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Research Article

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Triiodothyronine and Thyroxine in Hyperthyroidism

COMPARISON OF THE ACUTE CHANGES DURING THERAPY WITH ANTITHYROID AGENTS

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ABSTRACT In 66 untreated patients with hyperthyroidism, serum triiodothyronine (T_3) and thyroxine (T_4) concentrations were measured by immunoassay. The mean T_3 level was 478±28 ng/100 ml (all values mean±SEM) and the T_4 was 20.6±0.6 μg/100 ml. The serum T_4/T_3 ratio by weight was 48±2 as opposed to a value of 71±3 in euthyroid adults. There was a significant inverse correlation of the T_4/T_3 ratios with serum T_3 ($r = 0.77$; $P < 0.01$) but not with serum T_4 ($r = 0.21$). These results suggested that relative overproduction of T_3 is consistently present in patients with hyperthyroidism.

To examine the acute effects of various antithyroid agents on serum T_3 and T_4 concentrations, iodide, propylthiouracil (PTU), and methylmercaptoimidazole (MMI) were given alone to nine patients, and serial T_3 and T_4 measurements were made. There was an acute decrease in serum T_3 over the first 5 days in the three iodide and three PTU-treated patients which was greater than that seen in the MMI group. This suggested that PTU and MMI had different effects on T_3 production.

To compare the effects of PTU and MMI under conditions in which thyroidal hormone release was minimized, these drugs were given in combination with iodide. The mean daily dosage of PTU was 827 ($n = 11$) and of MMI was 88 ($n = 8$). In the PTU + iodide group, the initial serum T_3 concentration was 586±61 ng/100 ml and decreased significantly to 326±41 on day 1 and to 248±21 and 231±20 on days 2 and 3, respectively, and did not change further on days 4 and 5. In the MMI + iodide group, basal serum T_3 was 645±90 ng/100 ml and decreased to 568±81, 452±73, and 344±51 on days 1, 2, and 3, respectively, and did not change thereafter. While the initial T_3 concentrations in serum were not different in the PTU and MMI groups, the T_3 concentrations in the PTU patients were significantly lower on days 1 and 2 and during the apparent plateau period on days 3–5. Serum T_4 concentrations decreased gradually in both groups, from 23.9±2.0 μg/100 ml, initially, to 17.5±1.6 on day 5 in the PTU group and from 22.0±2.6 to 14.6±2.0 in the MMI-treated patients. The T_4 values were not significantly different at any time. These changes resulted in increases in the serum T_4/T_3 ratios in both groups, but these ratios were substantially higher in the patients treated with PTU + iodide. The initial serum T_4/T_3 ratio was 43±3 and increased to 74±7 and 88±7 on days 1 and 2 in the PTU group, reaching a plateau value of 91±7 during days 3–5. Comparable values for MMI-treated patients were 35±2, 42±3, 52±6, and 54±3 during the plateau period.

Previous investigations have shown that PTU inhibits T_4 deiodination in hyperthyroid patients and decreases T_3 production from T_4 in animals. The greater acute decrease in serum T_3 and the higher serum T_4/T_3 ratios in the PTU-treated patients seems best explained by an inhibition of peripheral T_3 production by this agent. This conclusion is further supported by a direct relationship between the T_4/T_3 ratio on days 3–5 and the dose of PTU administered. These results further suggest that both thyroidal and extrathyroidal pathways contribute substantially to the apparent overproduction of T_3 in hyperthyroidism.

INTRODUCTION

There is increasing evidence that triiodothyronine (T_3)[1] plays an important role in normal thyroid physiology. It has even been speculated that thyroxine (T_4) exerts

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[1] *Abbreviations used in this paper:* MMI, methylmercaptoimidazole; PTU, propylthiouracil; SSKI, saturated solution of potassium iodide; T_3, triiodothyronine; T_4, thyroxine.

little metabolic effect unless it is deiodinated to T_3 in the peripheral tissues (1). Although thyrotoxicosis is most commonly associated with increases in circulating levels of both T_4 and T_3, review of the available studies indicates that the concentration of the latter is generally elevated to a greater extent than is T_4 (2). The mechanism of this disproportionate increase in T_3 and its metabolic implications are not clearly understood. Since serum T_3 elevations appear to be consistently present in hyperthyroid patients and since T_3 may be the active form of thyroid hormone, it was of interest to document the changes in its concentration during therapy with commonly used antithyroid agents. In addition, the half-life of T_3 is short so that inhibition of T_3 production should be rapidly reflected in decreases in serum hormone concentrations. Preliminary studies from this laboratory have indicated that substantial changes in circulating T_3 may occur within 24 h of initiation of therapy (3). The studies reported below were performed to compare changes in T_3 and T_4 levels during the early time periods after starting treatment with propylthiouracil (PTU) or methylmercaptoimidazole (MMI) alone or in combination with iodide.

