acromegaly | 27 | 6 | | 21 | | 11 | | 16 | |
| Cushing's disease | 3 | 1 | | 1 | 1 | 2 | | 1 | |
| Sheehan's syndrome | 2 | | | 2 | | 2 | | | |
| Idiopathic hypopituitarism | 6 | 1 | 4 | 1 | | 4 | 2 | | |
| Amenorrhoea syndromes: | | | | | | | | | |
| Delayed puberty—primary amenorrhoea | 4 | 1 | | 2 | 1 | 2 | | 2 | |
| Anorexia nervosa | 13 | 6 | | 2 | 5 | 8 | | 2 | 3 |
| Secondary amenorrhoea and galactorrhoea | 15 | 7 | | | 8 | 14 | | | 1 |
| Polycystic ovary syndrome | 3 | 2 | | | 1 | 2 | | 1 | |
| Turner's syndrome | 2 | | | | 2 | | | | 2 |
| Male syndromes: | | | | | | | | | |
| Delayed puberty | 3 | 3 | | | | 2 | | 1 | |
| Precocious puberty | 1 | 1 | | | | 1 | | | |
| Testicular feminization | 1 | | | | 1 | | | | 1 |
| Primary gonadal failure | 7 | 2 | | | 5 | 1 | | | 6 |
| Anorexia nervosa | 1 | | | 1 | | | | 1 | |
| Galactorrhoea | 3 | 2 | 1 | | | 2 | | 1 | |
| Gynaecomastia | 2 | 2 | | | | 2 | | | |
| Miscellaneous: | | | | | | | | | |
| Internal hydrocephaly | 2 | 1 | 1 | | | 2 | | | |
| Werner's syndrome | 1 | | | | 1 | | | | 1 |
| Total | 155 | 54 (35%) | 16 (10%) | 60 (39%) | 25 (16%) | 95 (61%) | 10 (7%) | 36 (23%) | 14 (9%) |

*Tumours.*—Two patients with other space-occupying lesions involving the hypothalamus were tested. One female with histiocytosis X had an impaired LH but normal FSH response. The other, a male with a tumour of unknown nature, had an absent LH but impaired FSH response. These responses were not improved by clomiphene administration.

## PITUITARY DISEASE

*Functionless Pituitary Tumours.*—There were 31 patients with apparently non-secreting tumours of the pituitary and 25 were clinically hypogonadal. Eighteen patients had been treated with surgery or irradiation or both, and of these 17 were hypogonadal. Despite this there was some LH and FSH secretion after LH/FSH-RH in all patients except one male with absent LH but normal FSH response, and he had had a hypophysectomy, was hypogonadal, hypothyroid, and GH deficient but had a normal ACTH reserve. In the other eight male patients, all of whom had either reduced or absent potency, an impaired LH response was seen in seven; only in two did the FSH fail to rise normally. Of 22 females investigated 16 had had secondary amenorrhoea for between six months and 22 years, but all showed secretion of gonadotrophins, though there was an impaired LH response in 11 and one showed impaired FSH release. Clomiphene was administered to seven patients and there was a rise above the upper limit of the normal basal range for serum LH in five women but in neither man; menstruation followed in three of the five responsive patients after clomiphene. In five patients with secondary (pituitary) hypothyroidism four had an impaired LH response to LH/FSH-RH though in only one was FSH release impaired. Impaired LH but normal FSH release was, however, seen in four patients with a normal protein bound iodine who were clinically euthyroid; of these three had a delayed TSH rise after TRH. Despite normal LH responses a high basal FSH level with an exaggerated response to LH/FSH-RH was seen in one postmenopausal woman with a pituitary tumour and primary hypothyroidism due to thyroiditis. The TSH response to TRH was characteristically high.

