

# Propylthiouracil Blocks Extrathyroidal Conversion of Thyroxine to Triiodothyronine and Augments Thyrotropin Secretion in Man

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**ABSTRACT** Propylthiouracil (PTU) inhibits peripheral deiodination of thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) and decreases the metabolic effectiveness of  $T_4$  in animals. To assess the effect of PTU on extrathyroidal conversion of  $T_4$  to  $T_3$  in man, 15 studies were performed in 7 athyreotic patients treated with 100 or 200  $\mu\text{g}$  of L- $T_4$  daily for 1 mo before the addition of PTU, 250 mg every 6 h for 8 days. Serum  $T_3$ ,  $T_4$ , and thyrotropin (TSH) were measured daily by radioimmunoassay; serum TSH response to 500- $\mu\text{g}$  thyrotropin-releasing hormone (TRH) was measured before and on the last day of giving PTU.

On the 100- $\mu\text{g}$  L- $T_4$  dose, serum  $T_3$  fell from  $120 \pm 5$  (SE) to  $83 \pm 6$  ng/dl ( $P < 0.005$ ) with return to  $113 \pm 5$  ng/dl after stopping PTU; serum  $T_4$  ( $4.5 \pm 0.3$   $\mu\text{g}/\text{dl}$ ) did not change. Similar results were seen in patients taking 200  $\mu\text{g}$  of L- $T_4$  daily. On the 100- $\mu\text{g}$  dose of L- $T_4$  the fall in  $T_3$  was accompanied by a reciprocal rise in serum TSH to  $195 \pm 33\%$  of initial concentration ( $P < 0.01$ ) with return to  $104 \pm 8\%$  after PTU. The serum TSH response to TRH ( $\Delta\mu\text{U}/\text{ml}$  over base line) was greater during PTU therapy than during the control period. On 100- $\mu\text{g}$  L- $T_4$ ,  $\Delta\text{TSH}$  rose from  $64 \pm 19$  to  $101 \pm 23$   $\mu\text{U}/\text{ml}$  ( $P < 0.005$ ). Expressed as percent of base-line TSH concentration, TSH rose from  $140 \pm 52$  to  $280 \pm 44\%$  (control vs. PTU) at 15 min,  $265 \pm 72$  to  $367 \pm 63\%$  at 30 min,  $223 \pm 54$  to  $313 \pm 54\%$  at 45 min,  $187 \pm 45$  to  $287 \pm 51\%$  at 60 min, and  $145 \pm 22$  to  $210 \pm 28\%$  at 120 min after TRH.

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The data suggest that PTU blocks extrathyroidal conversion of  $T_4$  to  $T_3$ , thus increasing pituitary TSH secretion and augmenting the TSH response to TRH.

## INTRODUCTION

Antithyroid drugs of the thiocarbamide type, such as propylthiouracil (PTU),<sup>1</sup> have been used for the treatment of hyperthyroidism for over 30 yr. PTU appears to exert its primary effect on the synthesis of the thyroid hormones, thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ), by blocking oxidative iodination within the thyroid gland itself (1, 2). In addition, some of the thiocarbamides alter the metabolism of thyroid hormones outside of the thyroid gland by interfering with the peripheral deiodination of  $T_4$  and  $T_3$  in experimental animals (3-10) and in man (10-13). This extrathyroidal action is independent of the first effect (14). The inhibition of peripheral deiodination is associated with a decrease in the biologic effectiveness of administered  $T_4$  as measured by a decrease in metabolic rate or induction of oxidative enzymes in vivo (15-20) and in vitro (21-23) and an increase in thyrotropin (TSH) secretion (24-28). The thiocarbamide drugs that decrease  $T_4$  deiodination are the ones that also decrease its metabolic effectiveness (14). These same drugs also decrease  $T_3$  deiodination but have no effect on the biologic effectiveness of  $T_3$  or actually potentiate it (5, 14, 19).

