Regulation
of Thyroid Function

International Thyroid Symposion
Düsseldorf, Federal Republic of Germany
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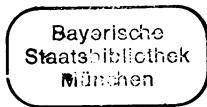
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Anterior Pituitary and TSH[*]

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In 1971, at the Laurentian Hormone conference, Dr. Reichlin (82) has reviewed the evidence in favour of positive feedback regulation of TRH synthesis by thyroid hormones. In the introduction to this outstanding review two factors controlling *directly* the secretion of TSH were classified as *primary* regulators:
1. the negative feedback inhibition by thyroid hormones and
2. the stimulatory effect of TRH.

Several factors act probably indirectly in the control of TSH secretion (82), including the peripheral degradation of TSH, of thyroid hormones and of TRH, the physiochemical state of the circulating thyroid hormones, and the pituitary conversion of T_4 to T_3 (2, 39, 84 a, 89, 98). Even with the additional consideration of the circadian rhythms (14, 66, 67, 94), the role of liver and kidney for the production rates and metabolism of TRH, TSH and thyroid hormones (3, 10, 13, 33, 50), and of inducable changes of TBG levels as one possible alteration of the physiochemical state of the thyroid hormones, it is probably justified to classify these factors as of secondary importance for the TSH regulation (82, 85, 87).

Therefore, this review will concentrate on:
1. problems of TSH structure,
2. recent developments in TSH assays,
3. deficiency and excess of TRH and
4. deficiency and excess of thyroid hormones.

1. Structure and heterogeneity of TSH

The TSH molecule can be dissociated by the treatment with propionic acid into the subunits α and β. As it has been shown for other glycoproteohormones, the β-subunit carries the immunological and biological confirmation specific for TSH.

Radioimmunoassays specific for these *subunits* have been developed (6, 47, 48). So far, the β-hTSH radioimmunoassay represents no improvement in terms of specificity and sensitivity as compared to the widely used homologous radioimmunoassay for hTSH (6). More important, KOURIDES et al. (49) have provided evidence that β-TSH subunits are secreted by the pituitary gland (16), but that β-TSH is not detectable in serum of euthyroids or in patients with Graves' disease, respectively. In addition, the elevated levels of β-TSH in primary hypothyroidism were suppressed by thyroxine administration. The finding of a normal regulation of β-subunit secretion in terms of a negative feedback inhibition by thyroxine (49) is of interest with respect to the studies of KOHN and WINAND (45, 46). These authors have claimed receptors in the retroorbital tissue capable of binding of bovine TSH, of β-TSH and of an exophthalmogenic product formed by pepsin digestion of bovine TSH, the binding being enhanced by γ-globulins from patients with Graves' disease. The pathophysiological involvement of human β-TSH or other TSH related factors in Graves' ophthalmopathy remains however to be established, if the observation of KOURIDES (49) is confirmed.

In addition to the data on subunits, the earlier work (15) about *size heterogeneity* of TSH circulating in primary hypothyroidism has been extended by GOLSTEIN and VANHAELST (26). Using a radioimmunoassay system for β-TSH, these authors observed a high molecular weight fraction in the serum of patients with primary hypothyroidism. Taking a somewhat different approach, ERHARDT (20) has obtained a high molecular weight, TSH immunoreactive preparation from human pituitaries, using Sephadex G-100 filtration and subsequently affinity chromatography with sepharose linked anti-TSH. The material constitutes 1 – 3 % of the total TSH immunoreactivity in human pituitaries. The information about this material is still preliminary. We know however, that "big" TSH is stable upon rechromatography, has an approximate molecular weight of 200000 on Sephadex G-200, shows paralellism in the TSH radioimmunoassay system (MRC standard), has a RNA content below the limits of detection (ethidium bromide fluorescence), is stable in 6 M guanidine-HCl pH 5.1, 0.25% Triton X 100 (37° C, 1h), and shows formation of regular size immunoreactive TSH by trypsin digestion. – It appears therefore likely, that the chapter of TSH structure and its relation to human pathophysiology is not yet closed.