*Acromegaly.*—In all there were 27 patients, and some LH and FSH secretion was seen in each. Twenty-one had been treated with surgery or irradiation or both. There were 12 males 10 of whom were hypogonadal at the time of testing. Ten had an impaired LH response at 20 minutes but only five had an impaired 60-minute value. The serum FSH responses were normal in 11 of the 12 patients. All patients had active acromegaly in that the GH failed to suppress to less than 5 ng/ml during a glucose tolerance test. Eleven patients had GH levels above 30 ng/ml. After partial hypophysectomy in one male it was still possible to induce the release of LH and FSH, though the levels were impaired. GH levels were still raised in this patient. In the 15 female patients tested amenorrhoea had been present in each for between one and 10 years, and 11 had active disease. Two were aged 62 and 64 years at the time of the study but their basal gonadotrophin levels were low, and they have been considered with the hypogonadal group. Reduced basal LH levels were seen in 12 of the 15, but in seven a normal value was achieved by 60 minutes. The basal FSH levels were reduced in seven but each achieved a normal 60-minute value.

*Cushing's Disease—Untreated.*—Two women were investigated. One aged 40 had secondary amenorrhoea of five years' duration with an impaired and delayed LH rise but a normal FSH level by 60 minutes. The other, aged 38, had irregular periods but with a normal LH and FSH response. The only male patient had a rise in LH and FSH outside the normal range despite normal basal levels and was not clinically hypogonadal.

*Sheehan's Syndrome.*—Two patients with secondary amenorrhoea after postpartum haemorrhages showed impaired release of LH, while FSH was within the normal range.

*Idiopathic Hypopituitarism.*—Six patients are included in whom there was no obvious disease to account for their hypopituitarism. Of five males three had an absent LH response; in one it was impaired but normal in the fifth. The FSH response was normal in three and absent in two. A normal FSH response was seen in one male patient in whom LH levels had remained undetectable, and the same differential response was seen in the only female patient in this group.

## AMENORRHOEA SYNDROMES

*Delayed Puberty and Primary Amenorrhoea.*—There were four patients in this group, aged between 19 and 26 years, without evidence of ACTH, GH, or TSH deficiency. In two both LH and FSH responses were impaired, one had a normal response of both gonadotrophins, and the fourth had an exaggerated LH but a normal FSH rise. Menstruation followed clomiphene administration in this patient.

*Anorexia Nervosa in Females.*—Secondary amenorrhoea was associated with anorexia nervosa in 13 females aged 12-27 years.

Menstruation had ceased between three months and six years before admission. Of these undetectable levels were recorded in seven for LH and one for FSH. All but two patients responded to LH/FSH-RH with a normal rise in serum LH, three had excessive levels at 20 minutes, and five at 60 minutes. Two patients had an impaired FSH response though in three the responses were excessive. Neither the basal levels of either gonadotrophin nor their responses to LH/FSH-RH appeared to be related to whether they were in the recovery or static phase of the illness. Seven patients were tested with clomiphene and four showed normal LH responses. The clomiphene non-responders had LH and FSH responses to LH/FSH-RH within the normal range, though one patient had an exaggerated LH response.

*Galactorrhoea-Amenorrhoea Syndrome in Females.*—Secondary amenorrhoea of 18 months to seven years' duration was associated with galactorrhoea in 15 patients aged between 21 and 35 years. Of these, five had pituitary tumours and seven had no discernible pituitary, hypothalamic, or gonadal disorder. Of the remaining three women one had acromegaly, one the polycystic ovary syndrome, and in another the condition followed oral contraceptive treatment. The basal values for LH were above the normal range in three patients, normal in six, and subnormal in a further six. All patients responded to LH/FSH-RH, and in seven the LH response was normal. Exaggerated values occurred at 20 or 60 minutes in the remaining eight patients. Basal FSH levels were raised in one, normal in nine, and reduced in five. There was a normal FSH response in all but one subject. This patient had a raised basal value with an exaggerated response at 60 minutes. All of the six patients who were tested with clomiphene showed a normal response. In five patients the basal prolactin levels ranged between 7·5 and 203 ng/ml (normal range up to 26 ng/ml). There was no correlation between basal LH and FSH levels and either the maximum values attained during the standard LH/FSH-RH test or with the basal prolactin levels. In three patients prolactin was measured during a standard TRH test and again there was no clear relation between the maximum level of prolactin achieved and the gonadotrophin response to the decapeptide.

