

## Suppression of Pituitary TSH Secretion in the Patient with a Hyperfunctioning Thyroid Nodule

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### Research Article

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In eight patients, basal serum TSH concentrations failed to increase after the intravenous administration of 200 μg of thyrotropin-releasing hormone (TRH); minimal increases in serum TSH concentrations were observed in two patients. The suppression of TSH was evident despite "normal" concentrations of circulating thyroid hormones. The observation that normal serum concentrations of T<sub>4</sub>D, FT<sub>4</sub>, T<sub>3</sub>D, and FT<sub>3</sub> may be associated with undetectable basal serum TSH concentrations and suppressed TSH response to TRH was also found in [...]

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# Suppression of Pituitary TSH Secretion in the Patient with a Hyperfunctioning Thyroid Nodule

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**ABSTRACT** 10 patients with a single hyperfunctioning thyroid nodule each were studied for pituitary thyrotropin (TSH) suppression. They were judged to be euthyroid on clinical grounds. The total thyroxine ( $T_4D$ ), free thyroxine ( $FT_4$ ), total triiodothyronine ( $T_3D$ ), and free triiodothyronine ( $FT_3$ ) were normal in most of the patients. Incorporation of  $^{131}I$  into the hyperfunctioning thyroid nodules was not suppressed by the administration of physiological doses of  $T_3$ . Basal serum TSH concentrations were undetectable ( $< 0.5 - 1.0 \mu U/ml$ ) in all patients. The metabolic clearance of TSH in one patient before and after excision of the thyroid nodule was unchanged (40 vs. 42 ml/min) whereas the calculated production rate was undetectable before the operation ( $< 29$  mU/day) and normal after (103 mU/day). These data, in one patient, suggest that the undetectable concentration of TSH in these patients is a result of suppressed TSH secretion rather than accelerated TSH clearance.

In eight patients, basal serum TSH concentrations failed to increase after the intravenous administration of 200  $\mu g$  of thyrotropin-releasing hormone (TRH); minimal increases in serum TSH concentrations were observed in two patients. The suppression of TSH was evident despite "normal" concentrations of circulating thyroid hormones. The observation that normal serum concentrations of  $T_4D$ ,  $FT_4$ ,  $T_3D$ , and  $FT_3$  may be associated with undetectable basal serum TSH concentrations and suppressed TSH response to TRH was also found in four hypothyroid patients given increasing doses of L-thyroxine and sequential TRH stimulation tests.

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## INTRODUCTION

It has been assumed, on the basis of anatomical (1) and physiological data (2, 3), that the hyperfunctioning thyroid nodule functions independently of pituitary thyroid-stimulating hormone (TSH).<sup>1</sup> We have recently studied 10 patients with hyperfunctioning thyroid nodules in an attempt to define the basal concentrations of serum TSH as well as the pituitary reserve of TSH after the administration of thyrotropin-releasing hormone (TRH).

## METHODS

*Patients.* 10 patients, each with a single hyperfunctioning thyroid nodule, were studied. They were judged to be euthyroid on clinical grounds. The patients had been followed for 2-15 yr before study without any antithyroid therapy. For comparative data of basal TSH serum concentrations and the response of pituitary TSH to TRH, similar studies were performed on the following groups of patients. There were 56 controls, who were judged euthyroid by clinical assessment; 11 of these were studied in detail, with a correlation of serum total thyroxine ( $T_4D$ ),<sup>2</sup> free thyroxine ( $FT_4$ ), total triiodothyronine ( $T_3D$ ), basal serum TSH, and TSH response to TRH. There were 11 hyperthyroid patients as judged by a classical clinical presentation, elevated serum  $T_4D$ ,  $FT_4$ ,  $T_3D$ , and radioiodine (RAI) uptake. There were four patients with primary hypothyroidism as documented by low  $T_4D$ ,  $FT_4$ ,  $T_3D$ , and an elevated serum TSH concentration. Three of the patients, M. S., M. Q., and L. L., had Hashimoto's thyroiditis, proved by a thyroid biopsy, and one (J. S.) had had a subtotal thyroidectomy for hyperthyroidism 15 yr previously. Each of these four patients was given sodium-L-thyroxine (Synthroid, Flint, Eaton & Co., Morton Grove, Ill.) orally, starting at 50 or 100  $\mu g$ ; then the dose was

<sup>1</sup> Abbreviations used in this paper: MCR, metabolic clearance rate; RAI radioiodine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

<sup>2</sup> Abbreviation of total thyroxine ( $T_4D$ ), free thyroxine ( $FT_4$ ), total triiodothyronine ( $T_3D$ ), free triiodothyronine ( $FT_3$ ), and dialyzable  $T_3$  ( $\%FT_3$ ) are those recommended by The American Thyroid Association (4).

increased gradually every 4 wk. Before each incremental increase in the L-thyroxine dosage, the patients had a TRH stimulation test in an attempt to correlate pituitary TSH suppression with circulating levels of T<sub>4</sub>D, FT<sub>4</sub>, T<sub>3</sub>D, and RAI uptake.

