CLINICAL EXPERIENCE WITH THE THYROTROPHIN RELEASING HORMONE (TRH) STIMULATION TEST IN PATIENTS WITH THYROID, PITUITARY AND HYPOTHALAMIC DISORDERS

By
Bengt E. Karlberg and Sven Almqvist

ABSTRACT

The clinical value of a standardized iv TRH-stimulation test was studied in 96 patients with thyroid, pituitary and hypothalamic disorders. A lack of TSH-response to TRH, 50–200 μg iv was observed in 38 patients with overt hyperthyroidism. Nor was there any response in three clinically euthyroid patients with suspected hyperthyroidism, normal routine thyroid tests and failing suppressibility after the administration of T₃ or T₄. Twenty-one patients with primary hypothyroidism had high basal TSH-levels (mean ± sem = 85.6 ± 12 μU/ml). Furthermore, a prolonged TSH-response was characteristic of this group. No correlation was found between the degrees of clinical hypofunction and basal TSH or TSH-responses. Nine patients with hypothyroidism secondary to pituitary lesions did not respond to TRH-stimulation.

In clinically euthyroid patients with pituitary chromophobe adenomas, two exhibited normal and five impaired TSH-responses. Nine out of 12 patients with active acromegaly showed no or impaired TSH-response, and, on an average, there was a slight increase in the serum TSH at 20 minutes in response to TRH. A several-fold increase in serum STH occurred after TRH in five acromegalic patients. A normal TSH-response was obtained in four of six patients with hypothalamic lesions.

In conclusion, the TRH-stimulation test is of special clinical value in patients with hyperthyroidism (no response), in discriminating between primary and secondary hypothyroidism and in assessing the functional pituitary TSH-reserve in pituitary and hypothalamic lesions.
The purification and isolation (Guillemin et al. 1966; Schally et al. 1966) as well as the identification (Böler et al. 1969; Schally et al. 1969; Burgus et al. 1970) and subsequent synthesis (Folkers et al. 1969; Gillesen et al. 1970) of the thyrotrophin releasing hormone (TRH) is a major advance in endocrinology. With the advent of large scale synthesis and general availability of this potent hormone, many investigators have, in a short time, presented a considerable amount of work on its usefulness in testing the hypothalamic-pituitary-thyroid axis (Hall et al. 1970; Andersson et al. 1971; Karlberg et al. 1971; Ormston et al. 1971a). The iv TRH-stimulation test (Hershman & Pittman 1971; Ormston et al. 1971b; Karlberg & Almqvist 1972) has already been shown to be a reliable, safe and simple procedure for testing the pituitary thyrotrophin (TSH) reserve, as well as for estimating the TSH-response in primary thyroid disorders (Haigler et al. 1971; von zur Mühlen et al. 1971b; Gual et al. 1972).

For this evaluation there is a need to define clinically as well as possible the location of a lesion to the TSH-secreting cells, the degree of TSH-deficiency and, furthermore, to measure the degree of deficiencies of pituitary hormones other than TSH.

The aim of this paper is to report our clinical experience with a standardized iv TRH-stimulation test (“the TRH-test”) in a group of 96 patients with thyroid, pituitary or hypothalamic diseases including both typical and oligosymptomatic cases.

**MATERIALS AND METHODS**

**Patients.** — All patients in the present case material were studied as out-patients or in-patients in the Medical Department, University School of Medicine, Linköping, or in the Department of Endocrinology and Metabolism, Karolinska Hospital, Stockholm, Sweden. Each patient underwent a detailed clinical examination before the test (Karlberg & Almqvist 1972). Thyroid function was followed by measurements of PBI, cholesterol, T3-resin uptake, thyroid auto-antibodies against thyroglobulin by conventional methods. The 6 and 24 h uptake of 131I by the thyroid gland was determined before and after suppressive doses of triiodothyronine (T3) 80 μg daily for eight days (McC Harden 1971), or a single dose of thyroxine (T4) of 3.0 mg (Wallack et al. 1970).

Pituitary functions were tested by the following methods: in acromegaly, by the glucose tolerance test (Ikkos & Luft 1957) with concomitant somatotrophin- (STH) determinations; STH-measurements by radioimmunoassay (Cerasi et al. 1966) and in patients with suspected STH-deficiency by the hypoglycaemic response to iv insulin, 0.10 IU/kg b.w.; ACTH indirectly by the metyrapone test and determinations of plasma cortisol by a fluorometric modification by Laurell (unpublished) according to De Moor et al. (1962); FSH and LH when necessary by immunoassays.