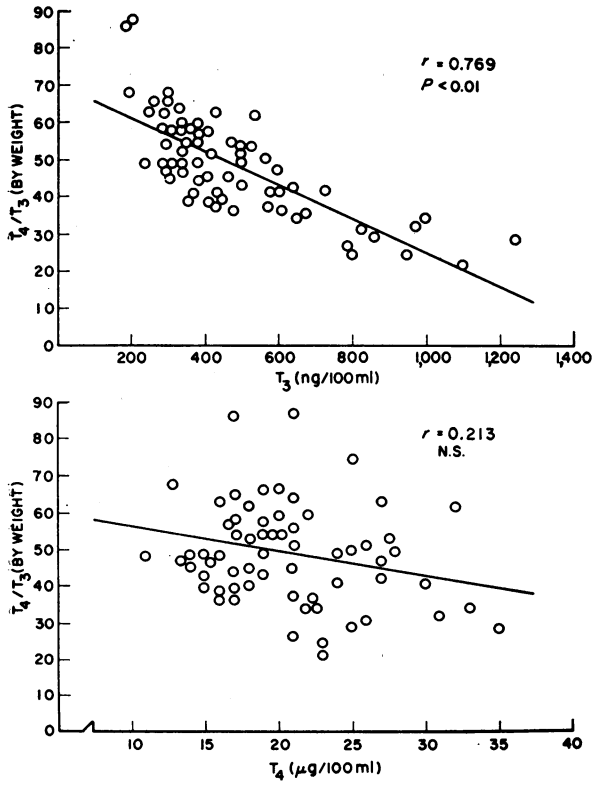

FIGURE 1 Correlation between serum T_4/T_3 ratios (by weight) and the concentration of T_3 and T_4 in the serum of 66 untreated hyperthyroid subjects. T_3 and T_4 were measured in the same sample.

METHODS

The patients employed in this study were clinically and chemically hyperthyroid. All were hospitalized at the University of Pittsburgh Health Center Hospitals. In 66 patients serum T_3 and T_4 concentrations were measured before treatment by radioimmunoassay techniques described previously (4, 5). 28 patients with Graves' Disease were studied during therapy while inpatients either in the Clinical Research Unit or the medical wards of the Presbyterian-University Hospital or V. A. Hospital. These patients were given various drug regimens on a random basis. All drugs were administered orally every 6 or 8 h with one exception where NaI was administered intravenously. Collection of blood samples was performed at two different times before therapy and every 12–24-h after initiation of therapy and for 5 days in most cases. The samples were allowed to clot, and the serum was separated and frozen until assayed. Serial determinations of T_3 and T_4 were performed in duplicate, at two dilutions, in the same assay for each patient, and at least in two different assays. T_4/T_3 ratios were calculated on a weight basis. The study groups were as follows:

(*a*) PTU, MMI, or iodide alone. Nine patients were studied during therapy with either PTU (three), MMI (three), or iodide alone (three). Mean daily doses were 817 mg (range 750–900 mg) for PTU, 80 mg (range 60–90) for MMI, and 15 gtt. of saturated solution of potassium iodide (SSKI) in the three patients receiving iodide.

(*b*) PTU or MMI in combination with iodide. 19 patients were studied in this group. 11 received PTU + iodide and eight received MMI + iodide. Mean daily doses were 827 mg (range 300–1,600 mg) for the PTU group and 88 mg (range 75–120) for the MMI group. Iodides were usually given as SSKI, 5 gtt. every 8 h.

RESULTS

Serum T_3, T_4, and T_4/T_3 ratios in untreated thyrotoxicosis. The mean T_3 and T_4 concentrations in the serum of 66 untreated hyperthyroid patients were 478± 28 ng/100 ml and 20.6±0.6 µg/100 ml.[2] In virtually all patients the circulating levels of these two hormones are increased, but greater increases in T_3 were apparent in most. As a result, in all but two of the subjects studied the T_4/T_3 ratio in serum is lower than the mean value of 71±3 which we have observed in euthyroid subjects (2). The mean T_4/T_3 ratio in the hyperthyroid subjects was 48±2. When the T_4/T_3 ratios are plotted against the concentrations of either T_3 or T_4 in the same specimen, there is a significant inverse correlation between the T_4/T_3 ratios and the concentration of T_3 (Fig. 1). In contrast, there is no significant correlation between T_4/T_3 ratios and T_4. These findings indicate that increases in circulating T_3 in hyperthyroidism are not accompanied by proportionately large increases in serum T_4.