2. Recent developments in TSH assays

The information about the regulation of the secretion of TSH depends obviously on the methods available for the determination of TSH.
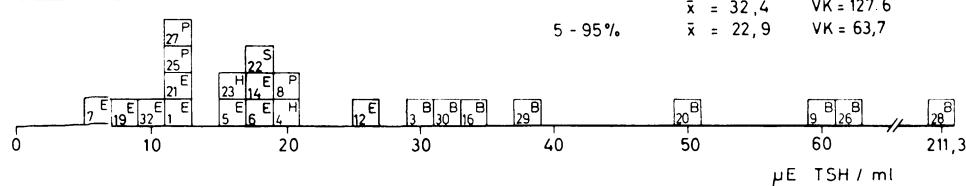
Recently, the principle of the highly sensitive *cytochemical* assay has been applied to TSH determinations, using the induced lysosomal instability (7, 29). PETERSEN reported in Boston and elsewhere (71), that the TSH level of 0.31 μU/ml in one normal sub-

ject was suppressed by daily administrations of 120 μg T_3 to 0.17 μU/ml after 4 days and to 0.02 μU/ml after 8 days. The latter values are lower than the "TSH" levels of 0.28 μU/ml measured in untreated Graves' disease by this method [71]. However, it may be too early to accept fully the differentiation between TSH and LATS made merely on the basis of different reaction kinetics in the cytochemical assay [71]. A TRH stimulation test increased the TSH level of euthyroid controls from 0.6 to 7.0 μU/ml in this assay [71]. These values are in good agreement with data obtained by the radioimmunoassay.

I have to omit any comments on radioreceptor assays [29], which are at present in development or in use in several laboratories (cf. SCHLEUSENER). – Instead, I should like to discuss briefly two aspects of the *radioimmunoassay* for TSH. This method has rapidly become a valuable tool for the clinical judgement of thyroid patients [1, 18, 19, 28, 29, 70]. A vast number of modifications and commercial kits favours its widespread use. However, in addition to the obvious limitations of the TSH radioimmunoassay in terms of sentitivity and specificity, we have to realize, that this method lacks adequate interlaboratory comparability. This may be concluded from a recent "Ringversuch" or collaborative survey, performed under the auspices of the Thyroid Section of the German Endocrine Society [56].
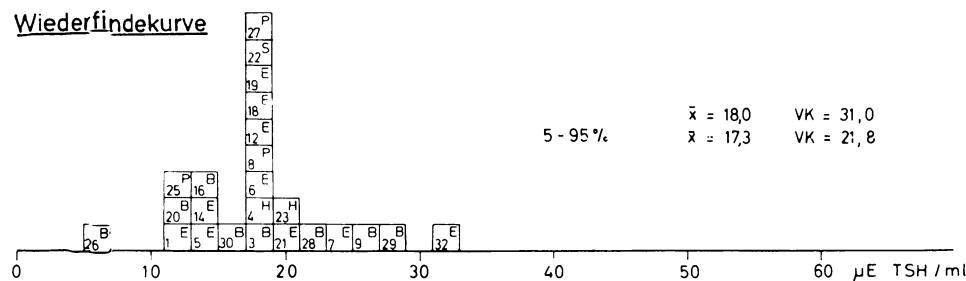
Fig. 1. *"Ringversuch", i. e. collaborative survey on the radioimmunoassay for TSH.*
The individual means of triplicate determinations of one of 8 unknown samples obtained from 24 participating laboratories may be read on the abscissas of the histogram. "Wiederfindekurve" stands for standards in "hormone free" serum. Each rectangle depicts the number of the participant and a symbol for the method used. The interlaboratory means (x) and coefficients of variation (VK) are given for all participants and for the group between 5 and 95 % of the Gaussian curve (mean ± 1.7 SD), respectively [56].

As shown in Fig. 1, the better 90% of 24 participants produced a mean of 22.9 μU/ml for the first of the unknowns, using their own standard curves. There was a wide variation of the single laboratories between 8 and 60 μU/ml, with a coefficient of variation of 64%. Using common standards in "hormone free" serum (18, 21, 70), the results were definitely improved with a more correct mean of 17.3 μU/ml and with a reasonable coefficient of variation of 21.8% between laboratories. Some commercial kits have since been improved as a consequence of this study (56).