**TSH radioimmunoassay.** The TSH radioimmunoassay was a modification of the method of Odell, Wilber, and Utiger (5) and similar to that recently reported by Patel, Burger, and Hudson (6). Purified human thyrotropin for labeling and rabbit anti-human thyrotropin serum were obtained from the National Pituitary Agency. Human thyrotropin research standard B, used as the primary standard for these assay, was obtained from the Medical Research Council, Mill Hill, England. TSH was labeled with <sup>125</sup>I (specific activity 50–100 μCi/μg) by the method of Hunter and Greenwood (7), and the [<sup>125</sup>I]TSH was purified by gel chromatography on Sephadex G-100. Duplicate serum samples of TSH standards containing an equivalent amount of suppressed serum were preincubated with the anti-TSH for 24–48 h at 4°C before the addition of approximately 0.05 ng [<sup>125</sup>I]TSH. After a further 72-h incubation, antibody-bound TSH was precipitated within 24 h by the addition of appropriate amounts of goat anti-rabbit gamma globulin. The tubes were then centrifuged, the supernates decanted, and the precipitates counted in a standard autogamma spectrometer. Less than 2% of the radioactivity was nonspecifically precipitated in tubes without anti-TSH, and greater than 80% was precipitated with excess anti-TSH. The sensitivity of the method was 0.5–1.0 μU/ml serum. Less than 10% of normal controls had levels that were not detected.

**Laboratory tests.** Serum T<sub>4</sub>D was measured by a modification of the method of Murphy and Pattee (8) by the Boston Medical Laboratory, Waltham, Mass., which achieved a recovery of thyroxine from serum of approximately 95% (9, 10). Serum FT<sub>4</sub> was measured by a modification of the method of Sterling and Brenner (11).

Serum T<sub>3</sub>D was measured by a modification (12) of the method of Sterling, Bellabarba, Newman, and Brenner (13), in which the chromatographic separation of T<sub>4</sub> and T<sub>3</sub> was verified by gas chromatography, showing approximately 0.5% T<sub>4</sub> contamination of T<sub>3</sub>. The method of Nauman, Nauman, and Werner (14) was employed for the determination of dialyzable T<sub>3</sub> (%FT<sub>3</sub>) by Joseph Benotti at the Boston Medical Laboratory. Several modifications were employed. [<sup>131</sup>I]T<sub>3</sub> in 50% propylene glycol was obtained from Abbott Laboratories, North Chicago, Ill., with a specific activity that varied from 30 to 60 mCi/mg. The [<sup>131</sup>I]T<sub>3</sub> was purified as follows. An aliquot of the original [<sup>131</sup>I]T<sub>3</sub> solution was diluted to 10 ml with 50% propylene glycol so that 1.0 ml contained about 100 μCi [<sup>131</sup>I]T<sub>3</sub> and ~3 μg T<sub>3</sub>. 1 ml of the diluted material was added to normal serum in the ratio of 1/3 (vol/vol) and allowed to equilibrate at room temperature for 10 min. 200 mg of resin (Rexyn 201 Anion Exchange, Fisher Scientific Co., Pittsburgh, Pa.) was added and the mixture was agitated with a Vortex mixer (Scientific Industries, Inc., Queens Village, N. Y.) for 30 s and then allowed to settle. The purified [<sup>131</sup>I]T<sub>3</sub> was removed by aspiration. Its purity was checked by paper chromatography and trichloroacetic acid precipitation and found to be 95% pure. A 0.1-ml aliquot of the purified [<sup>131</sup>I]T<sub>3</sub> was added to 1.2 ml of test serum, agitated with a Vortex mixer, and then allowed to equilibrate at room temperature for 30 min. A 0.5 ml aliquot of this mixture was placed in a dialysis tubing (Arthur H. Thomas Co., Philadelphia, Pa., pore

diameter 48 Å) that was bent in a V shape, allowing the serum to rest in the apex of the V. The portion of the tubing containing the serum was placed in a 24-ml Erlenmeyer flask and totally immersed in 9.0 ml of the 0.01 M phosphate buffer, pH 7.4, containing 10 μg of tetracycline. The flask was placed into a constantly shaking water bath at 37°C for 17 h (100 strokes/min). The tubing was removed and 0.8 ml of pooled normal serum was added to the dialyate in the flask. The contents were mixed and allowed to stand at room temperature for 10 min. 750 mg Rexyn 201 anion exchange resin was added and the mixture was shaken for 2 min at 37°C at maximum shaking speed. The amount of resin-free [<sup>131</sup>I]T<sub>3</sub> per milliliter of dialyate was expressed as a fraction of the [<sup>131</sup>I]T<sub>3</sub> in 1 ml of serum within the dialysis tubing. The percent FT<sub>3</sub> was obtained by multiplying by 100 and appropriate dilution factors for the serum within the tubing. All serum samples were run in the same assay and in duplicate.

T<sub>3</sub> suppression tests were performed by measuring the 24-h RAI uptake before and after the administration of T<sub>3</sub>, 25 μg three times/day for 10 days, a normal response being a decrease in the RAI uptake of greater than 50% (15, 16). TSH stimulation tests were done by performing a 24-h RAI uptake and scan before and after the administration of bovine TSH (thyrotropin, Armour Pharmaceutical Co., Chicago, Ill.), 10 U intramuscularly daily for 3 days (17).

**TRH infusion.** TRH stimulation tests were performed by injecting TRH (Abbott Laboratories) in a 200 μg intravenous bolus and collecting serum samples over a 180-min period for TSH, T<sub>4</sub>D, FT<sub>4</sub>, and T<sub>3</sub>D (18–20).

