ENDEMIC GOITER AND CRETINISM: CONTINUING THREATS TO WORLD HEALTH

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HYPOTHALAMIC AND PITUITARY CONTROL OF THYROID FUNCTION*

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To remain within reasonable limitations of space, this discussion of the hypothalamic and pituitary control of thyroid function is restricted to selected aspects of the problem. Reviews are available (*1-3*). The diagram of the regulation of the system (Figure 1) is a familiar one. It depicts schematically the hypothalamic area, where biosynthesis and release of the hypophyseotropic hormone TRH take place. The synthetic tripeptide 1-pyro-glutamyl-1-histidyl-1-prolinamide is identical with natural thyrotropin-releasing hormone of a large number of species. TRH stimulates the release and the formation of thyrotropin (TSH) in the thyrotrophs of the anterior pituitary. TSH in turn stimulates the thyroid, so that appropriate levels of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) are provided. A minute part of the thyroid hormones circulates in free form. There is ample evidence that free T_4 and free T_3 are the direct effectors of the system as far as biological effects and the negative feedback upon TSH secretion are concerned. It may be somewhat surprising that the other regulatory interrelations of this system are still far from clear-cut.

Looking at the role of catecholamines, we note that chronic administration of L-dopa reduces the TSH response to TRH stimulation (*4*). Rapoport and co-workers (*5*) observed a decrease in the elevated TSH levels of hypothyroid patients after acute administration of L-dopa. So far, neuroendocrinologists have tended toward the interpretation that L-dopa acts by increasing the formation of hypothalamic dopamine. The findings just mentioned might be better explained by a direct inhibitory effect of L-dopa on the thyrotroph. However, there is yet another hypothesis: Noel and co-workers (*6*) have reported that the response of human pituitary prolactin to TRH is reduced after L-dopa. These authors explain their observation as a direct pituitary inhibition, or alternatively as an L-dopa-stimulated secretion of prolactin inhibiting factor (PIF) exceeding the effect of exogenous TRH. Likewise, a hypothalamic inhibitor of pituitary TSH release has recently come into consideration through the observations of Bowers and co-workers (*7*). These authors confirmed that the synthetic tetradecapeptide GIF (growth hormone inhibitor, also called somatostatin) inhibits the TSH response to TRH *in vitro*. The physiologic role of a possible hypothalamic inhibitor of TSH secretion remains unknown.

From the clinician's standpoint it is desirable to have a function test which would stimulate the entire axis from the hypothalamus through the pituitary and thyroid (Figure 1), comparable to the insulin hypoglycemia test. Such a test does not exist. Cold exposure has been tried in this respect, since it increases TSH levels in rats and in infants and children (*8, 9*). However, no TSH rise could be detected in adult human subjects following short-term cooling or surgical hypothermia (*8, 9*).

I should like to discuss briefly the question of the specificity of TRH in releasing pituitary hormones. An exception to its specificity is observed in some acromegalic patients who respond to TRH stimulation with an increase in GH levels (*10*). Moreover, as already mentioned, TRH stimulates prolactin secretion in addition to TSH secretion in humans. Following the injection of synthetic TRH in pharmacologic dosages, the prolactin levels of females