The second point, which I would like to discuss, is the need for automation of the radioimmunoassay for TSH, as for other hormones. We have developed a modular analyzer system (57), for which the working instructions for TSH include as the important points: standards in hormone free serum, "cold" preincubation of antibody with non-labeled hormone, tracer of rather low specific activity, classical double antibody method with discontinuous filtration for b/f separation etc. (57). – In summary, the proper radioimmunoassay for TSH has turned out to be relatively simple, reliable and satisfactory for diagnostic purposes.

a) TRH stimulation test

Today, the intravenous TRH stimulation test has been widely accepted as a valuable extension (28, 78, 87, 97, 103) of the diagnostic possibilities provided by the TSH radioimmunoassay. In our hands, the normal range of 2.7 to 23.6 μU/ml (18, 19) for the TSH increment 30 min after injection of 200 μgTRH has been satisfactory for diagnostic purposes. Numerous and sometimes conflicting reports have been published about sex and age dependence of the TSH response (51, 68, 97), about other TRH doses recommended (5), about the effects of the menstrual cycle and of antiovulatory steroids (23, 51, 63, 81, 96, 97), and other drugs (17, 83, 102), particularly corticoids (69), of stressful situations and cold (12, 25, 58), of malnutrition respectively anorexia nervosa (53, 62, 64), of 2-Br-α-ergocriptine (61), somatostatin (4, 90, 93, 95), prostaglandins (9) and of diseases of the liver and the kidneys (3, 10, 13, 33). However, time does not allow to discuss all these data. In general, all these factors rarely diminish the diagnostic usefulness of the normal range mentioned.

3. Deficiency and excess of TRH

At first, the regulation of the TSH secretion in the *absence* of endogenous TRH has to be considered.

In a series of elegant experiments, REICHLIN et al. (82) have shown, that in rats with lesions in the hypothalamic thyrotropic area, the sensitivity of the pituitary "thyro-

stat" towards thyroid hormones is changed. A diminished increase of TSH levels was only observed as late as 40 days after thyroidectomy. In addition to this decreased sensitivity of the TSH secretion towards a deficiency in thyroid hormones, the threshold for TSH suppression by thyroid hormones was lowered in the rats carrying the hypothalamic lesions. These experimental data are in agreement with the clinical observation of usually mild hypothyroidism with low, but definitely measurable TSH levels in patients with hypothalamic hypopituitarism. It has been repeatedly documented (28, 60, 74, 75, 78, 87, 92) that TRH stimulation tests in patients with suprasellar disease and secondary hypothyroidism result in normal or supranormal TSH increases. In addition, we also observed a normal stimulation of TSH secretion by TRH in most patients with pituitary adenoma and secondary hypothyroidism (74, 75). It would therefore appear, that in pituitary tumor patients, the hypothalamic TRH production or the TRH transport via the portal vessels of the pituitary stalk are more susceptible to disturbance than the TSH producing thyrotrophs of the anterior pituitary themselves.

TRH was shown to be present in human cerebrospinal fluid, and appears subsequently to its injection into the third ventricle of rats in the portal vessels of the pituitary stalk (27, 44, 79, 88). This observation allowed the further study of the problem mentioned above. FAHLBUSCH and PICKARDT (24) compared the normal TSH increment in patients after intravenous TRH with the TSH response, when 50μg TRH were injected into the 3rd or lateral ventricle on the occasion of diagnostic or therapeutic puncture of the ventricles. In "controls", the TSH response to intraventricular TRH was lower as compared to i. v. TRH, and was maximal only at 40 min or later. In cases with tumors in the 3rd ventricle or with pituitary adenomata expanding into the suprasellar region, no TSH response was seen after intraventricular TRH, whereas the response to i. v. TRH was regularly obtained. Hence, "portal vessel occlusion" (74, 75) may well be a pathophysiological mechanism for "hypothalamic" or secondary hypopituitarism in cases with pituitary adenoma.