**TSH metabolic clearance and production rates.** The metabolic clearance and production rates of TSH were determined by a constant infusion-to-equilibrium method (21, 22) recently applied to other polypeptide (23–25) and glycoprotein hormones (26, 27). In this method<sup>8</sup> highly purified human TSH was labeled with <sup>131</sup>I (7) to a specific activity of ~50 μCi/μg and separated over a G-100 Sephadex column. After infusion into patients and collection of serum samples at equilibrium, the [<sup>131</sup>I]TSH was separated by addition of excess rabbit anti-human TSH and precipitated after a 24-h incubation with goat anti-rabbit gamma globulin. The precipitates were counted in a standard autogamma spectrometer, and metabolic clearance rate (MCR) was determined by the formula:

$$\text{MCR} \frac{\text{ml}}{\text{min}} = \frac{\text{Infusion rate of } [^{131}\text{I}] \text{TSH (cpm)}}{\text{Serum concentration } [^{131}\text{I}] \text{TSH (counts/ml)}}$$

The endogenous production rate of TSH was then calculated by multiplying the MCR times the endogenous serum concentration of TSH. The mean normal MCR of TSH for this laboratory is ~50 ml/min with a range from 30 to 85 ml/min, which is similar to that found by Odell, Utiger, Wilber, and Condliffe (28), who utilized a single-injection method and determined the mean metabolic clearance rates in euthyroid subjects to be 42.5 ml/min with a range from 19.2 to 87 ml/min. The mean normal TSH production rate for this laboratory is ~75 mU/day with a range from < 25 to 150 mU/day as compared to the normal mean cited by Odell et al. of 165.2 mU/day (28).

<sup>8</sup> Ridgway, E. C., B. D. Weintraub, and F. Maloof. 1974. Metabolic clearance and production rates of human thyrotropin. *J. Clin. Invest.* In press.

TABLE I  
Laboratory Data on 10 Patients with Hyperfunctioning Thyroid Nodules

| Patients            | Sex | Age<br>yr | BMR<br>%    | Cholesterol<br>mg/100 ml | RT <sub>3</sub> U<br>% | T <sub>4</sub> D<br>μg/100 ml | FT <sub>4</sub><br>ng/100 ml | T <sub>3</sub> D<br>ng/100 ml | FT <sub>3</sub><br>pg/100 ml | 24 h<br>RAI<br>uptake<br>% | T <sub>3</sub><br>Suppression test<br>RAI uptake |             | TSH<br>μU/ml | Maximal<br>TSH<br>after TRH<br>(200 μg i.v.)<br>μU/ml |
|---------------------|-----|-----------|-------------|--------------------------|------------------------|-------------------------------|------------------------------|-------------------------------|------------------------------|----------------------------|--|-------------|--------------|---|
|                     |     |           |             |                          |                        |                               |                              |                               |                              |                            | before   | after       |              |   |
| M. C.<br>120 29 47  | F   | 20        | +4          | 125                      | 34                     | 9.0                           | 1.8                          | 235                           | 282                          | 47                         | 38   | 37          | <1.0         | <1.0  |
| A. C.*<br>120 96 22 | F   | 52        | -18         | 250                      | 30                     | 10.0                          | 1.7                          | 330                           | 284                          | 40                         |  |             | <1.0         | <1.0  |
| A. M.<br>168 82 79  | F   | 26        | -12         | 212                      | 26                     | 6.0                           | 1.0                          | 150                           | 165                          | 34                         | 28   | 20          | <1.0         | 1.4   |
| M. A.<br>126 17 75  | F   | 29        | -4          | 180                      | 26                     | 9.0                           | 2.0                          | 280                           | 274                          | 35                         | 32   | 34          | <1.0         | <1.0  |
| R. D.<br>021 78 80  | F   | 47        | -6          | 175                      | 31                     | 7.0                           | 1.3                          | 215                           | 194                          | 23                         | 27   | 23          | <1.0         | 2.6   |
| E. P.<br>137 40 84  | F   | 47        | +5          | 209                      | 34                     | 9.0                           | 1.8                          | 230                           | 299                          | 41                         | 43   | 41          | <1.0         | <1.0  |
| E. S.<br>164 59 19  | M   | 69        | +3          | 118                      | 34                     | 9.5                           | 1.8                          | 240                           | 384                          | 37                         |  |             | <1.0         | <1.0  |
| M. R.<br>54 55 86   | F   | 46        | -6          | 215                      | 33                     | 9.5                           | 2.1                          | 210                           | 273                          | 36                         | 37   | 21          | <1.0         | <1.0  |
| J. G.<br>159 55 66  | F   | 26        | -4          | 135                      | 30                     | 8.0                           | 1.5                          | 195                           | 215                          | 22                         | 36   | 22          | <1.0         | <1.0  |
| M. H.†<br>Mean ±SD  | F   | 48<br>41  | -3<br>-4 ±7 | 135<br>175 ±46           | 28<br>31 ±3            | 4.0<br>8.1 ±1.9               | 0.8<br>1.6 ±0.5              | 195<br>228 ±49                | 215<br>258 ±63               | 38<br>35 ±8                | 20<br>33 ±7                                      | 21<br>27 ±8 | <1.0<br><1.0 | <1.0<br><1.0  |
| Normal values       |     |           | +10- -10    | 150-280                  | 25-35                  | 4.0-11.0                      | 0.8-2.4                      | 150-250                       | 140-280                      | 20-50                      |  |             |              |   |

\* Patient on estrogen-stilbesterol 0.5 mg/day.

† Serum thyroxine-binding globulin capacity was 14 μg/100 ml (normal 15-25); serum thyroxine-binding prealbumin capacity was 191 μg/100 ml (normal 185-285).

## RESULTS

**Patients.** The patients with hyperfunctioning thyroid nodules included nine women and one man with ages ranging from 20 to 69 (Table I). All patients had normal values for T<sub>3</sub>D, FT<sub>3</sub>, RAI uptake, BMR, and T<sub>3</sub> resin uptake.