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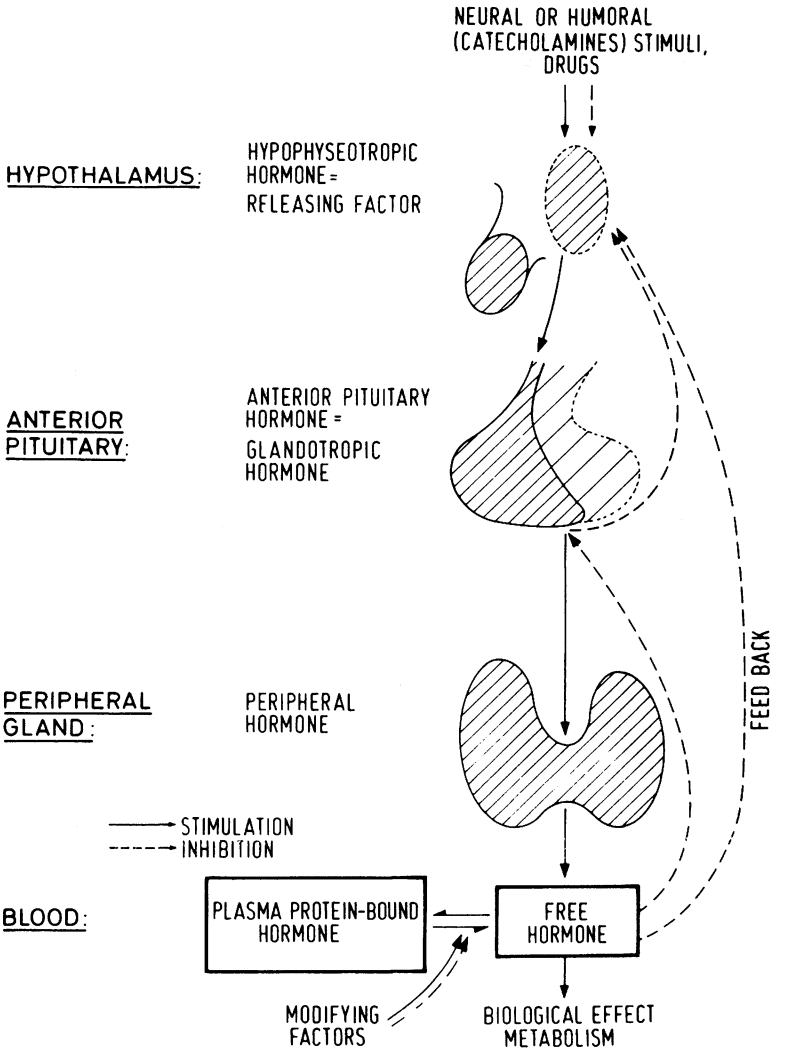
FIGURE 1. Schematic presentation of hypothalamic and pituitary control of thyroid function.



show a more pronounced rise than those of males (*11, 12*). After TRH stimulation of cows, Kelly and co-workers (*13*) observed an 11-fold increment in prolactin levels compared with a 3-fold rise in TSH. In cows TRH has no effect on milk production or composition. However, our veterinarian colleagues in Munich (*14*) have reported that treatment of heifers with TRH results in a stimulation of mammogenesis and lactogenesis, with milk yields subsequently increased by some 50 per cent, whereas galactopoiesis in cows was not affected.

From the effects of these pharmacologic amounts of TRH, conclusions as to the physiologic regulation of thyroid function by the hypothalamus and pituitary (Figure 1) can be drawn only with extreme caution. In thyroidectomized lambs both prolactin and TSH levels rise, presumably through increased secretion of endogenous TRH (*15*). Nursing increases prolactin levels 10-fold in women without concomitant TSH rises (*16*). At present it would appear that at least some physiologic stimuli affect TSH and prolactin secretion differently.

Our understanding of the hypothalamic regulation of the thyrotrophs can be expected to increase considerably as the result of direct determinations of TRH levels in the circulation. Radioimmunoassay procedures for TRH have been reported by the groups of Utiger (*17, 18*), Wilber (*19*), Porter (*20*), and Reichlin (*21*). Unfortunately, TRH is very rapidly inactivated *in vitro* by serum (*17*); in addition, the half-life of circulating TRH is very short and depends on the thyroidal status. Jackson and Reichlin (*21*) observed an increase in urinary TRH in rats following cold exposure, whereas Oliver and co-workers (*20*) could not detect TRH in peripheral plasma of thyroidectomized rats with an assay that showed detectable TRH levels in the peripheral and portal blood of normal rats. Thus, at present we cannot assess the importance under physiologic conditions, of positive or negative feedback of thyroid hormones upon TRH secretion, nor do we know the significance of negative feedback of TSH levels upon TRH secretion.

