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Clinical studies having relevance to molecular mechanisms; both clinical and molecular data should therefore be included.

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# THYROID 1979

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## PARAMETERS OF THYROID FUNCTION IN THYROID AUTONOMY

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### INTRODUCTION

The TSH response to intravenous TRH is well known to be abolished or markedly diminished in untreated hyperthyroidism [1,2]. However, the response of the hypophysis to TRH may be also inhibited in clinical situations where the patient is euthyroid as judged by standard clinical and biochemical criteria, because of the extreme sensitivity of the pituitary cell to thyroid hormones [3]. This situation is seen frequently in patients with autonomous nodules, but could also occur in patients with diffuse or nodular goiters [4–8]. In addition, other conditions have been described with impaired TSH response to intravenous TRH despite euthyroid function [9,10].

Therefore, a negative intravenous TRH test in euthyroid patients is not necessarily associated with early thyroid autonomy.

In our study we compared first clinical and scintigraphic findings in patients with suggested early thyroid autonomy and euthyroid controls. Patients with no scintigraphic evidence of autonomous thyroid nodules were further investigated by oral TRH stimulation, which seemed to be useful in the evaluation of patients with impaired TSH reserve but euthyroid function [11–13]. In addition, we investigated, if there were significant differences of parameters of thyroid function in these patients in comparison to euthyroid controls.

### MATERIALS AND METHODS

The study included a total of 815 outpatients (208 males and 607 females) with an age range of 16–72 years. They attended our clinic with the suspicion of thyrometabolic dysfunction. In all of these patients T<sub>4</sub> and T<sub>3</sub> determinations and standard 200 µg TRH tests had been performed. 705 of these patients were clinical euthyroid and revealed normal or borderline levels of T<sub>4</sub> and T<sub>3</sub>. Only these patients were further evaluated.

### HORMONE ASSAYS

TSH was measured by radioimmunoassay with use of kits obtained from Henning, Berlin, F.R.G. The reference range for basal TSH of euthyroid subjects was found to be 0.7–3.2 µU/ml (5–95%), mean 1.6 µU/ml. The reference range of



TSH 30 min after the application of 200  $\mu\text{g}$  TRH was 2.3–21.8  $\mu\text{U/ml}$  (5–95%), mean 10.9  $\mu\text{U/ml}$ .  $T_4$  was measured by enzymeimmunoassay with the use of kits from SYVA Company, Palo Alto, USA. Reference range was found to be 3.8–10.6  $\mu\text{g/dl}$  ( $\bar{x} \pm 2$  S.D.), mean 7.2  $\mu\text{g/dl}$ .  $T_3$  was determined by radioimmunoassay, kits were obtained from Amersham-Buchler, Braunschweig, F.R.G. Reference range was calculated to be 0.9–2.5 ng/ml ( $\bar{x} \pm 2$  S.D.), mean 1.7 ng/ml. Free  $T_4$  was measured by radioimmunoassay with use of kits from Corning Medical, Medfield, USA. The reference range was determined to be 0.8–2.2 ng/dl ( $\bar{x} \pm 2$  S.D.), mean 1.5 ng/dl. TBI was determined by enzymeimmunoassay test kit TBK, Boehringer Mannheim, F.R.G. Reference range of  $\text{FT}_4\text{I} = T_4/\text{TBI}$  was found to be 1.5–10.3 ( $\bar{x} \pm 2$  S.D.), mean 5.9. Radioimmunoassay of TBG were performed with kits obtained from Henning, Berlin, F.R.G. Reference range of  $T_4/\text{TBG}$  was calculated to be 1.8–6.2 ( $\bar{x} \pm 2$  S.D.), mean 4.0.

### Experimental Design

Intravenous TRH tests were performed after an overnight fast with a bolus-like injection of 200  $\mu\text{g}$  TRH (Hoechst). TSH levels were determined at 0 and 30 min. For oral TRH tests a 40 mg tablet of TRH (Thyroliberin Merck) was used. TSH levels were determined at 0, 60, 120, 180 and 240 min. There was an interval of 2–6 weeks between the intravenous and oral TRH tests. Statistical analysis were carried out by use of the Wilcoxon test.