Since the reintroduction of the concept that a sig-

<sup>1</sup>Abbreviations used in this paper: CPB, competitive protein binding; PBI, protein-bound iodine; PTU, propylthiouracil; RIA, radioimmunoassay; TRH, thyrotropin-releasing hormone; TSH, thyrotropin;  $T_3$ , triiodothyronine;  $T_4$ , thyroxine.

nificant amount of  $T_3$  is produced by the peripheral deiodination of  $T_4$  (29), interest has arisen in the clinical effects of PTU on the peripheral metabolism of  $T_4$ . Oppenheimer, Schwartz, and Surks (23) have demonstrated that PTU decreases the calculated rate of conversion of  $T_4$  to  $T_3$  in thyroidectomized  $T_4$ -treated rats. We have investigated the effect of PTU on the serum concentrations of  $T_3$ ,  $T_4$ , and TSH, and the TSH response to thyrotropin-releasing hormone (TRH) in athyreotic patients maintained on L- $T_4$ .

## METHODS

**Subjects.** 16 studies were carried out on 7 totally athyreotic male patients. Six patients had had total surgical thyroidectomies followed by ablative doses of radioactive iodine, and one patient had idiopathic myxedema. Proof of the athyreotic state was based on lack of significant radioiodine uptake and no evidence of its accumulation on scan, serum  $T_4$  less than 1  $\mu\text{g}/\text{dl}$  and  $T_3$  less than 50 ng/dl, and lack of  $T_4$  or  $T_3$  elevation in response to the TRH-mediated rise of serum TSH concentration.

Three patients had atherosclerotic cardiovascular disease, one of whom was taking digoxin during the time of study. One patient had a transitional cell carcinoma of the bladder resected a year before the study with no evidence of recurrence or of renal insufficiency. One patient had Parkinson's disease and was taking L-dopa and trihexyphenidyl hydrochloride during the study. None of the others was taking any medication known to affect thyroidal or pituitary function. The patients gave their informed consent to participate in the studies.

All patients were treated daily with 100  $\mu\text{g}$  of a commercial preparation of sodium levothyroxine (L- $T_4$ ) for at least 1 mo before admission to the metabolic unit. In addition, five of the patients were restudied after they had been taking 200  $\mu\text{g}$  of L- $T_4$  daily for at least 1 mo. A single commercial preparation of L- $T_4$  (lot ZE040) was kindly supplied by Flint Labs., Morton Grove, Ill., and used throughout the study. The  $T_3$  content was 0.76% (by weight) of the  $T_4$  content.

Bloods were collected daily for determination of serum TSH,  $T_4$ , and  $T_3$  during hospitalization. The patients' white cell counts and liver function were also monitored. After a control period of several days to determine basal concentrations, the L- $T_4$ -treated patients were given PTU, 250 mg every 6 h, for 8 days. TSH,  $T_4$ , and  $T_3$  concentrations were also determined before, and on the 7th day of, PTU treatment at 2, 6, 10, and 14 h after administration of the L- $T_4$  dose. TRH testing of pituitary TSH responsiveness was carried out at least once before, and on the last day of, PTU administration.

**Serum determinations.**  $T_3$  (30) and TSH (31) were measured by radioimmunoassay (RIA).  $T_4$  was determined by both RIA (32) and competitive protein binding (CPB) (33). Protein-bound iodine (PBI) (done by Bio-Science Laboratories, Van Nuys, Calif.), total protein, albumin, and  $T_3$  resin index (using the Thyopac-3 of Amersham/Searle Corp., Arlington Heights, Ill.) were determined on selected sera.

**Infusions.** Synthetic TRH was kindly supplied by Abbott Laboratories, North Chicago, Ill. It was administered in the morning after an overnight fast. A 19-gauge butterfly needle was inserted in an antecubital vein for collection of blood specimens 15 min before, at the time of, and 15, 30,

45, 60, 120, and 240 min after injection of a 500- $\mu\text{g}$  bolus of TRH.

**Statistics.** Change in serum concentrations of  $T_3$ ,  $T_4$ , and TSH were evaluated for significance by the method of paired *t* testing (34).