The mean T<sub>3</sub>D for the 10 patients with hyperfunctioning thyroid nodules was 228±50 ng/100 ml (SD). 2 of the 10 patients had slightly elevated levels; one of these two patients, A. C., was taking stilbesterol at the time of study. The normal range for T<sub>3</sub>D for about 1,000 patients in this laboratory has been 150–250 ng/100 ml; however, the T<sub>3</sub>D ranged from 140 to 215 ng/100 ml in the twelve normal patients used in this study to determine %FT<sub>3</sub>. The mean %FT<sub>3</sub> concentration was 0.11% (range 0.086–0.16) with the normal mean for 12 control patients being 0.12% (range 0.095–0.16, Table II). The mean calculated FT<sub>3</sub> concentration was 258 pg/100 ml (range 165–384 pg/100 ml) with the normal mean for 12 control patients being 211 pg/100 ml (range 140–247 pg/100 ml). Although 4 of the 10 patients had values for FT<sub>3</sub> that were above two standard deviations of the mean for the control group, there was no statistically significant difference between the mean %FT<sub>3</sub> or FT<sub>3</sub> of the patients with hyperfunctioning thyroid nodules and the 12 control patients. Patients with hyperthyroidism had a mean %FT<sub>3</sub> of 0.15% (range 0.09–0.27%) and a mean FT<sub>3</sub> of 827 pg/100 ml (range 282–3,350 pg/100 ml).

**T<sub>3</sub> suppression and TSH stimulation tests.** T<sub>3</sub> suppression tests done on eight patients were abnormal since the mean RAI uptake decreased only from 33 to 27%. Thyroid scans were done on all patients initially and showed a homogenous uptake exclusively in the hyperfunctioning nodule with failure to incorporate RAI in the extranodular tissue. TSH stimulation tests were done on 9 of the 10 patients, demonstrating an increased incorporation of RAI by the extranodular tissue.

**Basal serum TSH.** The mean serum TSH level in the fasting and basal state for the 56 control subjects was 1.63±0.79 μU/ml (SD); the mean serum TSH level for the 11 control subjects studied in detail was 1.67±

TABLE II  
FT<sub>3</sub> Concentration in the Serum of Normal Patients and those with Various Thyroid Disorders

|  | n  | T <sub>3</sub> D ±SD | %FT <sub>3</sub> ±SD | FT <sub>3</sub> ±SD |
|--|----|----------------------|----------------------|---------------------|
|  |    | ng/100 ml            | %                    | pg/100 ml           |
| Normals                                      | 12 | 178 ±30              | 0.12 ±0.02           | 211 ±34             |
| Hot nodules                                  | 10 | 228 ±50              | 0.11 ±0.02           | 258 ±63             |
| Hyperthyroid                                 | 9  | 484 ±352             | 0.15 ±0.04           | 827 ±912            |
| Hypothyroid                                  | 8  | 91 ±45               | 0.11 ±0.01           | 100 ±51             |
| Euthyroid after treatment of hyperthyroidism | 16 | 200 ±33              | 0.10 ±0.02           | 200 ±45             |

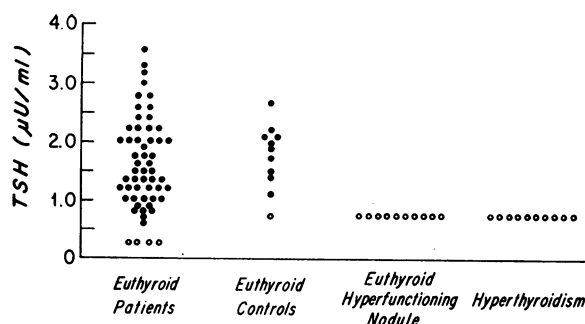


FIGURE 1 Basal serum TSH concentration in euthyroid patients (56), euthyroid controls (11), and patients with hyperfunctioning thyroid nodules (10) or hyperthyroidism (10). Open circle, 0, denotes an undetectable (< 0.5–1.0 μU/ml) TSH concentration.

0.68 μU/ml (SD), with 1 of the 11 subjects having an undetectable serum TSH concentration. In the patients with hyperfunctioning thyroid nodules, the basal serum TSH levels were not detected and not distinguished from those of hyperthyroid patients (Fig. 1). Serum TSH levels in the four hypothyroid patients were elevated in each case before therapy (Table III).

**TRH stimulation tests.** In 11 control subjects, the mean maximal TSH level after TRH stimulation was 11.9±3.2 μU/ml (SD) at 30 min (Fig. 2). Hyperthyroid patients failed to release TSH in response to TRH stimulation. In the group of patients with hyperfunctioning thyroid nodules, 8 of 10 failed to release TSH. 2 of the 10 patients had minimal responses to TRH stimulation that were well below the range of normal.

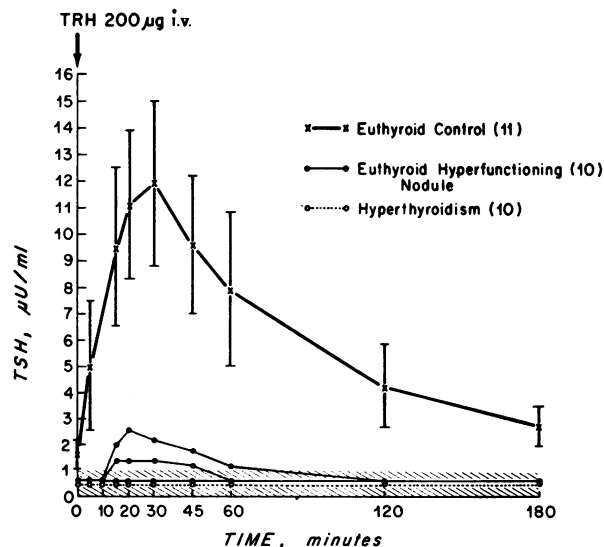


FIGURE 2 Serum TSH response to TRH stimulation. Euthyroid controls ×—×, hyperfunctioning thyroid nodule ●—●, hyperthyroidism ○—○.