## RESULTS

Ninety-nine of the 705 clinical euthyroid patients showed a negative or subnormal i.v. TRH test. The clinical and scintigraphic findings of these patients in comparison to the euthyroid controls with normal i.v. TRH test are shown in Table I. In 28% of patients with negative or subnormal i.v. TRH tests autonomous thyroid nodules were detected in comparison to only 1% in the euthyroid control group. Patients with suggested thyroid autonomy showed a normal thyroid gland in 26%, a diffuse goiter in 22%, a nodular goiter in 22%; in euthyroid controls thyroid gland was normal in 52%, in 22% a diffuse and in 16% a nodular goiter was found. Patients with scintigraphic established thyroid autonomy were not further investigated. To evaluate the possibility of insufficient TRH stimulation in the other patients with negative or subnormal i.v. TRH tests a prolonged stimulation with 40 mg TRH given orally was performed. Forty-two of the total of 71

TABLE I

CLINICAL AND SCINTIGRAPHIC FINDINGS IN 99 PATIENTS WITH SUGGESTED EARLY THYROID AUTONOMY AND 606 EUTHYROID CONTROLS

Diagnosis	e.t.a. (%)	e.c. (%)
Normal thyroid gland	26	51.7
Diffuse goiter I-III	22	23
Nodular goiter I-III	22	16
Comp. autonomous adenoma	14	1
Dec. autonomous adenoma	14	0.3
Part. res. goiter	2	8

patients could be reinvestigated. A selective TSH response to oral TRH application with a  $\Delta$  TSH  $> 2.1 \mu\text{U/ml}$  was found in 24 patients 180 min after the application of the releasing hormone (Fig. 1). Mean maximum TSH values were usually obtained at 180 min, but positive TSH stimulation was present between 120 and 240 min in all of these cases (Fig. 2). The 24 patients with selective response of TSH to oral TRH showed normal concentrations of  $T_4$  and  $T_3$ .

The 18 patients with negative or subnormal oral TRH tests revealed normal values of  $T_4$ ,  $T_3$  concentrations were normal in 14 and only slightly elevated in 4 cases (Fig. 3). However, statistical analysis demonstrated significant differences of mean values for  $T_3$  ( $2\alpha < 0.001$ ) and even for  $T_4$  ( $2\alpha < 0.005$ ) between these groups (Table II). In addition to evaluate the possible influence of free thyroxine concentrations  $T_4/\text{TBG}$ , free thyroxine index ( $\text{FT}_4\text{I}$ ) and free thyroxine ( $f\text{-T}_4$ ) were measured. In patients with selective response of TSH to oral TRH these parameters were within the normal range and not significantly different from euthyroid controls with normal i.v. TRH tests in accordance with euthyroidism (Table II). Patients with failing or impaired response of TSH to oral TRH stimulation showed significant higher values of  $T_4/\text{TBG}$  ( $2\alpha < 0.005$ ), free thyroxine index ( $2\alpha < 0.001$ ), and free  $T_4$  ( $2\alpha < 0.005$ ) suggesting early thyroid autonomy (Table II).

To investigate the possible presence of cardiovascular effects of thyroid hormones in these patients we measured the Q-Kd interval, which means timing of Korotkoff arterial sounds with reference to the electrocardiogram [19–21]. Cardiovascular effects of thyroid hormones could not be completely excluded in patients with absent or impaired response to oral TRH but seemed to be unlikely in patients with positive oral TRH stimulation tests (Table III).

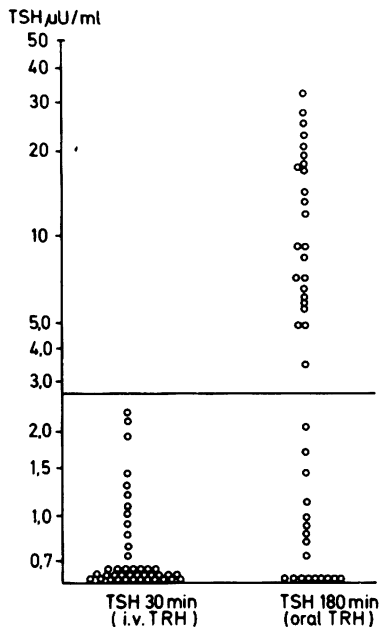


Fig. 1. Comparison of TSH values in 42 patients with failing or subnormal response 30 min after i.v. TRH and 180 min after oral TRH application.