## RESULTS

**Effect of PTU on  $T_3$ ,  $T_4$ , and TSH.** Fig. 1 shows the response to PTU in a typical patient taking 100  $\mu\text{g}/\text{day}$  of L- $T_4$  and a month later 200  $\mu\text{g}/\text{day}$  of L- $T_4$ . Fig. 2 depicts the average daily  $T_3$ ,  $T_4$ , and TSH concentrations during nine studies in the patients taking 100  $\mu\text{g}$  of L- $T_4$  each day. Serum  $T_3$  concentration decreased significantly after the 2nd day of PTU administration.  $T_3$  fell from a mean of  $120 \pm 5$  (SE) to  $83 \pm 6$  ng/dl by the 7th day on PTU ( $P < 0.005$ ). After discontinuation of PTU,  $T_3$  rose rapidly to initial serum concentrations ( $113 \pm 5$  ng/dl). Serum  $T_4$  concentrations did not change significantly, remaining at about  $5.5 \pm 0.3$  (by RIA) or  $4.5 \pm 0.2$   $\mu\text{g}/\text{dl}$  (by CPB). Average serum PBI was  $4.6 \pm 0.5$  before PTU and  $4.9 \pm 0.5$   $\mu\text{g}/\text{dl}$  on the 7th day of PTU. Serum TSH rose to  $195 \pm 33\%$  of average basal TSH concentrations during PTU ad-

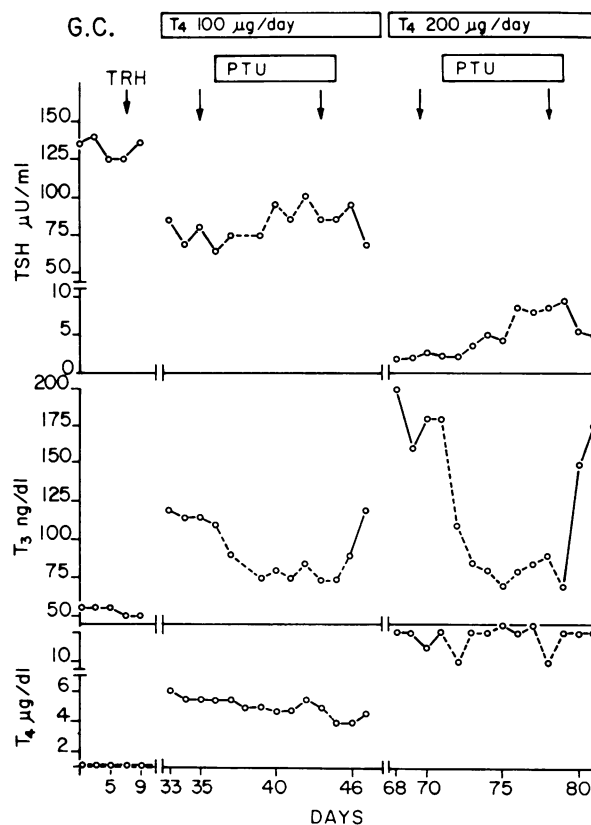


FIGURE 1 The effect of PTU 250 mg every 6 h on daily serum TSH,  $T_3$ , and  $T_4$ , measured by RIA in an athyreotic patient who had been receiving 100 and then 200  $\mu\text{g}$  of L- $T_4$  a day for 1 mo before study. Arrows indicate tests with TRH.

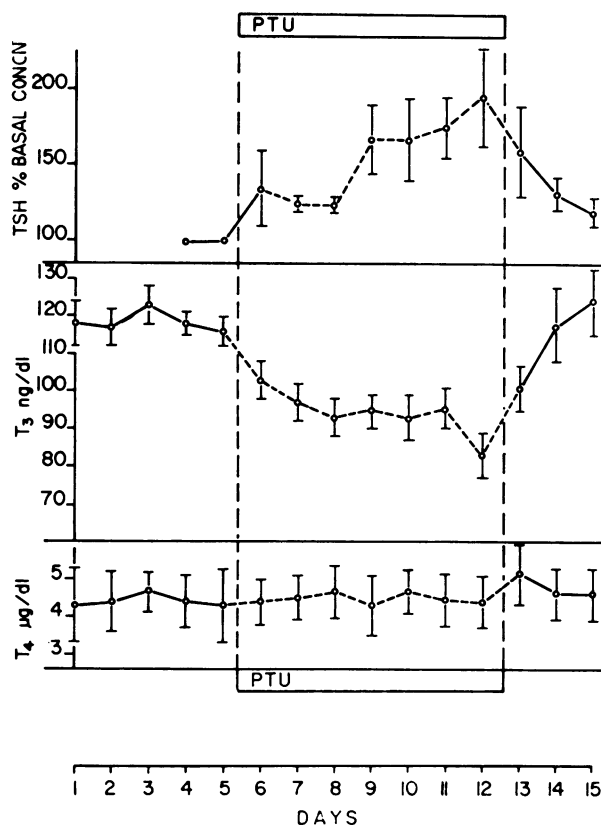


FIGURE 2 The effect of PTU 250 mg every 6 h on average daily serum concentrations of TSH,  $T_3$ , and  $T_4$  measured by RIA during nine studies in athyreotic patients who had been receiving 100  $\mu\text{g}$  of L- $T_4$  a day for 1 mo before study. Vertical bars represent SE.