The location of organic lesions in the pituitary gland and hypothalamus was examined by X-ray of the pituitary fossa including tomography and pneumo-encephalography, and visual field examination by Goldman perimetry.

The patient material is shown in Table 1.
<table>
<thead>
<tr>
<th>Group No.</th>
<th>Clinical diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>hyperthyroidism</td>
<td>38</td>
</tr>
<tr>
<td>II</td>
<td>primary hypothyroidism</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>pituitary lesions:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a secondary hypothyroidism (panhypopituitarism)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>b chromophobe pituitary adenoma</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>c active acromegaly</td>
<td>12</td>
</tr>
<tr>
<td>IV</td>
<td>hypothalamic lesions (postencephalitic, tumours)</td>
<td>6</td>
</tr>
</tbody>
</table>

Definitions

Hyperthyroidism included patients with thyrotoxicosis without goitre (n = 15), toxic diffuse goitre or Graves' disease (n = 9), toxic nodular goitre (n = 9), and toxic adenomas (n = 5); the latter group had typical scintiscans which remained unchanged during T₃- or T₄-suppression tests. The adenomas were also verified by cytological examination of fine-needle biopsies from the palpable adenomas. Equivocal cases of hyperthyroidism are presented in some detail in “Results” (n = 3).

Primary hypothyroidism indicates symptoms and signs of thyroid hypofunction, verified by a low PBI-level.

Secondary hypothyroidism was diagnosed clinically when patients with known pituitary lesions showed symptoms and signs of hypothyroidism, e.g. dry skin, and had low normal or subnormal PBI-levels and who responded to thyroxine replacement therapy. In the nine patients with hypothyroidism secondary to untreated or operated pituitary tumours (group IIa, Table 1) the thyroid hypofunction was part of the pan-hypothyroidism.

Among seven patients with chromophobe pituitary adenomas (group IIIb, Tables 1 and 2) six had a normal adrenal function and all were clinically euthyroid as shown by normal conventional thyroid tests. Two cases had secondary hypogonadism and five had normal gonadal function. The size of the chromophobe adenoma varied: in three cases the tumour was restricted to the pituitary fossa; the remaining four had large suprasellar tumours (> 10 mm).

The clinical activity of acromegaly (group IIIc, Tables 1 and 3) was evaluated as described elsewhere (Almqvist et al. 1961). All but three patient had high basal STH-levels as shown in repeated measurements (> 12 ng/ml). Six patients had only an intrasellar extension of their adenomas; four had a suprasellar growth between 1 to 10 mm; and two showed a large (> 10 mm) suprasellar extension.

The six patients with hypothalamic lesions (group IV, Tables 1 and 4) are presented in some details in “Results”. Hypothalamic tumours were found in five subjects and
a lesion with post encephalitic diabetes insipidus was diagnosed in one patient. Four of the six patients had permanent diabetes insipidus. Only patients M.S. and B.N. (Table 4) had irradiation therapy of their lesions.

The classification used by Fraser (1970, 1972) to express varying degrees of hypopituitarism was adapted, i.e. maximal deficiency (deficiencies of ACTH, STH, TSH, FSH and LH), intermediate deficiency (deficiencies of at least two anterior pituitary functions), slight deficiency (deficiency of only one pituitary function) and no deficiency (normal pituitary function).

TRH-stimulation test. – The "standard" iv TRH-stimulation test was carried out as previously described (Karlberg & Almqvist 1972) with minor modifications. The "standard" iv dose was initially 200 µg of TRH, but during the determination of the dose-response relationship between TRH and TSH it was found that the dose could be lowered to 50 µg of TRH (Karlberg & Almqvist 1972). However, some tests were carried out using 100 µg TRH.

Immunoassay of human TSH. – Assays were performed by a solid phase technique (Almqvist & Olin, to be published). Some of the properties of the assay have been described previously (Karlberg et al. 1971). The assay is specific for human TSH except for cross-reactions with pregnancy levels of human chorionic gonadotrophin. The sensitivity allowed the measurement of serum TSH in each of 150 normal subjects. When serum proteins were added to the standard tubes, normal adult TSH-values were 1–3 µU/ml (±2 sd range); without serum proteins the normal range was 11–25 µU/ml (mean 17 µU/ml). The total error of the method was ±12%. Recovery varied between 81 and 89%.