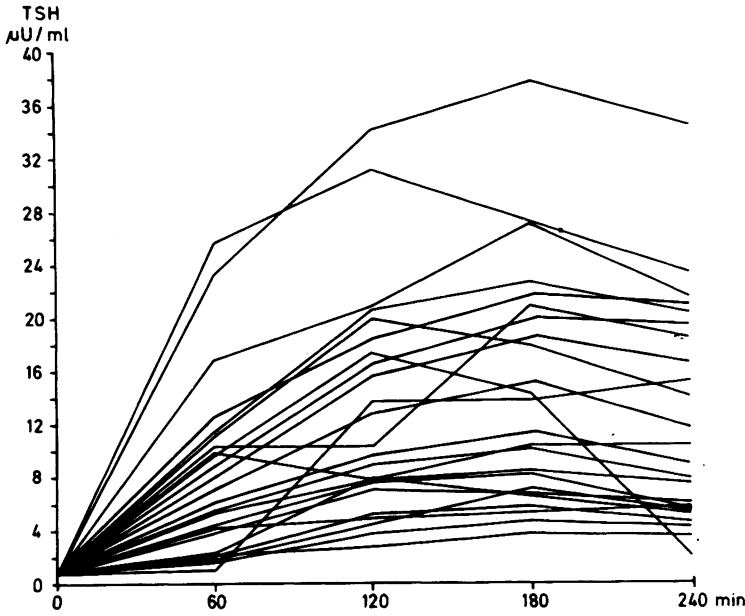


Fig. 2. TSH values in 24 patients with selective response to oral TRH 60, 120, 180 and 240 min after the application of the releasing hormone.

Clinical examination of the thyroid gland in the 24 patients with selective TSH response to oral TRH revealed a normal gland in 3 cases, a diffuse goiter in 12 and a nodular goiter in 9 cases. The 18 patients with failing response of TSH to oral TRH showed a normal thyroid gland in 2, a diffuse goiter in 8 and a nodular goiter in 8 cases.

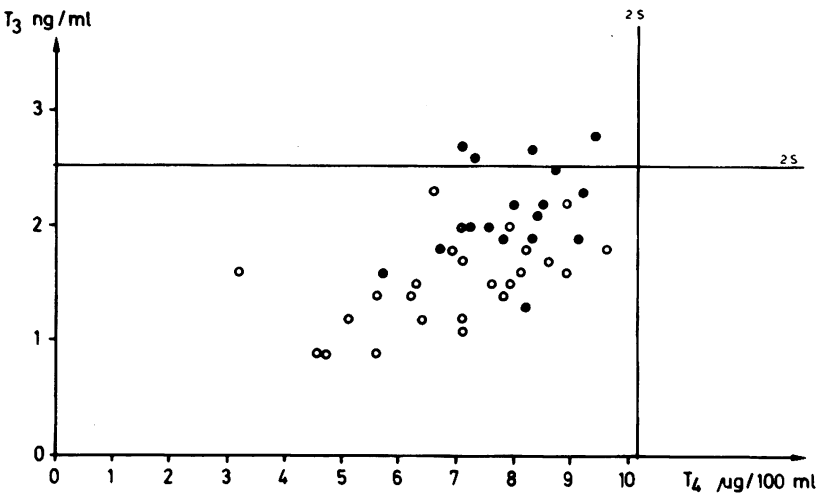


Fig. 3. Correlation of  $T_4$  and  $T_3$  in 24 patients ○ with selective TSH response to oral TRH and 18 patients ● with failing or subnormal response of TSH to oral TRH.

TABLE II

PARAMETERS OF THYROID FUNCTION IN THE 24 PATIENTS WITH SELECTIVE RESPONSE OF TSH TO ORAL TRH AND THE 18 PATIENTS WITH FAILING RESPONSE OF TSH TO ORAL TRH

	Selective response	Failing response
T <sub>4</sub>	6.9 ± 1.5 µg/dl	7.9 ± 0.9 µg/dl
T <sub>3</sub>	1.5 ± 0.4 ng/ml	2.1 ± 0.4 ng/ml
T <sub>4</sub> /TBG	3.8 ± 1.1	4.7 ± 1.5
FT <sub>4</sub> I	5.9 ± 2.2	7.9 ± 2.2
f-T <sub>4</sub>	1.5 ± 0.4 ng/dl	1.9 ± 0.5 ng/dl

These findings demonstrate that thyroid autonomy could occur not only in multinodular goiter but also in diffuse goiter and even in patients with normal thyroid gland.