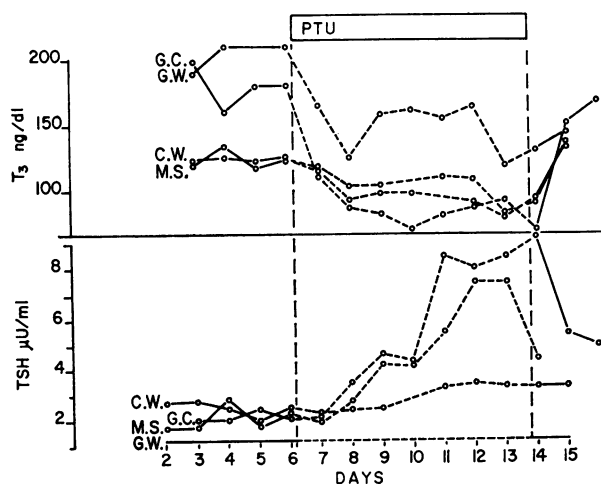


FIGURE 3 The effect of PTU 250 mg every 6 h on daily serum concentrations of  $T_3$  and TSH in four athyreotic patients who had been receiving 200  $\mu\text{g}$  of L- $T_4$  a day for 1 mo before study.

ministration. Based on analysis by paired *t*-testing of individual values in microunits per milliliter on the 5th and 12th days of the protocol, there was a significant increment in serum TSH ( $P < 0.01$ ). TSH returned to basal concentrations ( $104 \pm 8\%$ ) upon discontinuation of PTU.

Fig. 3 depicts individual values of several of the patients taking 200  $\mu\text{g}$  of L- $T_4$  a day whose serum TSH concentrations were detectable in our assay.  $T_3$  fell from a mean of  $150 \pm 19$  to  $97 \pm 9$  ng/dl during PTU administration. Serum  $T_4$  concentration (RIA) rose from 10.5 to 11.5  $\mu\text{g}/\text{dl}$ ; this change was not significant in this small group of patients. There was no change in serum PBI or  $T_3$  resin uptake before and during PTU administration in either group.

*Effect of PTU on TSH response to TRH.* Fig. 4 shows the TSH response to TRH during eight studies carried out in the patients taking 100  $\mu\text{g}$  of L- $T_4$  a day. Expressed as a percent of initial TSH concentrations, the TSH response in the control period compared with the response during PTU administration was significantly augmented from  $140 \pm 52$  to  $280 \pm 44\%$  at 15 min;  $265 \pm 72$  to  $367 \pm 63\%$  at 30 min;  $223 \pm 54$  to  $313 \pm 54\%$  at 45 min;  $187 \pm 45$  to  $287 \pm 51\%$  at 60 min, and  $145 \pm 22$  to  $210 \pm 28\%$  at 120 min after TRH. The  $\Delta\text{TSH}$ , defined as the maximal increase in TSH above basal TSH concentration, rose from  $64 \pm 19$  before PTU to  $101 \pm 23$