RESULTS

Controls

The amplitude of the response in healthy subjects to the standardized TRH-stimulation test, TRH 50 µg iv is shown in Fig. 1. The average increase was about 150% of the basal level (n = 11).

Patients

Hyperthyroidism. – (Group I, Table 1). The TRH-test was performed in 38 patients with hyperthyroidism. The dose of TRH was 200 µg in 23 patients, 100 µg in 3, and 50 µg in 12 patients. None of these doses evoked any TSH increase in any of the patients (Fig. 2). The mean ± SEM (n = 38) for serum TSH was, at -10 min, 24.1 ± 1.4 µU/ml; at 0 time, 22.1 ± 1.5 µU/ml; at +20 min, 22.0 ± 1.4 µU/ml; and at +60 min, 22.0 ± 1.7 µU/ml. PBI-values were, at zero time, 11.2 ± 0.6 µg/100 ml, and at +6 h, 11.5 ± 0.7 µg/100 ml, i.e. no significant change (P > 0.05).

Three cases had a controversial clinical picture and were suspected of hyperthyroidism and are reported in some detail.

Case B. B., male, aged 63 years, presented with atrial flutter, episodes of paroxysmal tachycardia for one year without loss of body weight or any heat
TSH-responses to 50 µg of TRH iv (mean ± SEM) in 11 healthy volunteers.

Fig. 2.
TSH-responses (mean ± SEM) to TRH in 38 patients with overt hyperthyroidism.

intolerance. A left sided slight exophthalmos was present, but no other symp-
toms or signs of hyperthyroidism developed.

*Case B. L.*, female, aged 57 years, had had periods of tachycardia and
tremor, a slight diffuse goitre, lid retraction and mild, bilateral proptosis.
Case O. L., male, aged 69 years, developed frequent episodes of ventricular tachycardia, but no other clinical signs of hyperthyroidism. Initially, a slightly elevated PBI-value soon became normal despite persisting heart symptoms and failure of suppression by both T₃ and T₄.

All three patients had normal routine thyroid tests including PBI-levels, measurements of T₃-resin uptake and radioiodide by the thyroid gland at 6 and 24 h, but were not suppressed after T₃- or T₄-administration. No TSH-response after 200 µg of TRH was obtained in any of these cases. Case B. B. was re-tested twice with TRH 50 µg iv without TSH-response.

Primary hypothyroidism. – (Group II, Table 1). Twenty-one patients with various degrees of hypofunction, however, passed a TRH-test. Every patient had increased basal TSH-levels. The TRH-dose was 50 µg in 3 of the patients, 100 µg in 4 and 200 µg in another 14 patients. The mean ± sem TSH-level for the whole group was 86.2 ± 14.9 µU/ml at -10 min, 85.6 ± 12.0 µU/ml at zero time, 155.2 ± 21.2 µU/ml at +20 min, 145.9 ± 21.4 µU/ml at +60 min, and 127.9 ± 22.1 µU/ml at +120 min (n = 10). The maximum increase occurred at +20 min in 16 patients and at +60 min in five patients, and was of the same magnitude (in percentage of basal levels) in these patients as compared to normal subjects. The major difference between these patients and healthy subjects was, in addition to high basal levels, a prolonged TSH-increase, which had not returned to the initial level at 2 h after the TRH-injection (Fig. 3). PBI-levels (mean ± sem) remained low and unchanged, from basal levels of

![Fig. 3. TSH-responses to TRH in 21 patients with primary hypothyroidism.](image-url)
2.5 ± 0.3 μg/100 ml to 2.5 ± 0.4 μg/100 ml at 6 h. There was no relationship between the degree of clinical hypothyroidism and the TSH-response to TRH.