I should now like to discuss briefly the effects of prolonged exogenous *TRH excess*. Repeated administration of TRH leads to a rapid decline of the TSH responses of the pituitary (65, 80, 91). This observation is of some clinical interest, since oral TRH treatment plays a role in certain psychiatric diseases, namely depression. Interestingly, MAEDA et al. (54), have recently shown in depressed patients, that single TRH stimulation is followed by an abnormal increase of growth hormone, with concomitantly enhanced prolactin responses, but blunted TSH responses.

Repeated oral administration of 40 mg TRH per day causes only transitory increases of T_3 and T_4, within the normal range (39, 80, 91). Daily application of 40 mg TRH over a period of 4 weeks leads finally to diminished basal TSH levels and to a blunted TSH response to 200μg TRH i. v. (Table 1). This indicates, that the suppressive effect of initially rising thyroid hormone levels on TSH release is more potent than the stimulating effect of continued oral TRH (40).

Table 1. Effect of oral TRH application to healthy subjects (N = 12; 40 mg per day over a period of four weeks), from HORN et al. (39, 40).

		Before TRH	After TRH
Serum TSH	basal	2.0 ± 0.8	1.0 ± 0.5*
(μU/ml)	ΔTSH 30 min	8.1 ± 3.0	3.0 ± 1.9*
Serum T_4 (μg/100 ml)		6.2 ± 1.9	6.5 ± 1.8
Serum T_3 (ng/100 ml)		112 ± 22	109 ± 32

* Significance $p < 0.005$

Table 2. TSH and PRL producing pituitary adenoma.

- Female, 22 y., enlarged sella.
- Recurrent goiter and thyrotoxicosis.
- Galactorrhea-amenorrhea syndrome.
- TSH (12 – 29 μU/ml) and PRL (200 – 300 ng/ml) refractory to exogenous thyroid hormones and to TRH stimulation (200 μg i. v.).
- TSH ans PRL suppressed by bromocriptine (5 mg p. o.)
- Identification of "thyrotrophs" and "lactotrophs" evenly distributed throughout the adenoma (electronmicroscopy, immunofluorescence).

HORN, K. et al., Proceed. Int. Thyroid Conf., Boston, 1975 (40).

The fact, that continued oral application of excess TRH failed to induce hyperthyroidism, may be taken as another strong argument against any hypothalamic form of thyrotoxicosis.

Finally, the effect of primary pituitary *TSH excess* should be briefly considered. A TSH producing adenoma of the pituitary gland is a rare finding; I am only aware of three well documented cases published in the literature (22, 31, 52). Recently we had the opportunity to study a patient with a so far unique adenoma producing both, TSH and prolactin concomitantly (40). Table 2 summarizes the findings in this patient. It may be concluded, that the "thyrotrophs" of this TSH producing adenoma lack the adequate receptor or sensitivity for negative feedback inhibition by thyroid hormones and for TRH stimulation, respectively. This corresponds to other hormonally active pituitary adenomata, in which the phenomenon of "receptor degeneration" (99) has been demonstrated.

4. Deficiency and excess of thyroid hormones

The remainder of this contribution will be devoted to regulatory TSH increases and decreases by the thyroid hormone negative feedback mechanism. Obviously, most of

the diagnostic information obtained by TSH radioimmunoassay is derived from patients with primary thyroid disease, since it has been realized, that feedback alteration of the TSH secretion currently represents the most sensitive indicator for lack or excess of thyroid hormones (72, 82, 87). Innumerous studies dealing with different aspects of this field have been published and cannot be reviewed within the limitations of time. Also, the interesting questions of intrapituitary conversion of T_4 to T_3, of pituitary preferential T_3-receptors, and of the relative contributions of T_4 and T_3 in the circulation to the negative feedback regulation of TSH secretion (2, 39, 84a, 89, 98) have to be left to the discussion. Instead, we thought it worthwhile to discuss briefly and as a clinical example some problems related to endemic goiter. Nontoxic goiter is known to be the most frequent thyroid disease in the Federal Republic of Germany, which has recently again been shown to be as a whole an area of endemic goiter (41) and of substantial iodine deficiency (30, 86).