TABLE III  
*TSH Response to TRH in Four Hypothyroid Patients Given Increasing Doses of L-Thyroxine and Sequential TRH Stimulation Tests*

| Patient                    | Date of TRH (200 µg i.v.) stimulation | L-thyroxine dosage | Basal TSH | Maximal TSH after TRH | T <sub>4</sub> D | FT <sub>4</sub> | T <sub>3</sub> D | 24-h RAI uptake |
|----------------------------|---------------------------------------|--------------------|-----------|-----------------------|------------------|-----------------|------------------|-----------------|
|                            |                                       | µg                 | µU/ml     | µU/ml                 | µg/100 ml        | ng/100 ml       | ng/100 ml        | %               |
| M. S.<br>MGH No. 154 03 29 | 2/12/72                               | 0                  | 84        | 203                   | 2.5              | 0.4             | 95               | 31              |
|                            | 3/16/72                               | 50                 | 46        | 180                   | 4.5              | 1.0             | 140              | 13              |
|                            | 4/14/72                               | 100                | 9         | 72                    | 6.5              | 1.1             | 110              | 6               |
|                            | 5/12/72                               | 150                | 7         | 45                    | 7.0              | 1.2             | 150              | 5               |
|                            | 6/9/72                                | 200                | <0.5      | 3                     | 7.5              | 1.4             | 170              | <1              |
|                            | 7/7/72                                | 300                | <0.5      | <0.5                  | 10.5             | 2.4             | 290              | <1              |
| M. Q.<br>MGH No. 120 03 45 | 8/7/71                                | 0                  | 35        | 102                   | 2.5              | 0.4             | 80               | 36              |
|                            | 8/25/71                               | 100                | 8         | 36                    | 6.5              | 1.2             | 110              | 9               |
|                            | 9/16/71                               | 150                | <0.5      | 5                     | 8.5              | 1.9             | 190              | <1              |
|                            | 10/22/71                              | 200                | <0.5      | <0.5                  | 9.5              | 2.4             | 160              | <1              |
|                            | 12/3/71                               | 300                | <0.5      | <0.5                  | 11.5             | 2.3             | 240              | <1              |
| L. L.<br>MGH No. 122 20 53 | 5/31/71                               | 0                  | 18        | 115                   | 3.0              | 0.5             | 150              | 18              |
|                            | 6/26/71                               | 0                  | 10        | 88                    | 4.5              | 0.7             | 115              |                 |
|                            | 8/21/71                               | 100                | 4         | 31                    | 7.0              | 1.3             | 125              | 5               |
|                            | 9/18/71                               | 150                | 4         | 48                    | 6.5              | 1.2             | 175              | 10              |
|                            | 10/9/71                               | 200                | <0.5      | 4                     | 9.5              | 2.5             | 200              | <1              |
|                            | 11/6/71                               | 300                | <0.5      | <0.5                  | 11.0             | 2.3             | 255              | <1              |
|                            | 12/4/71*                              | 300                | <0.5      | <0.5                  | 9.0              | 1.7             | 190              | <1              |
| J. S.<br>MGH No. 108 72 69 | 7/24/71                               | 0                  | 6         | 85                    | 3.0              | 0.7             | 155              | 35              |
|                            | 8/10/71                               | 100                | <0.5      | 11                    | 7.0              | 1.5             | 150              | 9               |
|                            | 8/31/71                               | 150                | <0.5      | <0.5                  | 9.0              | 1.7             | 245              | <1              |
|                            | 9/21/71                               | 200                | <0.5      | <0.5                  | 9.0              | 2.2             | 180              | <1              |
|                            | 10/19/71                              | 300                | <0.5      | <0.5                  | 12.5             | 2.5             | 360              | <1              |
| Euthyroid controls         |                                       | None               | 1.67      | 11.9                  | 6.2              | 1.4             |                  | 24              |

\* TRH — 1.0 mg used for this study.

The data on the four hypothyroid patients are presented in Table III. Serial TRH stimulation tests given at intervals of 3–4 wk on increasing doses of oral L-thyroxine were correlated with RAI uptake and circulating levels of T<sub>4</sub>D, FT<sub>4</sub> and T<sub>3</sub>D. In each case the TSH response to TRH was blunted at a time when the circulating levels of T<sub>4</sub>D, FT<sub>4</sub> and T<sub>3</sub>D were within the normal range: T<sub>4</sub>D, 7.5–9.5 µg/100 ml; FT<sub>4</sub>, 1.4–2.5 ng/100 ml, and T<sub>3</sub>D, 170–245 ng/100 ml. Each patient appeared to have complete inhibition of TRH stimulation after the administration of L-thyroxine that varied from 150 to 300 µg daily. Patient L. L. was completely suppressed on 300 µg of L-thyroxine and failed to respond to either 200 or 1,000 µg of TRH given intravenously. The completely suppressed TSH response to TRH was associated with an RAI of less than 1%.

*TSH metabolic clearance and production rates.* Only one patient (J. G.) was available for serial studies before and after partial thyroidectomy. Preoperatively the patient had an undetectable TSH concentration and no re-

sponse to TRH stimulation (Fig. 3), a TSH MCR of 40 ml/min and an undetectable TSH production rate of < 29 mU/day (Table IV). After the operation, the circulating T<sub>4</sub>D, FT<sub>4</sub> and T<sub>3</sub>D dropped to low normal levels by the 4th day. Subsequently, the serum TSH rose to elevated levels of (10 µU/ml) during the 2nd post-operative wk (Fig. 4) and then dropped to a normal level as the T<sub>4</sub>D, FT<sub>4</sub> and T<sub>3</sub>D rose to nearly preoperative levels. 1 mo after the operation, the patient had a normal serum TSH concentration of 1.7 µU/ml and a positive response to TRH stimulation (Fig. 5). At this time the TSH MCR was unchanged at 42 ml/min, but the TSH production rate was 103 mU/day (Table IV).