Let us now consider briefly the control of thyroid function in the absence of endogenous TRH. In patients with hypothalamic disease, moderate hypothyroidism is usually observed, with TSH low but by no means completely absent. TRH stimulation of patients with suprasellar disease and secondary hypothyroidism results in normal or supranormal TSH increases (Table 1). Surprisingly, we likewise observed a normal stimulation of TSH secretion by TRH in most patients with pituitary adenomas and secondary hypothyroidism (*22*). In patients with pituitary tumors it would therefore appear that hypothalamic TRH production or TRH transport via the portal vessels of the pituitary stalk is more susceptible to disturbance than the TSH-producing thyrotrophs in the anterior

TABLE 1. TSH response to a standard TRH stimulation test (200 μg i.v.) in disorders of the hypothalamus and the pituitary(*22*).

			SERUM – TSH μU/ml INCREMENT 30 MIN AFTER TRH (200μg)		
		N	NORMAL RANGE (log) 2.73 - 23.6 μU/ml		
NUMBER OF OBSERVATIONS		84	REDUCED	NORMAL	RAISED
HORMONALLY INACTIVE PITUITARY ADENOMA PREOPERATIVELY	EUTHYROID	12		12	
	HYPOTHYROID	13	1	[11]	[1]
HORMONALLY INACTIVE PITUITARY ADENOMA POSTOPERATIVELY	EUTHYROID	3	[1]	2	
	HYPOTHYROID	20	12	[6]	[2]
INTRA- AND SUPRASELLAR TUMORS AFTER TREATMENT	EUTHYROID	1	[1]		
	HYPOTHYROID	6	5	1	
SUPRASELLAR DISEASES	EUTHYROID	2		2	
	HYPOTHYROID	9		6	[3]
ACTIVE ACROMEGALY	EUTHYROID	9	1	4	[4]
	SEC. HYPOTH.	2	1	[1]	
	PRIM. HYPOTH.	2		[1]	1
OTHER HORMONALLY ACTIVE PIT. ADENOMA	EUTHYROID	5	[3]	2	

THE SO□ DENOTED NUMBERS REPRESENT SURPRISING RESULTS.

pituitary itself. The residual regulation of TSH secretion in rats with hypothalamic lesions, which would eliminate TRH, is slow in terms of TSH response to thyroidectomy and more sensitive to T_4 with respect to TSH suppression (*23*).

As we all know, TSH stimulates the release and synthesis of thyroid hormone, as well as thyroidal growth. To relate endemic goiter to the biochemical action of TSH, one might recall the study of Pisarev and co-workers (*24*), who were able to produce goiters in mice by chronic application of cyclic AMP. It may have more clinical relevance to remember the various causes of thyroidal growth in the absence of TSH. We have observed (Table 2) cases of proven TSH deficiency with either thyroidal growth or hyperthyroidism, or both (*25*). Along these lines, we should mention briefly the phenomenon of thyroidal autoregulation (*26*), which will be dealt with elsewhere at this meeting. Of interest, iodine depletion studies in rats (*27*) have shown an increased sensitivity of the iodine-depleted gland to the goitrogenic effect of TSH.

It is apparent, then, that despite significant advances in our knowledge of the physiology and pathophysiology of thyroid regulation by the hypothalamus and pituitary, there are still many open questions which must be answered through continued research.

Certain diagnostic implications of the thyroid-pituitary feedback have, in the view of many, led to major clinical progress. During the last two or three years, the radioimmunological determination of TSH in serum and its stimulation with synthetic TRH have been broadly applied by many investigators.

TABLE 2. Differential diagnosis of thyroid growth and/or thyrotoxicosis in the absence of TSH (*25*).