Acute changes in serum T_3, T_4, and T_4/T_3 ratios in hyperthyroid patients treated with iodide, MMI, or PTU

[2] All values are given as mean±SEM unless indicated.

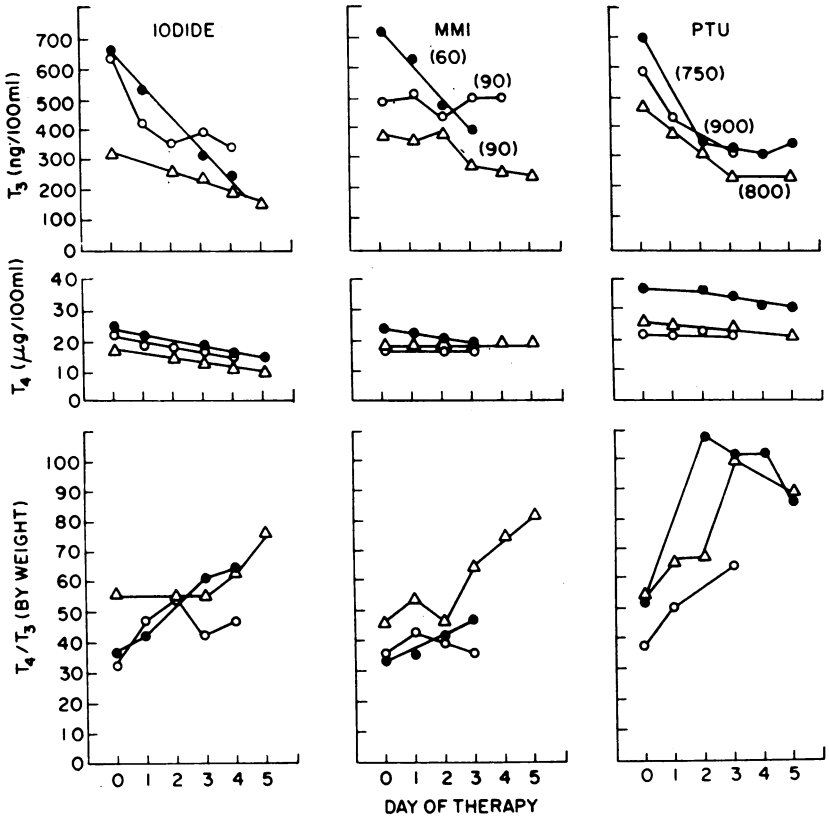

FIGURE 2 Serum T_3, T_4, and T_4/T_3 ratios in hyperthyroid subjects treated with iodide, MMI, or PTU alone. Numbers in parentheses are the daily dosages. Iodide was given as SSKI 5 gtt. q. 8 h in the three subjects shown.

alone. In Fig. 2 are shown results of preliminary studies performed to explore the quantitative changes in T_3 and T_4 in patients receiving these agents. With iodide therapy, there is an acute decrease in circulating T_3 to 50% of the initial level by day 4. T_4 values are also significantly lower on day 4, but the decrease is only to 70% of control levels. The mean T_4/T_3 ratio at 4 days was 58 compared to 42 initially. The more rapid decrease in serum T_3 than in serum T_4 was anticipated following inhibition of thyroidal secretion since the half-life of T_3 is considerably shorter than T_4. Therefore, the increase in the T_4/T_3 is consistent with an acute inhibition of thyroidal secretion which has been previously demonstrated to occur during iodide administration to hyperthyroid subjects (6, 7). The failure of serum T_3 to fall to normal levels is presumably a reflection of both incomplete inhibition of thyroidal release as well as persistence of T_3 production from T_4 in the periphery.

With MMI therapy the pattern of changes varies. In one patient there is an acute decrease in serum T_3 to about 55% of the initial level by day 3 and an associated decrease in serum T_4 of less magnitude. In the other two patients, a slight decrease in T_3 levels to about 70% of the initial level was seen in one, no change in T_3 in the other, and neither showed significant changes in T_4. The heterogeneity of the response pattern of these patients to MMI is not surprising since this drug inhibits synthesis of thyroid hormones but has no effect on the release of previously formed hormonal stores. Since these may vary quantitatively in different individuals with hyperthyroidism, early changes in serum T_3 and T_4 concentrations during treatment with MMI would be expected to vary accordingly.

During treatment with PTU the decreases in serum T_3 concentrations were more uniform. Mean serum T_3 concentrations decreased significantly to 50% of the initial level on day 3. The decreases in serum T_3 occurred in the absence of significant decreases in serum T_4 and are reflected in marked acute increases in the T_4/T_3 ratios. The uniformity of the response to PTU and the magnitude of the decrease in serum T_3 concentrations suggested an effect different from that of MMI.