**Pituitary lesions: secondary hypothyroidism.** – (Group IIIa, Table 1). Nine patients had a maximal deficiency of the anterior pituitary gland, including clinical secondary hypothyroidism with basal PBI-values of 4.6 ± 0.5 μg/100 ml (mean ± sem). TSH-values (mean ± sem) were, at -10 min, 23.7 ± 4.5 μU/ml; at zero time, 20.0 ± 3.1 μU/ml; at +20 min, 19.9 ± 3.5 μU/ml; at +60 min, 23.6 ± 3.9 μU/ml; and at +120 min, 24.5 ± 6.6 μU/ml (Fig. 4). PBI-levels at 6 h were unchanged: 5.1 ± 0.6 μg/100 ml. Our “standard” dose of TRH (50 μg), and fourfold doses, gave no TSH-increase in any of these patients.

**Clinically euthyroid patients with chromophobe pituitary adenomas.** – (Group IIIb, Tables 1 and 2). Seven patients with a pituitary chromophobe adenoma, later verified by surgery in 6 of 7 cases, and without clinical signs of thyroid insufficiency were studied with the TRH-test, dose 200 μg (Fig. 5). The TSH-levels (mean ± sem) were normal at -10 min, i.e. 16.5 ± 2.6 μU/ml, 15.2 ± 1.6 μU/ml at zero time, with a measurable increase to 20.6 ± 2.7 μU/ml at +20 min and 21.7 ± 2.2 μU/ml at +60 min and 17.8 ± 2. μU/ml at +120 min (n = 5). The PBI-levels were, at zero time, 5.5 ± 0.2 μg/100 ml and 5.7 ± 0.1 μg/100 ml at 6 h. The individual TSH-increases were scattered, ranging from +3 to

![Panhypopituitarism](image)

**Fig. 4.**

TSH-responses (mean ± sem) to TRH 200 μg iv in nine patients with panhypopituitarism and secondary hypothyroidism.

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Table 2.

Pituitary functions and size of tumours in 7 patients with chromophobe pituitary adenomas.

<table>
<thead>
<tr>
<th>Patients</th>
<th>initials</th>
<th>sex</th>
<th>a</th>
<th>STH1)</th>
<th>ACTH</th>
<th>Thyroid2) function</th>
<th>FSH LH</th>
<th>Vasopressin</th>
<th>Suprasellar growth mm</th>
<th>Visual fields</th>
<th>Visual acuity dx sin</th>
<th>Result of TRH-test, + Δ TSH, %</th>
<th>TSH-reserve</th>
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<tr>
<td>E. A.</td>
<td>M</td>
<td>65</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>restricted</td>
<td>1.0 0.7</td>
<td>30 impaired</td>
<td>impaired</td>
</tr>
<tr>
<td>O. J.</td>
<td>M</td>
<td>66</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>&gt;10</td>
<td>restricted</td>
<td>0.1 0.3</td>
<td>25 impaired</td>
<td>impaired</td>
</tr>
<tr>
<td>S. B.</td>
<td>M</td>
<td>61</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>0</td>
<td>normal</td>
<td>1.0 1.0</td>
<td>164 normal</td>
<td>normal</td>
</tr>
<tr>
<td>T. K.</td>
<td>M</td>
<td>61</td>
<td>--</td>
<td>impaired</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>80</td>
<td>restricted</td>
<td>1.0 1.0</td>
<td>85 normal</td>
<td>normal</td>
</tr>
<tr>
<td>B. J.</td>
<td>F</td>
<td>53</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>20</td>
<td>restricted</td>
<td>1/60 0.9</td>
<td>50 impaired</td>
<td>impaired</td>
</tr>
<tr>
<td>E. K.</td>
<td>F</td>
<td>49</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>&gt;10</td>
<td>restricted</td>
<td>1.0 0.1</td>
<td>60 impaired</td>
<td>impaired</td>
</tr>
<tr>
<td>S. K.</td>
<td>F</td>
<td>34</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>restricted</td>
<td>1.0 1.0</td>
<td>30 impaired</td>
<td>impaired</td>
</tr>
</tbody>
</table>

1) + = present; - = absent.
2) before TRH-stimulation test.
Fig. 5.
TSH-response to TRH in seven clinically euthyroid patients with pituitary chromophobe adenomas.

Fig. 6.
Individual TSH-response to TRH in euthyroid patients with pituitary chromophobe adenomas.