Deficiency in thyroid hormones is known to give rise to elevated basal TSH levels, an observation which may be further elucidated by the observation of increased TSH responses to i. v. TRH stimulation tests. I should like to leave possible controversies about the term "subclinical hypothyroidism" (68, 72) to the discussion. I would rather emphasize, that TSH radioimmunoassays have already been used for screening programs e. g. for neonatal hypothyroidism (36).

Approximately 20% of the iodine deficiency goiter patients of Munich (72, 73, 77) were shown to display an increased TSH response to TRH stimulation. This increase above the upper limit of normal, usually shown in a logarithmic scale, is quite remarkable in some patients. This finding has been confirmed for Essen and Göttingen (100). The elevated TSH levels are obviously not related to the tendencies of these patients towards low-normal or slightly decreased T_4 levels and towards normal or slightly elevated T_3 levels (Fig. 2). The latter phenomenon is known as preferential T_3 secretion in iodine deficiency states (37, 39, 72). The elevated TSH secretion in 1/5 of the goiter patients may be interpreted as evidence for

1. slight thyroid hormone deficiency in this group and/or
2. a phase of further growth of the already enlarged thyroid.

The fact, that 80% of our patients have normal TSH responses despite their thyroid enlargement, may be interpreted als indicative for

1. no actual progression of their goiter and/or,
2. if there is further goitral growth, this might indicate an enhanced thyroid sensitivity to normal circulating levels of TSH as proposed by BRAY (8).

Interestingly, the thyroidal adaptation to iodine deficiency in terms of an elevated serum T_3/T_4 ratio is reversible without measurable alteration of the TSH secretion. HORN et al. (38) have shown, that administration of 200 μg iodine per day as potassium iodide tablets over a period of four weeks reduced the elevated T_3/T_4 ratio towards normal. Since the mean basal TSH levels and the TSH responses to 200 μg TRH i. v.
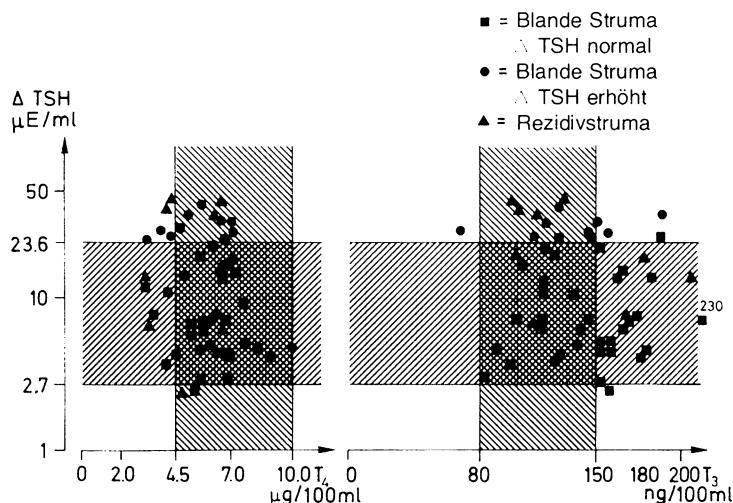
Fig. 2. *Total serum T_4 and T_3 as related to the TSH response (Δ TSH 30 min) to 200 µg TRH i. v.* "Blande Struma" is synonymous with nontoxic goiter, "Rezidivstruma" with recurrent goiter after operation (37, 39, 73, 78).

were the same prior to and after 4 weeks on 200 µg iodine per day, it was concluded, that this may represent an example of thyroidal autoregulation (42).

The treatment of goiters with TSH suppressive doses of thyroid hormones may readily be controlled by TRH stimulation tests and radioimmunoassay for TSH (77, 78, 103).

Finally, we have to focus on the impact of *thyroid hormone excess* on the TSH secretion. Again, TSH suppression and, even more, the failure of TRH to induce a TSH response is widely accepted as a very sensitive tool for the diagnosis of endogenous or exogenous excess of thyroid hormones. Notedly, the sensitivity of this feedback inhibition carries the general diagnostic disadvantage, that TSH suppression may persist for prolonged intervals after e. g. sufficient and successful treatment of hyperthyroidism. The latter observation has been described by VON ZUR MÜHLEN in 1971 (103) and was confirmed repeatedly (11, 32, 84, 104).