#### DISCUSSION

In 1947 Cope, Rawson, and McArthur (1) demonstrated that hyperfunctioning thyroid nodules in hyperthyroid patients were associated with anatomical atrophy and physiological inactivation of the extranodular tissue. Dobyns and Lennon (29) confirmed the physiological

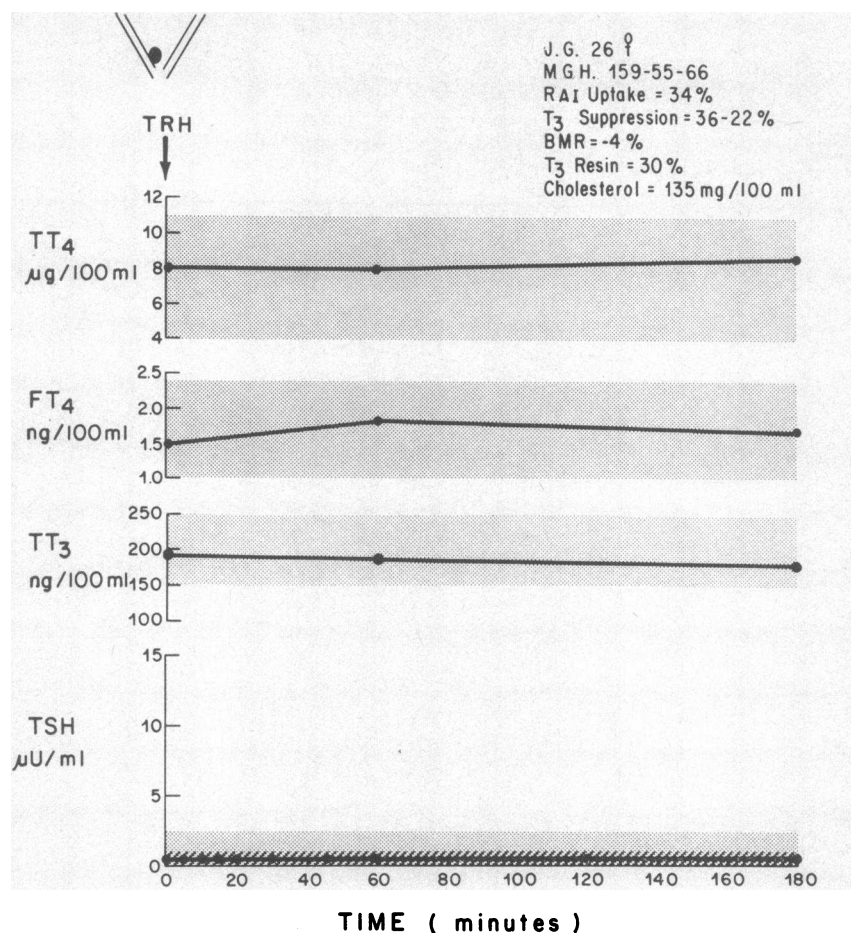


FIGURE 3 Preoperative TSH response to TRH stimulation in patient J. G. Stippled area denotes normal range; slashed area denotes undetectable range of serum TSH concentration. Thyroid scan in upper left corner denotes radioactivity in the single nodule on right.

inactivation of the extranodular tissue by radioautography demonstrating that the extranodular tissue concentrated much less  $^{131}\text{I}$  than the hyperfunctioning nodule, regardless of whether the patient was clinically hyperthyroid or euthyroid. Subsequently, Sheline and McCormack (2) reported that the administration of bovine TSH to patients with hyperfunctioning thyroid nodules led to the incorporation of RAI in the extranodular tis-

sue. The latter effect was also noted by Green and Ingbar (3) after removal of the hyperfunctioning thyroid nodule. These observations gave strong support for the assumption that anatomical and physiological inactivation of the extranodular tissue was a direct result of suppressed endogenous TSH secretion.

The present study, utilizing a sensitive radioimmunoassay that distinguished low from normal levels of se-

TABLE IV  
Effect of Partial Thyroidectomy on Circulating Levels of Thyroid Hormones, TSH Concentration, TSH Response to TRH, TSH Metabolic Clearance, and Production Rates

|        | T <sub>4</sub> D | FT <sub>4</sub> | T <sub>3</sub> D | Basal TSH | Maximal TSH after TRH | TSH MCR | TSH PR* |
|--------|------------------|-----------------|------------------|-----------|-----------------------|---------|---------|
|        | μg/100 ml        | ng/100 ml       | ng/100 ml        | μU/ml     | μU/ml                 | ml/min  | mU/day  |
| Before | 8.0              | 1.5             | 195              | <0.5      | <0.5                  | 40      | <29     |
| After  | 7.5              | 1.4             | 155              | 1.7       | 24                    | 42      | 103     |

\* PR, production rate.

