

## Anomalous Thyrotropin Values

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We studied problems associated with use of an "ultrasensitive" thyrotropin (TSH, thyroid-stimulating hormone) assay for diagnosis of hyperthyroidism. Of 955 TSH assays performed in our laboratory during four months, 135 gave TSH values  $<0.1$  milli-int. unit/L. We noted low TSH values at all concentrations of free thyroxin ( $FT_4$ ) in plasma. Nine of 13 patients with a normal or low  $FT_4$  and no obvious endocrine explanation for a low TSH were elderly and ill. This raises questions about the pituitary function in such patients. Twenty-seven patients who had high  $FT_4$  and non-suppressed TSH were clinically euthyroid, 20 of them being on treatment with thyroxin or amiodarone. Low TSH values in a hospital environment do not always indicate hyperthyroidism, although a normal value for TSH probably indicates euthyroidism.

The relatively ultrasensitive thyrotropin (TSH) assay has been advocated as the "front line" assay for diagnosis of hyperthyroidism (1, 2).<sup>1</sup> Using an ultrasensitive TSH assay, we observed a few very low TSH values in the absence of high free thyroxin ( $FT_4$ ). We therefore examined TSH results obtained during a four-month period to see if there were any problems associated with the use of TSH values for the diagnosis of hyperthyroidism.

### Materials and Methods

**Patient's samples.** Routine plasma samples received between January 1 and April 30, 1986, were studied. The patients were mainly inpatients and outpatients of the Royal Melbourne Hospital and the Mount Royal Geriatric Hospital. We performed 955 TSH assays during this period. Clinical data were obtained from examination of the patient's records or from the attending physicians.

**Quality control.** "Tri-level Ligand Control" (Gilford, Irvine, CA 92714) was used at TSH concentrations of 5.8, 13, and 35 milli-int. units/L. A human plasma pool with a TSH value of 0.15 milli-int. unit/L was used as a low-concentration control.

**Methods.**  $FT_4$  was measured by using "Amerlex-M" and total triiodothyronine ( $T_3$ ) with "Amerlex" reagents from Amersham International. TSH was measured with reagents from Henning-Berlin Komturstrass 58-62, D1000, Berlin 42, F.R.G. The assay procedure was according to the manufacturer's instructions. The TSH assay included an overnight incubation at 4-8 °C of <sup>125</sup>I-labeled monoclonal antibody and sample. Under these conditions the TSH assay had a sensitivity (detection limit) of 0.02 milli-int. unit/L and a CV of 15% at 0.15 milli-int. unit/L, 6% for higher concentrations. Our laboratory reference intervals for the three assays are:  $FT_4$  9-26 pmol/L,  $T_3$  0.9-2.3 nmol/L, and TSH 0.20-4 milli-int. units/L.

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<sup>1</sup> Nonstandard abbreviations: TSH, thyrotropin;  $FT_4$ , free thyroxin;  $T_3$ , total triiodothyronine.

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### Results and Discussion

Table 1 shows the number of TSH values  $<0.10$  milli-int. unit/L at different  $FT_4$  concentrations. TSH values  $<0.10$  milli-int. unit/L were found in patients at each  $FT_4$  concentration, and not all patients with  $FT_4$  value  $>27$  pmol/L had suppressed TSH. Below, we discuss the patients who had anomalous findings: those with TSH  $<0.10$  milli-int. unit/L in Groups 1 to 3, where the  $FT_4$  was unambiguously low or normal (the "false positives"), and those in Group 6 with high  $FT_4$  who did not have suppressed TSH (the "false negatives").

**"False positives" in Groups 1 and 2.** Clinical findings in these two groups were similar. The  $T_3$  ranged between 0.4 and 1.7 nmol/L, with one exception.

Nine of the 20 patients were very ill. An 80-year-old woman in intensive care had adult respiratory distress syndrome and died four days later. Four patients, ages 66 to 80 years, had cardiac failure, three of them having atrial fibrillation and one acute pulmonary edema. A 58-year-old man had chronic renal failure, and another 58-year-old man had perforation of the transverse colon and died. A 76-year-old woman had dementia and severe cachexia (weight 23 kg). The last, a 93-year-old woman, had diarrhea.

Of the remaining 11 patients, three had hypopituitarism; two were being treated with thyroxin. Four patients were being treated for hyperthyroidism and had high  $FT_4$  concentrations one to three months before the test. Two patients were puzzling: a 60-year-old euthyroid diabetic with a massive goiter had a  $T_3$  value of 2.9 nmol/L but normal values for free  $T_3$  by both an analog (Amersham) and a nonanalog (Henning-Berlin) assay; a 64-year-old woman who had had her toxic nodular goiter removed a year previously had normal  $FT_4$  and  $T_3$  values for 11 months before the test. We have no information on the remaining two except that one was 93 years old.