Selecting the endemic goiter patients again for this consideration, I should like to draw the attention to what was called the "functional cycle of the autonomous adenoma" by PICKARDT et al. (76, 85). This concept was derived from observations of numerous patients at different stages of the disease, extending the work of MILLER et al. (59). Fig. 3 describes schematically the development of an adenoma, its poorly understood acquisition of autonomy, the gradual addition of toxicity with the concomitant in-
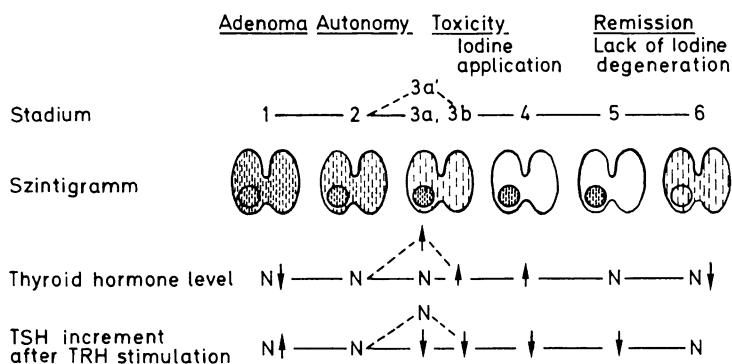
Fig. 3 *Functional cycle of the autonomous adenoma.*
After PICKARDT, C. R. et al., Dtsch. med. Wschr. *98*: 152 (1973).

crease of thyroid hormones and decrease of the TSH secretion and response to TRH, and finally the possible spontaneous remission. One has of course only rarely the occasion to follow this cycle throughout all stages in one single patient. However, spontaneous transitions have been observed in between all stages depicted. The most frequently observed transition is certainly from stage 2, which is an autonomous nodule with normal T_4 and T_3 and positive TSH response to TRH stimulation – usually called compensated autonomous adenoma - to stages 3 or 4 with normal or elevated T_4 and T_3 and suppressed TSH, which is commonly called decompensated autonomous adenoma. The latter transition has been regularily observed in a somewhat courageous study of MAHLSTEDT and JOSEPH (55), when practically all compensated autonomous adenomata in patients were converted to "decompensated" ones by contrast media used for cholecystography. TRH stimulation tests show easily in the patients with decompensated autonomous adenoma, that the TSH secretion is in fact suppressed, as it was correctly predicted by the earlier indirect methods of nuclear medicine. The existence of suppressed paranodular thyroid tissue around the hot nodule can be documented by simple palpation or by ^{99m}Tc scintigraphy with increased sentitivity (35, 101), avoiding the disadvantages of a TSH stimulation test, which may be only justified if concomitant cold nodules have to be depicted. The hazards of the exogenous TSH stimulation test consist mainly in the sometimes dangerous elevation of the thyroid hormones (34) by stimulation of the paranodular tissue and of the hot nodule itself (43), which is thus not "autonomous" in this respect.

In conclusion, I should like to express my hope, that it was not against the intentions of the convenors, that the emphasis of this presentation was put on clinical aspects.

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Discussion

SCHLEUSNER raised the question of the binding of the TSH β-subunit to thyrocyte
membrane preparations. WOLFF pointed out that bovine β-subunit binds to bovine

membranes at about 8 % of the TSH potency (Bethesda). The more complicated the stimulated cell function, the more intact the tissue is, the less active is the β-subunit.

VON ZUR MÜHLEN suggested to study the question of the biological acticity of the "big TSH" originating from human pituitaries. Reference was made by RALL to the studies of WEINTRAUB and ROSEN, in which they looked at tumors, bronchogenic carcinoma, mostly, that produced ectopic TSH. They could isolate different clones of cells from these tumors, and some of the clones would produce normal TSH, the alpha-beta material, some would produce just the alpha and some would produce just the beta. And this gets back to the fundamental question as to whether they are synthesized as separate polypeptide chains and combined then in an entirely physical way? The mentioned data tended to suggest the latter, which makes then the "big TSH" a difficult protein to swallow.