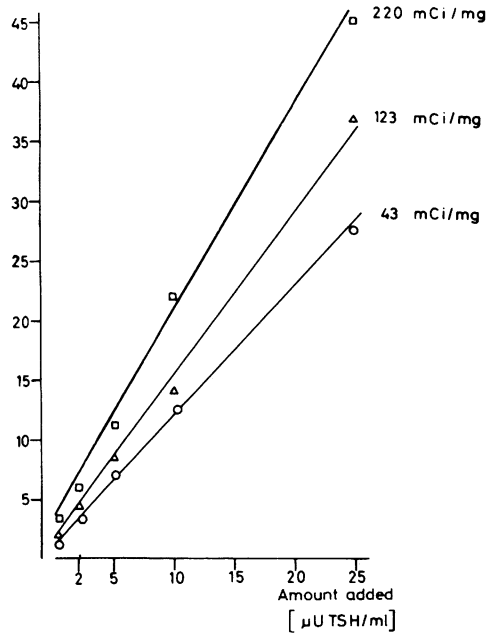
- Thyroid Malignancy Primary or Secondary
- Thyroiditis (Hashimoto)
- Acromegaly (Visceromegaly)
- Graves Disease (LATS?)
- Autonomous Adenoma
- (Thyrotoxicosis factitia)

TSH—one of the glycoproteohormones of the anterior pituitary—was shown to consist of two subunits (*α* and *β*) by Pierce and co-workers (*28*). Recently, Shome and Parlow (*29*) announced the primary structure of human **β-TSH**, which differs from bovine **β-TSH** in 12 amino acids. Radioimmunoassays for the hormone-specific **β-subunit** will probably soon be introduced into clinical endocrinology.

The radioimmunoassay for TSH, though widely used, still presents some problems. Adams and co-workers (*30*) demonstrated lack of identity for TSH levels below 5 μU/ml, when bioassay and radioimmunoassay were compared. In addition, using gel chromatography, Dimond and Rosen (*31*) showed heterogeneity of circulating TSH when compared with pituitary TSH. The use of standards dissolved in hormone-free serum—as recommended, for example, by Patel and co-workers (*32*)—corrects erroneously high TSH levels, which will be found if a tracer TSH of too high specific activity is used. As can be seen in Figure 2, tracer of a rather low specific activity will give the correct recovery values for the TSH added. As for the sensitivity problem, various measures have been proposed, including incubation at room temperature, preincubation of TSH antibody and cold hormone, low tracer concentration, and use of dilute antiserum (*32-34*). Despite these efforts, the basal TSH levels of control groups are still found to vary from below the limit of detection to 3 or 4 μU/ml. With this sensitivity, low normal and suppressed basal TSH levels may not be discerned.

For diagnostic purposes, however, the apparent lack of sensitivity can be readily overcome by the introduction of TRH stimulation tests. A standard TRH stimulation test is now performed by many groups, with rapid i.v. injection of 200 μg TRH and 0 and 30-minute sampling for TSH determination. This procedure has resulted in a normal range—mean ± 2

FIGURE 2. Effect of the specific activity of tracer TSH on the radioimmunoassay of TSH: Comparison of standards in serum and in buffer solution (*33*).



SD—of the TSH increment (Δ TSH $_{30\ min}$) of 2.7 to 23.6 µU/ml, assuming a log-normal distribution for Δ TSH $_{30\ min}$ (*33, 35*).

Some authors (*36, 37*) have reported that the normal range of the TSH increment is sex dependent. From the data of Snyder and Utiger (*38*), and from our own results, it would appear that the controversial sex dependency would probably not affect the diagnostic value of the TRH test as regards the nonstimulation of TSH levels in thyrotoxicosis and the clearly exaggerated responses in hypothyroidism. The same applies to possible age dependency (*38, 39*).

Spontaneous bursts of TSH secretion do not present a problem for the evaluation of TRH-stimulated TSH levels when compared with other episodically secreted hormones of the anterior pituitary. A circadian rhythm of TSH secretion was detected only when the sampling intervals were reduced from one hour (*40*) to 30 minutes (*41*). Fortunately, the early morning peak from 4 a.m. to 6 a.m. does not interfere with normal times for routine endocrine test procedures.