*Polycystic Ovary Syndrome.*—Three patients aged between 20 and 25 years were diagnosed as having polycystic ovaries on gynaecogram or biopsy evidence or both. Secondary amenorrhoea had been present without galactorrhoea for between six and 18 months. The basal LH level was reduced in one but FSH was low in all three patients. No patient showed raised basal gonadotrophin levels. One showed normal LH and FSH responses to the decapeptide, while the FSH response was impaired in one and LH response was exaggerated in another.

*Turner's Syndrome.*—Two patients aged 19 and 20 years were investigated for primary amenorrhoea and found to have Turner's syndrome with raised basal levels of both LH and FSH, and both had exaggerated responses to LH/FSH-RH.

### MALE SYNDROMES

*Delayed Puberty.*—There were three patients aged between 16 and 19 years who were prepubertal; one had undescended testes while another had Crohn's disease. All showed LH and FSH secretion within the normal adult range with the exception of the 19-year-old in whom an impaired FSH level was seen.

*Precocious Puberty.*—Precocious puberty in a 9-year-old boy was associated with a normal LH and FSH response.

*Testicular Feminization.*—A 22-year-old patient with this syndrome had raised basal LH and FSH levels which rose excessively with LH/FSH-RH. Plasma 17-OHA levels were within the normal adult male range.

*Primary Gonadal Failure.*—There were seven patients in this group. The three with Klinefelter's syndrome all had normal potency with raised basal gonadotrophin levels. Only one patient had normal basal gonadotrophin values, though oligospermia or azoospermia was common to all subjects. There was an exaggerated LH and FSH response in all but the one subject. In one patient with azoospermia with a normal karyotype a normal LH but exaggerated FSH response was seen.

*Anorexia Nervosa.*—A 22-year-old man with weight loss to the point of extreme emaciation had an impaired LH and FSH response to the releasing hormone.

*Galactorrhoea.*—Three male patients with galactorrhoea were studied and each complained of lack of potency. One patient had previously had a chromophobe adenoma removed, and had a raised serum prolactin of 77 ng/ml and undetectable LH levels though a normal FSH response to the releasing hormone. In another patient with an asymmetrical fossa on *x*-ray examination, serum prolactin levels were also raised at 103 ng/ml. He had normal basal LH and FSH levels but an impaired LH response to clomiphene (2·4 mU/ml rising to 3·1 mU/ml after 10 days clomiphene 3 mg/kg). After LH/FSH-RH his LH rose normally but the FSH response was impaired. The third male with galactorrhoea had a normal pituitary fossa on *x*-ray examination, a resting morning serum prolactin of 15·6 ng/ml, and normal thyroid, adrenocortical, and growth hormone secretory function under dynamic testing. His basal 17-OHA level was low (3·8 ng/ml). Both the gonadotrophin responses to LH/FSH-RH were normal, but the responses to clomiphene (3 mg/kg for 10 days) were impaired.

*Gynaecomastia.*—In two patients there was a normal response to the releasing hormone.

### MISCELLANEOUS

Of two 19-year-old patients with internal hydrocephaly one had primary amenorrhoea with undetectable LH levels throughout the test but with a normal FSH response. The other, a 19-year-old man, responded normally. A male patient with Werner's syndrome and clinical hypogonadism had raised basal values of LH and FSH with an exaggerated response to the releasing hormone.

## Discussion

It has been shown previously that the synthetic decapeptide, LH/FSH-RH, causes a dose-related secretion of both LH and FSH in man. By using this information we have devised a standardized test in which 100 $\mu$g of the material is given intravenously as a bolus, and applied it to the investigation of various endocrine diseases. Of the 155 patients investigated by this procedure 137 (88%) were clinically hypogonadal at the time of testing, yet in all but 19 patients it was possible to produce some rise in either LH or FSH, and 132 (85%) showed a rise in both gonadotrophins. FSH responses remain normal more often than the LH responses. The TRH test can often differentiate between hypothalamic and pituitary lesions since usually in the former group there is a delayed rise in TSH—the 60-minute value being higher than that seen at 20 minutes. However, this is evidently not the case for the gonadotrophins using LH/FSH-RH, since some patients with clear hypothalamic lesions failed to respond at all and others with primary pituitary disease responded normally with LH and FSH secretion. Furthermore, "delayed" patterns of LH and FSH secretion as defined by comparisons of the 20- and 60-minute value were seen in both these groups and in normal subjects.