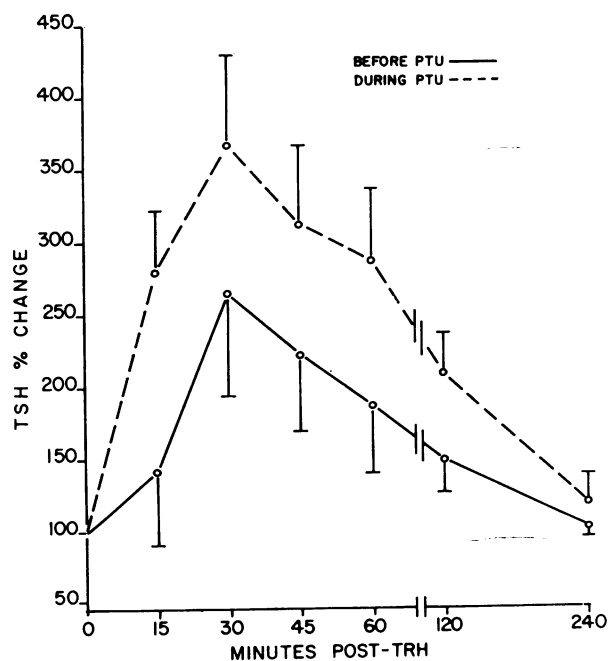


FIGURE 4 The effect of PTU 250 mg every 6 h for 8 days on the TSH response to TRH (500- $\mu\text{g}$  i.v. bolus) during eight studies in athyreotic patients who had been receiving 100  $\mu\text{g}$  of L- $T_4$  a day for 1 mo before study. Vertical bars represent SE.

$\mu\text{U/ml}$  during PTU administration ( $P < 0.005$ ). Similar findings of augmented TSH response to TRH are depicted in Fig. 5 for three patients who had detectable levels of TSH while taking 200  $\mu\text{g}$  of L-T<sub>4</sub> a day.

### DISCUSSION

PTU significantly decreased serum T<sub>3</sub> concentrations in the athyreotic patients taking 100 or 200  $\mu\text{g}$  of L-T<sub>4</sub> a day. The fall in serum T<sub>3</sub> derived exclusively from administered T<sub>4</sub> is consistent with the PTU-induced decrease in total deiodination of T<sub>4</sub> previously described in experimental animals (3–10) and in man (10–13). In clinical studies of the metabolism of [<sup>125</sup>I]T<sub>4</sub>, PTU decreased the urinary excretion of urinary <sup>125</sup>I by 30–40%, increased hepatic accumulation of <sup>125</sup>I, increased biliary secretion and fecal excretion of organic <sup>125</sup>I by 40–70%, raised PBI and [<sup>125</sup>I]PBI slightly, and decreased the rate of disappearance of [<sup>125</sup>I]PBI from the serum (10–14). Another mechanism to explain our findings might be that PTU increases the metabolic clearance of T<sub>3</sub>. Oppenheimer et al. (23) showed that PTU reduced the calculated rate of conversion of T<sub>4</sub> to T<sub>3</sub> in thyroidectomized rats and also reduced the fractional rate of deiodination of both T<sub>3</sub> and T<sub>4</sub>. To conclusively establish the mechanism for the reduction of serum T<sub>3</sub> induced by PTU in man, direct kinetic analysis of T<sub>4</sub> and T<sub>3</sub> metabolism must be carried out.

The PTU-induced decrease in the peripheral deiodination of T<sub>4</sub> to T<sub>3</sub> has been shown to be associated with a decrease in biologic activity of T<sub>4</sub> in vivo (15–20) and in vitro (21–23). Methimazole and other thiocarbamide drugs which do not affect the deiodination of T<sub>4</sub> do not interfere with its metabolic effectiveness (14). This extrathyroidal effect of PTU probably contributes to its effectiveness in the treatment of hyperthyroidism. Abuid and Larsen (35) demonstrated a significantly greater fall in T<sub>3</sub> concentration and T<sub>3</sub>/T<sub>4</sub> ratio in hyperthyroid patients being treated acutely with PTU plus iodine compared with those treated with methimazole plus iodine suggesting that the inhibition of T<sub>4</sub> to T<sub>3</sub> conversion by PTU may play a significant role in its therapeutic effectiveness.

We did not measure absolute free thyroid hormone concentrations. However, it has been shown previously that PTU has no effect on thyroid hormone binding to human plasma proteins (10, 13). There was no significant change in T<sub>3</sub> resin uptake or plasma protein concentration during PTU administration in our patients.