+18 μU/ml (i.e. in percentage increases from +25 to +164 %) above normal initial levels (Fig. 6). The average maximal response occurred at +60 min which is later than normal. There was no relationship between the size of the
<table>
<thead>
<tr>
<th>Patients, sex, age</th>
<th>Acromegaly clinical activity</th>
<th>Basal STH ng/ml</th>
<th>Suprasellar growth mm</th>
<th>Visual fields</th>
<th>Pituitary hormone deficiencies</th>
<th>Maximal TSH-response before %/min</th>
<th>after surgery % min</th>
<th>Maximal STH-response before ng/ml min</th>
<th>after surgery ng/ml min</th>
<th>weeks post-op.</th>
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<tr>
<td>G. L. F 62</td>
<td>active</td>
<td>?</td>
<td>0</td>
<td>normal</td>
<td>0</td>
<td>5</td>
<td>60</td>
<td>252</td>
<td>20</td>
<td>15-52</td>
</tr>
<tr>
<td>O. K. M 59</td>
<td>active</td>
<td>79</td>
<td>10</td>
<td>restricted</td>
<td>0</td>
<td>18</td>
<td>120</td>
<td>67</td>
<td>20</td>
<td>258</td>
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<td>E. F. M 55</td>
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<td>7</td>
<td>restricted</td>
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<td>01)</td>
<td>0</td>
<td>2581)</td>
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<td>3091</td>
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<td>G. J. F 54</td>
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<td>15</td>
<td>5-10</td>
<td>restricted</td>
<td>0</td>
<td>23</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I. H. F 54</td>
<td>in regression after 8 m post-op.</td>
<td>5</td>
<td>0</td>
<td>normal</td>
<td>0</td>
<td>40</td>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K. O. M 50</td>
<td>active</td>
<td>?</td>
<td>normal</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>60</td>
<td>252</td>
<td>20</td>
<td>15-52</td>
</tr>
<tr>
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<td>5-10</td>
<td>restricted</td>
<td>TSH</td>
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<td>113</td>
<td>20</td>
<td>50</td>
<td>20</td>
<td>58-145</td>
</tr>
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<td>G. M. M 47</td>
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<td>11</td>
<td>?</td>
<td>restricted</td>
<td>0</td>
<td>113</td>
<td>20</td>
<td>50</td>
<td>20</td>
<td>58-145</td>
</tr>
<tr>
<td>C. P. M 43</td>
<td>active</td>
<td>50</td>
<td>0</td>
<td>normal</td>
<td>0</td>
<td>77</td>
<td>20</td>
<td>100</td>
<td>20</td>
<td>105</td>
</tr>
<tr>
<td>B. S. F 43</td>
<td>active</td>
<td>?</td>
<td>normal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>0</td>
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<td></td>
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<td>10</td>
<td>normal</td>
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<td>0</td>
<td>20</td>
<td>105</td>
<td>20</td>
<td>105</td>
</tr>
<tr>
<td>K. P. M 25</td>
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<td>41</td>
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<td>normal</td>
<td>0</td>
<td>60</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1) in 2 TRH-tests.
2) peak concentration was not titrated.
tumour and TSH-reserve, nor between the frequency of other hormone deficiencies and TSH-reserve.

Active acromegaly. – (Group IIIc, Tables 1 and 3). Twelve patients were studied. All but patient I. H. had clinically active disease. No signs of adrenal, thyroid or gonadal insufficiency had occurred in any of the patients at the time of the TRH-test except for patient E. F., female, aged 48 years who had secondary hypothyroidism (Table 3). Mean basal TSH-values were at the upper normal limit, i.e. 24.4 ± 4.6 μU/ml at -10 min and 23.2 ± 3.5 μU/ml at zero time. After TRH, 200 μg in six, 100 μg in two, and 50 μg in four patients, the mean TSH-level showed an insignificant rise (P > 0.05), to 26.6 ± 2.6 μU/ml at 20 min, returning to 22.9 ± 3.2 μU/ml at 60 min and 22.1 ± 2.0 μU/ml at 120 min (n = 7) (Fig. 7). Individual TSH-response varied from 0 to +113% (Table 3). In fact, there was no response (i.e. <50% TSH-increase) at any time in eight patients. A normal response was observed at 20 min in three cases (C. P., G. M. and B. S.). One patient (K. P.) had a subnormal response. In six patients concomitant measurements of STH-levels were performed during the TRH-test with a several-fold increase in five and no STH-response in one of them (Table 3).