#### DISCUSSION

The availability of synthetic TRH for clinical use led to detailed investigation of the interaction between TRH and the thyroid hormones at the level of the pituitary cells, which respond extremely sensitive to small excess of circulating thyroid hormone concentration [14–18]. Therefore, impaired or failing response of TSH to intravenous TRH is highly sensitive for detecting early thyroid autonomy. In our study about 14% of all apparently euthyroid patients revealed negative or subnormal intravenous TRH tests. In approximately 1/3 of these autonomous thyroid nodules were present. These findings underline that the i.v. TRH test is of considerable value in the detection of autonomous thyroid nodules in the absence of clinical signs or elevated thyroid hormones. However about 2/3 of the patients with impaired or absent response to i.v. TRH showed no scintigraphic evidence of autonomous thyroid regions. To evaluate the possibility of insufficient TRH stimulation a prolonged TRH test with 40 mg TRH given orally was performed, which led in about 60% to positive TSH stimulation. The oral TRH test seemed to be capable to divide patients with failing or impaired response to i.v. TRH in a group of 'low responders' and a group with early thyroid autonomy in accordance with findings of Staub et al. [12,13]. In single cases stimulated TSH values reached a maximum of 36 µU/ml. The different effects of oral TRH in comparison

TABLE III

Q-Kd INTERVAL IN THE 24 PATIENTS WITH SELECTIVE RESPONSE OF TSH TO ORAL TRH AND THE 18 PATIENTS WITH FAILING RESPONSE OF TSH TO ORAL TRH IN COMPARISON TO EUTHYROID AND HYPERTHYROID CONTROLS

	Q-Kd ms
Euthyroidism	217.3 ± 12.9
Selective response	210.4 ± 11.6
Failing response	200.2 ± 11.4
Hyperthyroidism	168.8 ± 16.6

to intravenous TRH are most likely due to the prolonged stimulation and not dependent from the different dosage, since similar TSH stimulations were seen after a 2 h infusion with 200  $\mu\text{g}$  TRH. Positive TSH stimulation by oral TRH has not been observed in patients with  $\text{T}_3$  concentrations above 3 ng/ml. In view of these results the oral TRH test seemed to be superior to the i.v. TRH test in differentiating euthyroidism from early thyroid autonomy. Therefore, for further classification of patients with absent or impaired response to i.v. TRH subsequent to scintigraphic studies an oral TRH test is recommended, if levels of thyroid hormones were normal or borderline.

In patients with negative or subnormal oral TRH tests early thyroid autonomy is likely to be present because of significant higher concentrations of thyroid hormones including free thyroxine. However, these results demonstrate that the determination of free thyroxine,  $\text{T}_4/\text{TBG}$  and free thyroxine index is not superior to the determination of thyroxine alone. All these parameters, including the determination of  $\text{T}_3$ , are not able to differentiate euthyroidism from early thyroid autonomy. Therefore, the value of free thyroxine,  $\text{T}_4/\text{TBG}$  and free thyroxine index (F- $\text{T}_4\text{I}$ ) in the routine diagnosis of thyroid function is only limited. Cardiovascular effects of thyroid hormones could not be completely excluded in patients with absent or impaired response to oral TRH but seemed to be unlikely in patients with positive oral TRH stimulation tests.

It is concluded that the oral TRH test is useful for the evaluation of patients with impaired TSH reserve. A normal response to oral TRH provides strong evidence of euthyroid function. Patients with failing response to oral TRH deserve further investigation and follow-up, since TSH suppression due to early thyroid autonomy is likely to be present.

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## DISCUSSION

**Elte:** (Leiden) Do you think that your results with the i.v. and the oral TRH-test point to a graded autonomy?

**Jüngst:** (Munich) I can only speculate on this, but we have found no differences in mean concentrations of thyroid hormones between euthyroid controls with normal i.v. TRH-tests and patients with normal response of TSH to oral TRH but negative i.v. TRH-tests. Negative i.v. TRH-tests in these patients are most likely caused by insufficient stimulation, since a prolonged application of 200 mcg TRH intravenously is as effective as 40 mg TRH given orally. These findings would point against a graded autonomy. However, we were surprised about the high rate of scintigraphic autonomy in our patients with negative or subnormal i.v. TRH-tests and I suppose if we had primarily performed the oral TRH-test, the number of detected patients with scintigraphic autonomy would be smaller. Therefore, I think that the i.v. TRH-test is the most sensitive parameter in the detection of thyroid autonomy.

**Crooks:** (Dundee) In the case of the oral TRH-test, how do you ensure that the patient actually takes the drug, since non-compliance with oral drug-taking is a universal problem? This will present considerable difficulties of interpretation in the case of non-responders to oral TRH.

**Jüngst:** (Munich) I don't think that the non-responders had failed to take the drug, since in our study each patient took the tablet in the clinic. Measurements of thyroid hormones showed small elevations, especially of T<sub>3</sub>, which is most likely due to early thyroid autonomy. However, in outpatients testing, this may play an important part in false negative results. Therefore, we would not recommend performing the oral TRH-test in the diagnosis of thyroid function primarily; this test is reserved for special cases only.