However, work from RYAN's group suggested, that large molecular weight gonadotropins might consist of one β-subunit and several α-subunits. Further work is needed to clarify these important questions.

CROOKS reported a study of pregnancy goiter and of normal controls from Iceland and Scotland, respectively, where the controls had the same frequency of thyroid antibodies. The Icelandic normal population has twice the level of plasma inorganic iodine of the controls of Scotland. The normal TSH levels in Iceland are lower, with a narrow range normal distribution, as compared to Scotland, where the normal range of TSH is spread widely yet still normally distributed.

This raised the question what actually regulates TSH at different levels in these two populations? A rather general answer would be, that the sum of interactions of anterior pituitary receptors for T_3, T_4 and possibly triac with the intracellular concentrations of these hormones at the site of the (nuclear) receptor should be the relevant event. There is a modulation by the TRH-thyrotroph system, but thyroid hormones are probably the most important factor.

Rare cases of evident hyperthyroidism with positive TSH response to TRH stimulation were reported from LOOS, Ulm and STAUB, Basel, the incidence being probably very low and the mechanism still obscure.

PINCHERA commented a study from Pisa. Patients with a completed course of antithyroid treatment showed an inverse relationship between the TSH response to TRH and the serum T_3 and T_4, respectively, whereas there was no correlation to the suppression test. However, the TRH stimulation test was of no predictive value for the question of relapse of hyperthyroidism. This was supported only in part from Dr. EMRICH, Göttingen, where in most but not in all patients treated for hyperthyroidism

follow up studies showed coincidence of negative suppression tests and negative TRH stimulation tests and vice versa. The persistance of negative TRH stimulation tests in the presence of low T_4 and T_3 after antithyroid treatment might also be a function of the duration of the preexisting thyrotoxicosis.

PINCHERA raised the question of the T_4 and T_3 response to TRH stimulation in goiter patients. LEMARCHAND-BÉRAUD gave comments to this question. In Switzerland (Lausanne), endemic goiter is accompanied by normal responses of T_4 and T_3 levels to TRH. In addition, the TSH response is usually normal and sometimes decreased. These findings are of interest in view of the installed iodine prophylaxis in Switzerland. As supported from KOUTRAS Athens, the TSH levels or responses are apparently the higher, the more severe the iodine deficiency is. In addition, high proportions of goiter patients with positive thyroid antibody titers tend to cause supranormal TSH levels (Helsinki, Brussels). From Brussels, further cases were reported with latent thyroiditis, with hypersecretive thyrotrophs and with high biological, but normal immunological TSH activity. All discussors agreed to treat patients with elevated TSH levels by administration of thyroid hormones.

WOLFF raised the question of the TRH test in patients under lithium therapy. LAMBERG commented on this. In a systematic study from Helsinki no changes were observed, neither in the TSH response to TRH nor in thyroid hormone levels. Studies from Athens and Freiburg however tend to show, that under lithium therapy some patients go through initially low T_4 and T_3 levels and that patients with lithium goiter are usually "hypothyroid".

OPPENHEIMER questioned the role of TRH in the practice of medicine in terms of diagnostic use and socioeconomical implications. The author of the above paper repeated the view, that TRH stimulation tests are at present the most sensitive tool for diagnosis of lack or excess of thyroid hormones, even with the drawback of persisting suppression after thyrotoxicosis, that they allow to choose a dose of thyroid hormone, which will suppress the TSH response for instance in the treatment of non-toxic goiter, or which alternatively normalizes the TSH response in substitutive therapy for myxedema. In addition, the facilitation of the diagnosis of an autonomous (toxic) adenoma was stressed. Finally, the TRH test is economical in terms of patients and doctors time if compared with repeated radioiodine uptake tests or suppression tests e. g., and that the actual costs for the radioimmunoassays of TSH can be lowered by automation. This view was challenged from GREER, and supported from HÖFER. In sum, the TRH test is used for practical diagnostic purposes in some places, and it is considered a research procedure in others.