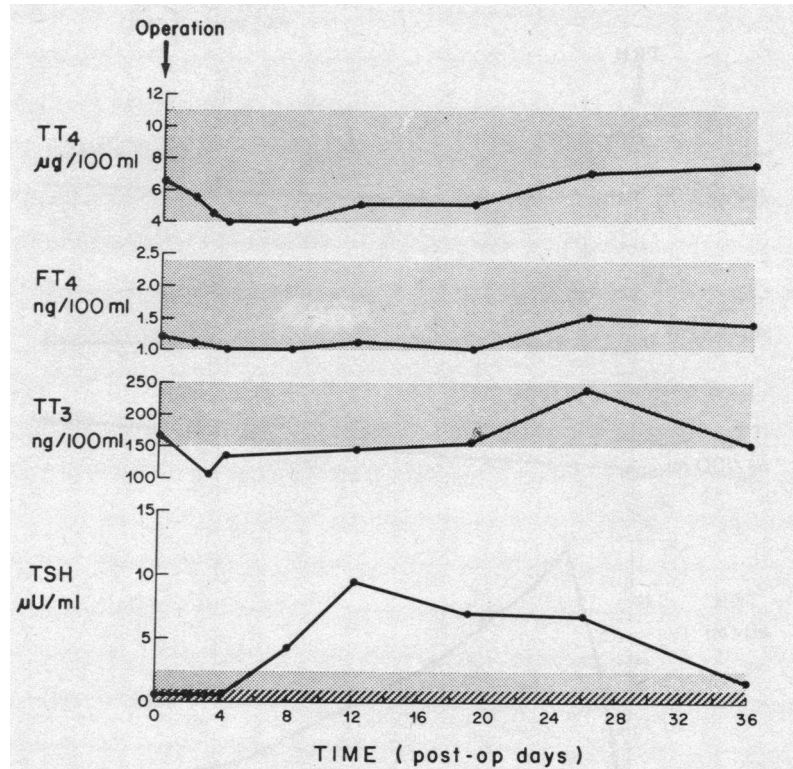


FIGURE 4 Postoperative course of patient J. G., correlating decreasing  $T_4D$ ,  $FT_4$ , and  $T_3D$  with increasing serum TSH concentration. Stippled area denotes normal range; slashed area denotes undetectable range of serum TSH concentration.

rum TSH, demonstrated that all patients with hyperfunctioning thyroid nodules had undetectable basal concentrations of serum TSH. These undetectable concentrations of serum TSH were not distinguished from those of patients with classical hyperthyroidism but did differ from those of control patients who had a mean serum TSH of  $1.67 \pm 0.68 \mu U/ml$ .

Stimulation of the pituitary thyrotropin cells by TRH revealed evidence consistent with suppression of the thyrotropin cells. In 8 of 10 patients with hyperfunctioning thyroid nodules, TRH failed to release TSH, data not distinguished from those seen in patients hyperthyroid secondary to Graves' disease (30, 31), toxic adenoma (32), or even in patients with euthyroid Graves' disease (33).<sup>4</sup> Two of the study patients released minimal amounts of TSH after the TRH challenge.

Serial studies in one patient, J. G., before removal of the thyroid nodule showed that an undetectable basal

serum TSH concentration and an absent TSH response after TRH stimulation were due to an undetectable TSH production rate. After removal of the nodule, a normal serum TSH concentration was associated with a normal TSH production rate and a positive TSH response to TRH stimulation without alterations in the metabolic clearance of the hormone. In addition, comparison of the pre- and postoperative  $T_4D$  (8.0 vs. 7.5  $\mu g/100 ml$ ),  $FT_4$  (1.5 vs. 1.4  $ng/100 ml$ ), and  $T_3D$  (195 vs. 155  $ng/100 ml$ ) concentrations suggests, that relatively small changes in the circulating thyroid hormones can produce significant alterations in TSH secretion.

In spite of the normal concentration of circulating thyroid hormones in a majority of these patients with hyperfunctioning thyroid nodules, basal concentrations of TSH were undetectable, and serum TSH failed to rise normally after TRH stimulation. Several possibilities for the suppression of pituitary TSH secretion have been entertained. First, the nodules may have produced an unidentified substance capable of suppressing pituitary TSH secretion, an hypothesis lacking experimental evidence. Second,  $FT_3$  concentrations were measured in pa-

<sup>4</sup>Cooper, D., E. C. Ridgway, L. Lorenz, and F. Maloof. 1972. The thyroid-pituitary-hypothalamic axis in euthyroid patients with Graves' ophthalmopathy. *Clin. Res.* 20: 864. (Abstr.)