Hypothalamic lesions. – (Group IV, Tables 1 and 4 and Fig. 8). According to Fraser's classification, two patients with hypothalamic lesions had intermediate deficiency of pituitary functions (B. N. and G. U., Table 4), three had slight deficiency (E. A., F. K. and V. T.) and one patient had no deficiency.

**Fig. 7.**
TSH-responses (mean ± sem) to TRH in 12 patients with acromegaly.

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Fig. 8.
TSH-responses (mean ± SEM) to TRH in six patients with hypothalamic lesions.

(M. S.). Mean basal TSH-levels were normal, i.e. at -10 min 16.8 ± 3.1 µU/ml, at zero time 16.2 ± 2.0 µU/ml, at +20 min 28.8 ± 4.3 µU/ml, at +60 min 26.3 ± 3.5 µU/ml, and at +120 min 21.5 ± 3.4 µU/ml (n = 4). Four of six patients had a normal TSH-increase in response to TRH-stimulation, 50 µg. An obviously impaired TSH-reserve was observed in one patient with a glioma of the optic chiasma (G. U.).

DISCUSSION

In the present patient material each individual has been carefully followed clinically with special regard to the interrelations between the hypothalamus, pituitary and thyroid glands. Our experience confirms and extends the clinical reliability of the TRH-test which is now established as a very informative clinical tool (Fleischer et al. 1970; Hershman & Pittman 1970; for a review, see Gual et al. 1972).

Our results in 38 patients with overt hyperthyroidism show that TRH in iv doses from 50 to 200 µg does not change basal serum TSH-levels. This result confirms, in a large group of patients with various degrees of hyperthyroidism, that maximal stimulation of pituitary TSH-secretion by TRH (Karlberg & Almqvist 1972) does not overcome the inhibitory effect by the increased T₃/T₄-concentrations characterizing this disorder (von zur Mühlen et al. 1970, 1971a; Ormston et al. 1971b). Consequently, initially raised PBI-levels do not change during 6 h after the TRH-stimulation.
<table>
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<th>Patients</th>
<th>initials</th>
<th>sex</th>
<th>age</th>
<th>STH</th>
<th>ACTH</th>
<th>Thyroid (^1) function</th>
<th>FSH</th>
<th>LH</th>
<th>Vasopressin</th>
<th>Lesions</th>
<th>Result of TRH-test, (\Delta) TSH, %</th>
<th>TSH-reserve</th>
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</thead>
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<td>V. T.</td>
<td>F</td>
<td>44</td>
<td>-1(^2)</td>
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<td>+</td>
<td>normal</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>meningioma suprasellar</td>
<td>56</td>
<td>impaired</td>
</tr>
<tr>
<td>E. A.</td>
<td>F</td>
<td>43</td>
<td></td>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>post encephalitic</td>
<td>140</td>
<td>normal</td>
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<tr>
<td>F. K.</td>
<td>M</td>
<td>29</td>
<td>+?</td>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>intracerebral cyst</td>
<td>85</td>
<td>normal</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td>hypothalamus (hyperphagia)</td>
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<tr>
<td>M. S.</td>
<td>M</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>normal</td>
<td>precocious puberty</td>
<td>+</td>
<td>astrocytoma hypothalamus</td>
<td>100</td>
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<td></td>
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<tr>
<td>B. N.</td>
<td>F</td>
<td>22</td>
<td></td>
<td>-</td>
<td>+</td>
<td>normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>hypothalamic eosinophil granuloma</td>
<td>111</td>
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<tr>
<td>G. U.</td>
<td>M</td>
<td>21</td>
<td></td>
<td>+</td>
<td>-</td>
<td>normal</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>glioma bilateral visual field defects</td>
<td>36</td>
<td>impaired</td>
</tr>
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</table>

1\(^1\) + = function present; - = function absent.

2\(^2\) with conventional thyroid test, TRH-test excepted.
The TSH-levels in hyperthyroidism are usually normal or low as measured by various immunoassay techniques. The immunoassay for TSH used in this study is obviously not sufficiently sensitive to distinguish between the low TSH and the normal. This may explain the levels obtained in our patients with hyperthyroidism and secondary hypothyroidism.