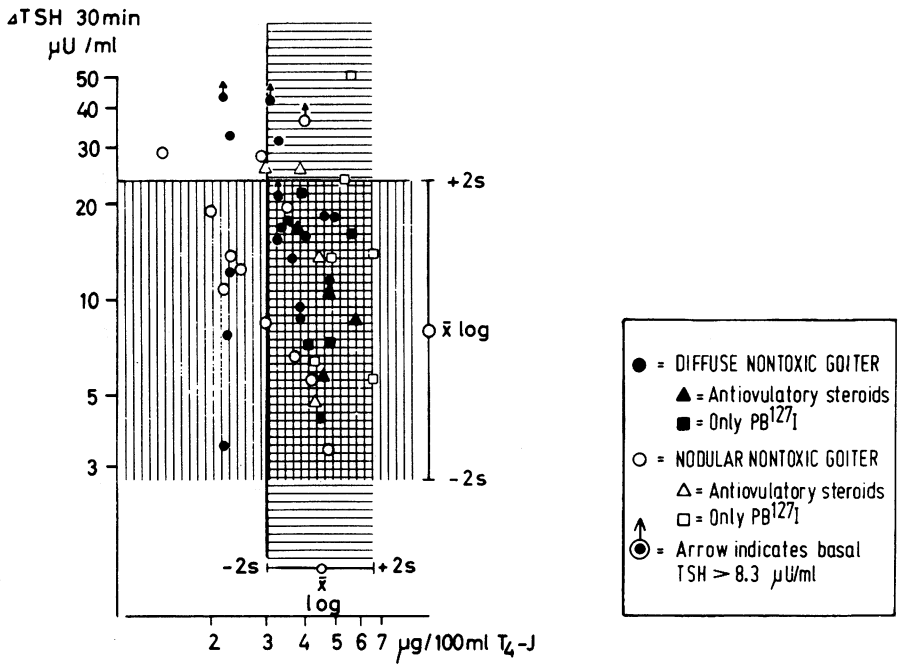
We all know that TSH secretion is increased in primary hypothyroidism. Monitoring of TSH levels (*42, 43*) allows a precise assessment of the daily T_4 requirements in hypothyroid patients, with an average dosage of 172 µg thyroxine per day recently being reported. Monitoring of the TSH response to TRH appears to be a still more sensitive parameter for the evaluation of borderline hypothyroidism. Thus, the normalization of basal TSH levels preceded the normalization of Δ TSH $_{30\ min}$ in a hypothyroid patient on thyroid hormone therapy.

In our area (Munich), we observed in patients with nontoxic goiter an elevated TSH response to TRH in approximately 20 per cent of the cases (Figure 3). Our interpretation is that these patients may be, first, in a period of further thyroid growth and, second, borderline hypothyroid (*35, 44, 45*). Monitoring Δ TSH $_{30\ min}$ in goiter patients has been a useful tool for determining the dosage of thyroid hormone necessary either for nonsurgical treatment of nontoxic goiter or for postoperative prophylaxis against recurrence of the goiter (*46*). This subject is dealt with in detail by Dr. Medeiros elsewhere in this volume (see p. 43).

Finally, I should like to discuss briefly the TRH stimulation test in cases of thyroid hormone excess. With practically no exception, TSH levels are low in thyrotoxicosis and may not be stimulated by TRH. The same phenomenon was, however, observed in euthyroid Graves' disease (*47*), as persisting suppression of TSH secretion following treatment for thyrotoxicosis (*48*), or when treatment with thyroxine was discontinued (*49*). In view of the purposes of this conference, I now want to draw your attention to the autonomous adenoma of the thyroid.