In the so-called "isolated gonadotrophin deficiency syndrome" most patients are capable of releasing gonadotrophins when tested with LH/FSH-RH, suggesting that the condition is due to a deficiency of gonadotrophin releasing hormone which is also required for synthesis of LH and FSH. Alternatively, it seems possible that there may be relative insensitivity of the pituitary cells to gonadotrophin releasing hormone. The two possibilities may be differentiated when assays for LH/FSH-RH are available which are sufficiently sensitive to measure endogenous releasing hormone levels. Similarly, patients of both

sexes with delayed puberty had normal LH and FSH release when tested, suggesting that hypothalamic or higher centres are involved in the initiation of puberty.

In patients with "functionless" pituitary tumours or those with active acromegaly, impaired LH release was often seen, though FSH reserve under the test conditions appeared intact. The ability of the pituitary to release gonadotrophins occurred in many patients independently of the functional pituitary reserve for other hormones. The three patients with pituitary-dependent Cushing's disease each showed a different type of response—normal, impaired, or exaggerated. Impaired or absent TSH responses to TRH were seen in these three patients and this is characteristic of this condition (Hall *et al.*, 1972).

When the 15 patients with amenorrhoea and galactorrhoea were investigated it was clear that basal gonadotrophin levels were normal or high in nine, and that normal or even exaggerated responses could occur after administration of the decapeptide. The response did not correlate with basal prolactin levels nor the levels achieved after administration of TRH. The cause of amenorrhoea in these women was clearly not due to inability to synthesize the gonadotrophins but was probably the result of failure of their cyclical release. Hyperprolactinaemia may be responsible, at least in part, for this functional abnormality, since when the prolactin levels were reduced with bromergocryptine galactorrhoea ceased and normal menstruation resumed; potency returned in male patients similarly treated (Besser *et al.*, 1972 b). Whether prolactin interferes at the hypothalamic-pituitary level or has a direct action on the gonads remains to be elucidated.

Gonadotrophin releasing hormone responsiveness was present in every patient with anorexia nervosa, and here again it is probably the failure of cyclical release rather than inability to synthesize gonadotrophins which is the major factor in the initiation and perpetuation of the amenorrhoea. Patients with primary gonadal failure showed the expected exaggerated response to the decapeptide.

In view of the fact that in most patients with hypogonadotrophic hypogonadism, of whatever cause, LH and FSH secretion can be induced with the synthetic decapeptide LH/FSH-RH, it is evident that the pituitaries of these patients contain LH and FSH. It would therefore appear that it is the impairment of release which is the primary cause of the hypogonadism rather than pituitary gonadotroph destruction in these patients. It is disappointing that the LH/FSH-RH test will not differentiate between hypothalamic and pituitary causes of hypogonadotrophic hypogonadism. However, since such a high proportion of these patients can be made to release LH and FSH in response to the decapeptide, it is possible that repeated administration of LH/FSH-RH might restore their fertility, and the results of therapeutic trials with this material are awaited.

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# Fertility after Unilateral Orchidectomy and Radiotherapy for Patients with Malignant Tumours of the Testis

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## Summary

**The results of treatment for patients with seminoma of the testis by orchidectomy and irradiation are so satisfactory that retroperitoneal lymph node dissection is no longer practised. However, this operation is still used routinely in some centres for patients with testicular teratomas despite the lack of evidence that it gives better results than those obtained with irradiation followed by removal of lymphographically demonstrable residual tumour and in the face of the high incidence of ejaculatory impotence which follows. On grounds of preservation of sexual function and fertility there is a great advantage to be gained from the latter form of treatment. Thirty-four of our patients between the ages of 25 and 45 years treated by irradiation to the para-aortic and iliac nodes for testicular tumours fathered 52 children to term after their treatment.**

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## Introduction

In previous publications (Smithers and Wallace, 1962; Smithers *et al.*, 1971; Smithers, 1972) we have reported our results in 446 patients with tumours of the testis treated before 1968 (255 seminomas, 191 teratomas). At least 95% with seminomas of the testis should be cured today by orchidectomy and irradiation, and there is no indication for radical node dissection in these patients.