Three of our patients with suspected hyperthyroidism were diagnostic problems since cardiac symptoms in combination with normal routine thyroid tests dominated the clinical picture. However, in each case there was no T₃- or T₄-suppression of the ¹³¹I uptake by the thyroid which correlated well with the lack of response in the TRH-stimulation test. In these and other controversial situations, no response to the TRH-test indicates increased concentrations of thyroid hormones in the serum even in the absence of overt hyperthyroidism.

In our study of patients with primary hypothyroidism all had high basal TSH-levels, and a normal (by percentage), but prolonged, response to TRH. A probable explanation for the prolonged response is the prolonged half life of serum TSH in primary hypothyroidism (Odell et al. 1967). Our results are thus in accordance with those reported by many groups of workers (review Gual et al. 1972).

Summarizing our clinical experience of the TRH-test in primary hypothyroidism most diagnoses can be made by single TSH-determinations without the need of TRH-stimulation.

Another nine patients with hypothyroidism secondary to pituitary tumours were subjected to the TRH-stimulation test (Fig. 4). There was a clear difference in the TSH-response between patients with secondary and primary hypothyroidism (compare Figs. 4 and 3, respectively). Patients with secondary hypothyroidism have normal or low initial TSH-levels (Hershman & Pittman 1971; Hall 1972) and do not respond to TRH. This finding confirm the reports of several groups of workers (Fleischer et al. 1970; Hershman & Pittman 1970; Anderson et al. 1971; Gual et al. 1972) who have studied patients with apparent deficiency of TSH-secretion and clinical hypothyroidism. On the other hand, a normal TSH-response can obviously be elicited in patients with the clinical picture of secondary hypothyroidism (Karlberg & Almqvist 1971; Faglia et al. 1971; Gual et al. 1972; Pickardt et al. 1972). The explanation may be the existence of some residual functional pituitary tissue in these cases, or the location of the primary lesion above the pituitary level. Some investigators have proposed that a normal TSH-response to TRH allows the diagnosis of hypothalamic or tertiary hypothyroidism in these patients (Pittman et al. 1971; Costom et al. 1971). This suggestion would fit with our findings or normal TSH-response to TRH in four of six patients with hypothalamic lesions (Table 4). A delayed return towards normal TSH-levels was also observed at 60 min.
Two clinically euthyroid patients with chromophobe pituitary adenomas had a normal TSH-reserve (≥ 80% of TSH-increase above abasal level) and five had an impaired TSH-reserve (Table 2). This varying TSH-response reflecting different degrees of functional TSH-reserve capacity in the pituitary gland has been reported elsewhere (Haigler et al. 1971 in six patients; Faglia et al. 1971 in four patients; Jaquet et al. 1972 in four patients; Pickardt et al. 1972 in nine patients).

The response to TRH-stimulation in the present patients with active acromegaly showed no or impaired response of TSH in nine of 12 patients. The mean basal TSH-level was at the upper normal limit and the average serum TSH showed but a slight increase (Fig. 7). Some patients with untreated, active acromegaly collected from the literature have shown a normal response of TSH to TRH-tests (Faglia et al. 1971; Haigler et al. 1971; Kastin et al. 1971; Gual et al. 1972; Ormston 1972; Pickardt et al. 1972).

Pituitary growth hormone levels increased two- to fourfold in response to TRH in five of six patients with active acromegaly (Table 3). Cross-reactions between human growth hormone and our h-TSH-assay did not occur. The TRH-tests were always performed under the same basal conditions. At present the observed large STH-increments in some patients with acromegaly seem to be specific reactions to TRH. This has been described earlier by Saito et al. (1971).

In summary, our present capacity to locate organic lesions in the hypothalamus and the pituitary gland are too limited to allow a correlation with the TSH-response to TRH.

Our present clinical experience allows some conclusions on the value of the TRH-stimulation test in practice:

1) no response of TSH allows the diagnosis of hyperthyroidism in the absence of hypothalamic and pituitary lesions;

2) the test discriminates between primary and secondary hypothyroidism; and

3) in pituitary lesions the test reflects the degree of functional TSH-reserve.

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REFERENCES

Andersson M. S., Bowers C. Y., Kastin A. J., Schally D. S., Schally A. V., Snyder P. J.,
Karlberg B. & Almqvist S.: Acta endocr. (Kbh.) 70 (1972) 196.

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