The increase in basal concentrations of serum TSH and the increased TSH response to TRH associated with the decrease in serum T<sub>3</sub> is of great interest. It occurred at a time when there was no significant change in serum T<sub>4</sub> concentration. Previous investigators have shown that PTU administration increased the amount of bioassayable TSH in the serum of thyroidectomized

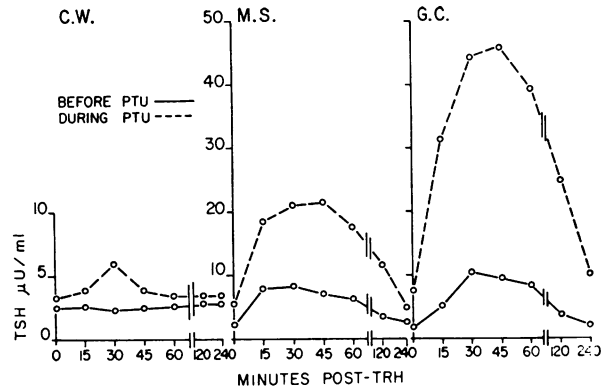


FIGURE 5 The effect of PTU 250 mg every 6 h for 8 days on the TSH response to TRH (500- $\mu\text{g}$  i.v. bolus) in three athyreotic patients who had been receiving 200  $\mu\text{g}$  of L-T<sub>4</sub> a day for 1 mo before study.

animals maintained on L-T<sub>4</sub> replacement at a time when serum PBI was unchanged or actually increased (24–28). In our patients, there was no significant change in PBI or T<sub>4</sub> (CPB or RIA) during PTU treatment in agreement with the findings of other clinical studies (14). The 30% decrease in serum T<sub>3</sub> concentration is equivalent to about 14  $\mu\text{g}$  of T<sub>3</sub>, assuming a volume of distribution of 35 liters for T<sub>3</sub>. In athyreotic patients, this would arise from 16  $\mu\text{g}$  of administered T<sub>4</sub>. Since T<sub>4</sub> has a volume of distribution of 10 liters, the increment in T<sub>4</sub> would be only 0.15  $\mu\text{g}/\text{dl}$ , or about a 3% rise in serum T<sub>4</sub>, a change which is too small to be detected reliably because of the variability of the measurement of serum T<sub>4</sub>.

Intravenous administration of TRH results in a prompt rise in serum TSH (36, 37). This response is also regulated by the circulating concentrations of thyroid hormones (38). The relative contributions of serum T<sub>4</sub> and T<sub>3</sub> concentrations to this regulation have not been defined precisely, in part, because of the conversion of T<sub>4</sub> to T<sub>3</sub> in peripheral tissues (29). Recent studies show that pituitary nuclei possess high affinity, low capacity binding sites for iodothyronines; the affinity of the binding site for T<sub>3</sub> is much greater than that for T<sub>4</sub> (39, 40). Presumably this specific binding plays a role in the control of pituitary TSH secretion.

When patients with primary hypothyroidism who have low circulating levels of thyroid hormone, high serum TSH, and exaggerated TSH response to TRH are fed small doses of L-T<sub>4</sub> plus L-T<sub>3</sub> in increasing amounts, there is eventual obliteration of the TSH response to TRH at a time when serum T<sub>3</sub> concentrations increase and before there is a significant increase in serum T<sub>4</sub> concentrations (41). Conversely, treatment of hyperthyroid patients who have elevated serum concentrations of T<sub>4</sub> and T<sub>3</sub> with antithyroid drugs has been reported to result in a return of TSH responsiveness

to TRH at a time when in some patients serum  $T_4$  is elevated but  $T_3$  has fallen to normal concentrations (42). Our findings are consistent with these observations. In our patients presumed blockade of deiodination of the administered L- $T_4$  to  $T_3$  resulted in increasing serum TSH concentration and augmentation of the TSH response to TRH at a time when serum  $T_3$  concentration fell, but  $T_4$  concentration remained unchanged. The TSH response was relatively consistent in those patients who were tested with TRH on two occasions before administration of PTU. Thus the larger response during administration of PTU is not attributable to the previous test with TRH.

We cannot completely exclude a direct stimulatory effect of PTU on TSH release by the pituitary. Bioassay data concerning the effect of thiocarbamides on thyroid hormone suppression of TSH release from the pituitary indicate that, although PTU decreases the effectiveness of a given dose of L- $T_4$ , it has no effect on the ability of L- $T_3$  to suppress TSH release (14). Therefore we suggest that the augmentation in basal TSH level and the TSH response to TRH in our patients was most likely due to the fall in serum  $T_3$  concentration caused by the effect of PTU on blocking the peripheral conversion of  $T_4$  to  $T_3$ . Our data are consistent with the hypothesis that  $T_3$  is more important than  $T_4$  for modulation of pituitary TSH secretion.

*Addendum.* Saberi, Sterling, and Utiger (43) have recently presented findings similar to those reported here.

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