Many patients with autonomous adenomata do not have supranormal levels of T_4, as Figure 4 shows. However, all those 14 patients failed to increase their TSH secretion with TRH stimulation. We found an excellent correlation

FIGURE 3. TSH response to standard TRH stimulation and thyroxine iodine in serum (CPB-analysis) in cases of nontoxic goiter as compared to normal ranges of control persons (*35*).



between negative TRH stimulation tests and positive thyrotropin stimulation tests (*50*). We therefore suggested that TSH stimulation tests be avoided. Another reason for this recommendation is the potential hazard of TSH stimulation, since it may increase T_4 to a level above the upper limit of normal (*51*). In addition, TSH injections are known to give rise to the formation of antibodies against bovine TSH.

Figure 5 depicts a scheme for the evolutionary cycle of the autonomous nodule of the thyroid (*50*). After the establishment of autonomy in a circumscribed area, thyroid hormone levels may rise and Δ TSH $_{30\ min}$ may fall, either subsequently or simultaneously. The addition of thyrotoxicity to the autonomy of a nodule is likely to occur when a patient with an already autonomous nodule is subjected to heavy loads of iodine, e.g. through X-ray procedures (*52*). This, however, is another aspect of the prophylaxis of endemic goiter, which is discussed in more detail elsewhere in this volume.

SUMMARY

1. Remarkable progress in our understanding of the hypothalamic and pituitary control of the thyroid gland has been achieved in recent years. Yet, many questions remain unanswered. Some of these were selected for discussion because of recent renewed interest. They include the role of hypothalamic catecholamines; the effect of cold exposure on the hypothalamo-pituitary-thyroid axis; the specificity of the effect of thyrotropin-releasing hormone (TRH), with emphasis on prolactin secretion; and the radioimmunoassay of TRH.

2. The thyroid-pituitary feedback in the absence of TRH is briefly discussed. Patients with hypothalamic disorders illustrate this problem.

FIGURE 4. TSH response to standard TRH stimulation in cases of autonomous adenoma of the thyroid (*50*). A nonsuppressible hot nodule with surrounding thyroid tissue, the latter showing suppressed ^{131}I-uptake in a subsequent test under exogenous T_3, is defined as *kompensiert*. The *dekompensierte* autonomous adenoma represents a hot nodule with surrounding thyroid tissue, when the latter is not seen in the first scan but shows ^{131}I-uptake under stimulation with exogenous TSH (*50*).

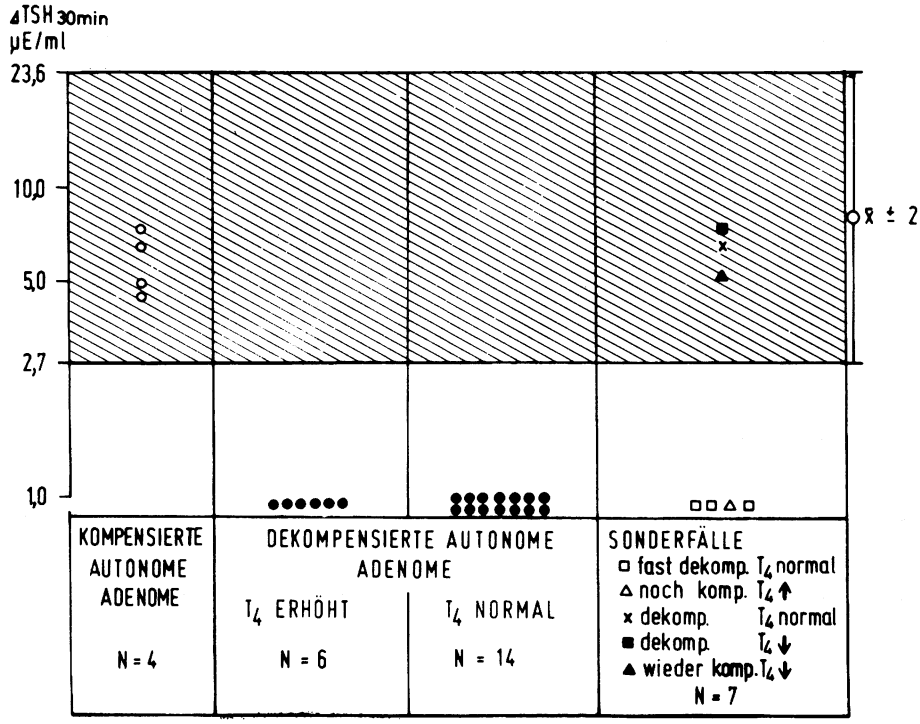
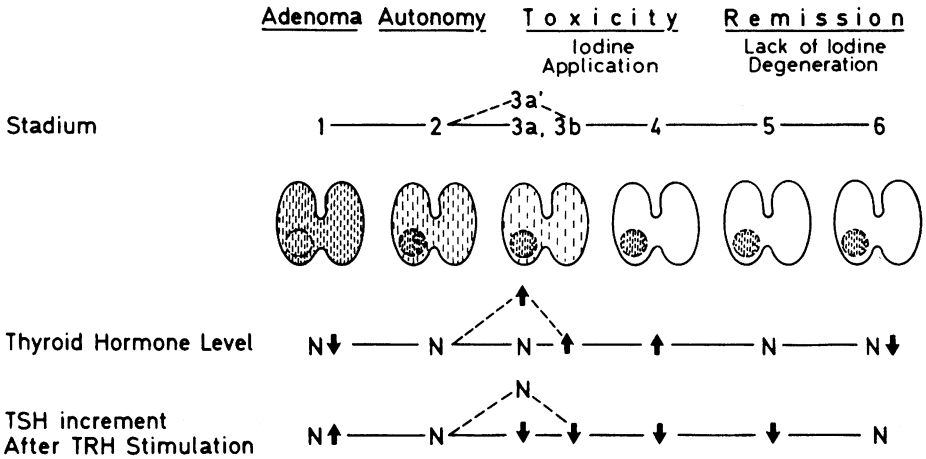