**"False positives" in Group 3.** The 14 patients in this group provide a different picture.  $T_3$  values ranged between 1.0 and 1.9 nmol/L, with one exception. All patients were well and were outpatients, except for one who had been admitted for elective surgery. One of the 14 was on treatment with thyroxin for hypopituitarism. The others were being treated for thyroid disease, two for hypothyroidism and the rest for hyperthyroidism. Four of these patients had had high  $FT_4$  concentrations one to four months before, three patients had for five to eight months before testing, and one was still "T<sub>3</sub> toxic" ( $T_3 = 2.5$  nmol/L). One puzzling case, a 76-year-old

**Table 1. Distribution of Low Thyrotropin (TSH) Values Related to Free Thyroxin ( $FT_4$ ) Concentrations**

Group	$FT_4$ , pmol/L	No. TSH assays	No. (%) with TSH $<0.10$ milli-int. unit/L
1	$<10$	120	6 (5)
2	10-14	325	14 (4.3)
3	15-19	211	14 (6.6)
4	20-23	161	27 (16.7)
5	24-26	64	27 (42)
6	$>27$	74	47 (63)
Total		955	135 (14)

woman, actually had her carbimazole dose reduced 10 months earlier because her TSH concentration was above normal. We have insufficient data on the remaining three.

"The false negatives" (Group 6). These 27 patients were all clinically euthyroid and hence perhaps true negatives. Nine were on replacement therapy with thyroxin ( $FT_4$  27–36 pmol/L,  $T_3$  1.0–2.0 nmol/L, TSH 0.1–4.9 milli-int. units/L), 11 were on amiodarone ( $FT_4$  27–34 pmol/L,  $T_3$  0.7–1.5 nmol/L; TSH 0.16–2.5 milli-int. units/L), one had familial dysalbuminemic hyperthyroxinemia. Of the remaining six patients, three had  $FT_4$  of 28–29 pmol/L and  $T_3$  of 0.7–1.6 nmol/L and perhaps represent biological variability of pituitary suppression; one had a high value for  $FT_4$ , which became normal within a day.

Two interesting patients remain. A 70-year-old woman had an  $FT_4$  change from 17 pmol/L before hypophysectomy for a chromophobe adenoma to 34 pmol/L after the operation. Her thyroxin concentration was above normal for at least three months, with  $T_3$  1.3–1.4 nmol/L and TSH 0.18–0.62 milli-int. unit/L. She was being treated with cortisone and metoprolol. The other patient was a 67-year-old man, who was on no treatment after  $^{131}I$  therapy six years earlier, and  $FT_4$  and total  $T_3$  values just above normal for all that time, while remaining euthyroid.

We have noted low TSH values at all  $FT_4$  concentrations. This finding is important because the test is used for diagnosis of hyperthyroidism. It would be difficult to argue that patients in Groups 1 and 2 with  $FT_4$  of 14 pmol or less would have had high  $FT_4$  values if a different  $FT_4$  method (e.g., equilibrium dialysis) was used. We believe that, as reported by Wehmann et al. (3), there is decreased secretion of TSH by the pituitary in very ill patients. This makes TSH assay of limited use in hospital inpatients. It is of no use, for example, to diagnose hyperthyroidism as causing atrial fibrillation in ill patients. Nor would the thyroliberin test be useful in this situation (4).

Many of the thyrotoxic patients in Groups 1, 2, and 3 who had attained low or normal  $FT_4$  concentrations with treat-

ment show evidence of long-term suppression of the pituitary, which is yet another cause of low TSH in the face of normal  $FT_4$ . In this study the duration of suppression seemed to vary from one to eight months.

Most patients (20/27) in the "false negative" group were on thyroxin or amiodarone therapy. The non-suppression of TSH in the face of high  $FT_4$  and the often-observed lag period between normalization of  $FT_4$  and TSH in patients on thyroxin for hypothyroidism has been variously attributed to non-compliance with treatment, low  $T_3$  (5), and delayed re-adaptation of the hypothalamo-pituitary axis (6). Amiodarone inhibits conversion of thyroxin to  $T_3$  in peripheral tissues and the pituitary, which leads to relatively high  $FT_4$  and low  $T_3$  with normal TSH. The normal values for TSH found in this group are supporting evidence for their clinical euthyroidism.

Our study demonstrates that a normal value for TSH very probably excludes hyperthyroidism but a low TSH is not diagnostic of hyperthyroidism in the hospital environment.

#### References

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