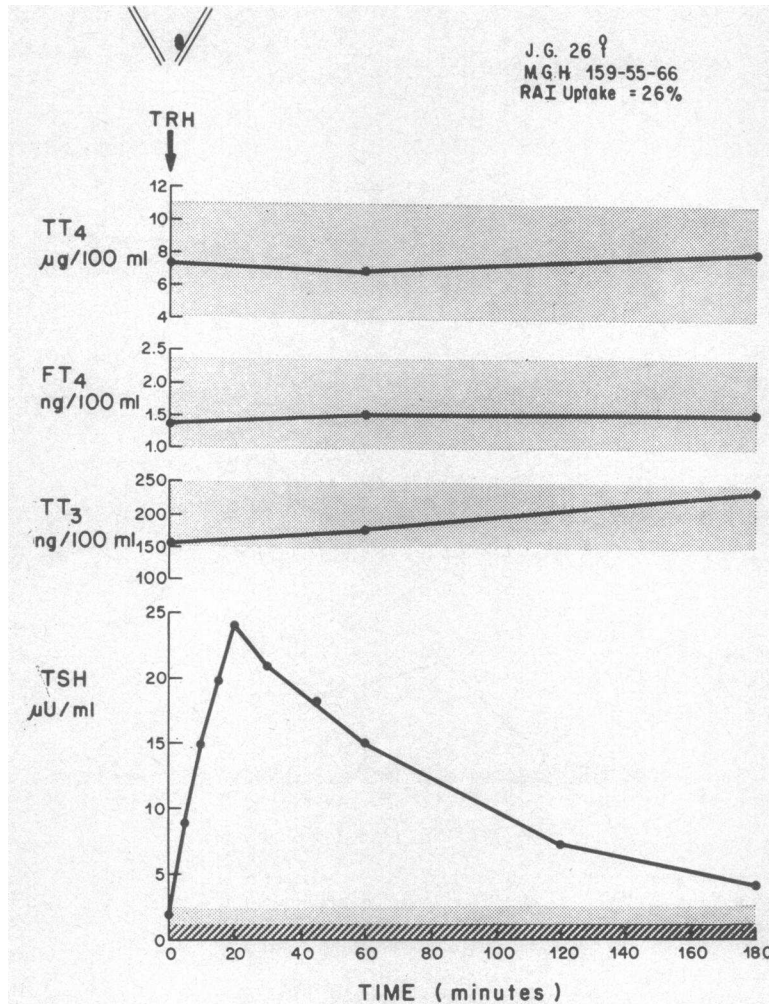


FIGURE 5 Postoperative TSH response to TRH stimulation in patient J. G. Stippled area denotes normal range; slashed area denotes undetectable range of serum TSH concentration. Thyroid scan in upper left corner denotes radioactivity in parathyroid tissue on left.

tients with various thyroid disorders (Table II). The dialyzable fraction of  $T_3$  for normal controls ( $0.12 \pm 0.02\%$ ) in our studies is considerably lower than those previously reported by Nauman et al. (14) for normals ( $0.46 \pm 0.14\%$ ) and slightly lower than those ( $0.28\%$ ) reported by Woeber, Hecker, and Ingbar (34). This probably stems from the variations and modification in the techniques of the assay. Purification of the labeled test substance (35, 36) and careful attention to the ionic strength and pH of the buffer and temperature (37) have led to a decrease over the years in the reported normal values of dialyzable  $T_3$  from about  $0.05\%$  (11, 38, 39) to about  $0.020\%$  (37), which is the value for the percent  $FT_3$  used in our studies. Although our percent  $FT_3$  is lower than the values reported by other investigators, the alterations in the dialyzable fraction in our patients with various thyroid disorders (Table II) were

similar to those reported by Nauman et al. (14). Our data reveal that there is an increase in the dialyzable  $T_3$  fraction in patients with hyperthyroidism but there was no increase in the patients with hyperfunctioning thyroid nodules when compared with controls. This is not surprising, since there were no apparent binding abnormalities in our patients and the  $T_4$ D concentrations were normal. It appears that a significant increase in the serum thyroxine is required to increase significantly the dialyzable fraction of  $T_3$  (34). Hence, an increase in the dialyzable  $T_3$  fraction is not an explanation for our findings of suppression of TSH secretion. Third, serum TSH concentration and pituitary TSH reserve may be more closely correlated with the production or disposal rates of  $T_4$  and  $T_3$  and not directly with their serum concentrations. Although production and disposal rates of  $T_4$  and  $T_3$  were not measured, one might postulate slightly

increased values. Fourth, although the serum concentrations of thyroid hormones found in these patients were within the normal range for the general population; they were excessive for these individual patients. Excessive thyroid hormone concentration usually produces signs of thyrotoxicosis but in these patients there were none of the usual signs or symptoms of thyrotoxicosis. Thus, the thyroid hormone concentrations may have been excessive enough to inhibit pituitary TSH secretion without producing clinical thyrotoxicosis.

The phenomena of pituitary suppression of TSH secretion in the presence of normal circulating concentrations of thyroid hormones were also documented in the four hypothyroid patients by the chronic administration of increasing doses of L-thyroxine. Each hypothyroid patient appeared to achieve suppression of pituitary TSH secretion after the administration of varying doses of L-thyroxine that led to a variable but normal level of T<sub>4</sub>D, FT<sub>4</sub>, and T<sub>3</sub>D. In addition, the TSH response to TRH stimulation was altered from partial to complete suppression in each hypothyroid patient after relatively small changes in the serum concentration of T<sub>4</sub>D, FT<sub>4</sub>, and T<sub>3</sub>D. These data are consistent with those of Snyder and Utiger (40) who have demonstrated the extreme sensitivity of the TRH-induced TSH release to inhibition in normal and hypothyroid subjects after the chronic oral administration of quantities of T<sub>4</sub> and T<sub>3</sub> that did not raise serum T<sub>4</sub>D and T<sub>3</sub>(RIA) above the normal range. The sensitivity of the TRH-induced TSH release to inhibition by single doses (50–100 µg) of T<sub>3</sub> has also been reported (41, 42). Thus it is evident that there is a very sensitive feedback control between the concentrations of circulating thyroid hormones and that of the secretion of TSH. Feedback inhibition by thyroid hormones may occur at different serum concentration of T<sub>4</sub> and T<sub>3</sub> in different patients and may occur with only minimal changes in the serum concentrations of T<sub>4</sub> and T<sub>3</sub> in any one patient.

In summary, these studies in 10 patients with hyperfunctioning thyroid nodules documented pituitary-thyrotropin-cell suppression on the basis of undetectable basal TSH concentrations, normal metabolic clearance of TSH, an undetectable production rate of TSH, and a failure of the pituitary to release TSH after TRH stimulation. Although the patients were judged to be euthyroid on clinical grounds, it appears that these patients are secreting an amount of thyroid hormone that is excessive for their pituitaries. Furthermore, these patients appear to exhibit a certain tolerance to slight increases in the serum concentration of thyroid hormone, since they fail to develop overt clinical evidence of hyperthyroidism.

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