FIGURE 5. Cycle of the autonomous adenoma (*50*).



3. A short review is given of conditions allowing thyroidal growth in the absence of TSH.

4. The introduction of the radioimmunoassay for serum TSH and of the TRH stimulation test has led to major progress in the field of clinical diagnosis of thyroid disorders. The following problems have been briefly discussed: the possible heterogeneity of circulating TSH and aspects of inadequate sensitivity and accuracy of the radioimmunoassay for TSH; the normal range for the TSH response to a standard TRH stimulation test, and the effects of sex and age; the diagnostic implications of supranormal TSH responses to TRH stimulation in terms of preclinical hypothyroidism and thyroidal growth; and the diagnostic implications of suppressed TSH responses to TRH stimulation, with special reference to the autonomous adenoma of the thyroid.

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DISCUSSION

Niepominiszcze: Your last slide reminded me of the study of McCormack and Sheline (*J Nuclear Med* 8: 701-708, 1967) in which 14 patients with autonomous hot nodules were followed without any treatment for a period of 4 to 8 years. Of these, 11 remained unchanged during that period, only 1 became thyrotoxic, and 2 had spontaneous remissions. I point this out because this study suggests that the majority of autonomous hot nodules did not follow a specific cycle.

Scriba: We certainly know that there may be spontaneous remissions in cases of autonomous adenomas. On the other hand, I think there is no doubt that when autonomous adenomas are loaded with iodine, some of them may produce severe thyrotoxicosis, for instance at the time of thyroidectomy. I think some of the other papers of this conference will address the problem of the risk of thyrotoxicosis in areas of endemic goiter with autonomous nodules, when there is a sudden great increase in iodine supplies, such as with the injection of iodized oil.

Medeiros-Neto: What are your thoughts on the so-called short feedback loop? Would a high TSH output block hypothalamic TRH, or would it further stimulate TRH secretion?

Scriba: I don't know the answer. I know of two conflicting reports, one of which says there is an increase in TRH excretion in the urine during cold exposure and the other that there is no TRH in peripheral plasma in a thyrodectomized rat. It seems clear that at present we don't know what the predominant mechanism of regulation is.