Previous studies have indicated that PTU inhibits peripheral deiodination of T_4 in hyperthyroid subjects (8, 9). Since this effect of PTU is associated with inhibition of T_3 production in animals, it seemed possible

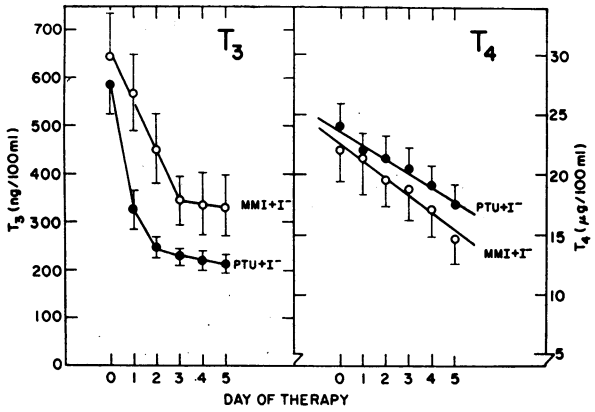

FIGURE 3 Serum T_3 and T_4 in hyperthyroid subjects treated with PTU or MMI in combination with iodide. Values are the mean±SEM of 11 subjects for PTU + iodide and eight subjects for MMI + iodide. The line joining the T_4 values was determined by least squares analysis of the regression curve.

that a similar mechanism could account for the acute decreases in serum T_3 seen in these patients (10). Therefore, we examined this possibility under conditions where the qualitative and quantitative contributions of secretion of preformed hormones was minimized by the concomitant administration of iodide. MMI, which has not been shown to have a peripheral effect in man, provided a control for the antithyroid effect of PTU (11, 12).

Acute changes in serum T_3 and T_4 in hyperthyroid patients treated with PTU or MMI combined with iodide. The effect of treatment of hyperthyroid patients with the combination of PTU or MMI with iodide is shown in Fig. 3, and the individual data are presented in Table I. Mean initial serum T_3 and T_4 concentrations were similar in both groups. Statistically significant differences in serum T_3 concentrations were observed on days 1 and 2, with greater decreases in serum T_3 obtained with PTU + iodide. In this group, mean initial T_3 was 586 ng/100 ml and fell to 326 in the first 24 h of treatment ($P < 0.001$). A decrease of similar magnitude was not observed until day 3 in the MMI + iodide group. A further decrease in T_3 concentration was observed in the PTU + iodide group on day 2, and during days 3–5 the T_3 levels were significantly lower than the initial levels but were not significantly different from each other. A similar plateau was observed on days 3–5 in the MMI + iodide group. The mean serum T_3 concentration during that period was 364±57 ng/100 ml for MMI + iodide and 225±18 for PTU + iodide ($P < 0.025$ for days 3–5 combined).

In contrast to serum T_3, T_4 concentrations in serum decreased gradually in both groups. The similar rates of fall in both groups resulted in mean values that were not significantly different at any point during the study period. The apparent half-time for the decrease in serum T_4 was 10 days in the PTU + iodide group and 8 days in the MMI + iodide group as determined by least squares analysis of the regression curves.

Comparison of the acute changes in the serum T_4/T_3 ratios. The simultaneous changes in serum T_3 and T_4 resulted in marked acute increases in the T_4/T_3 ratios in the patients receiving PTU + iodide (Fig. 4). In this group, there was an increase from 43±3 initially to 74±7 and 88±7 on days 1 and 2, respectively, after which an apparent mean plateau value of 91±7 was observed on days 3–5. In the MMI + iodide group, the mean initial T_4/T_3 ratio of 35±2 was not significantly different from the initial value in the PTU + iodide group. The T_4/T_3 ratios of 42±3 and 45±3 on days 1 and 2 and the plateau

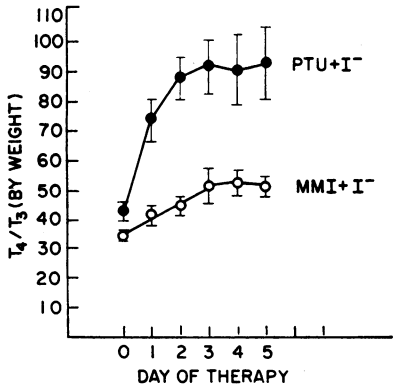

FIGURE 4 Serum T_4/T_3 ratios in hyperthyroid subjects during treatment with PTU or MMI in combination with iodide. Values represented are the mean±SEM.

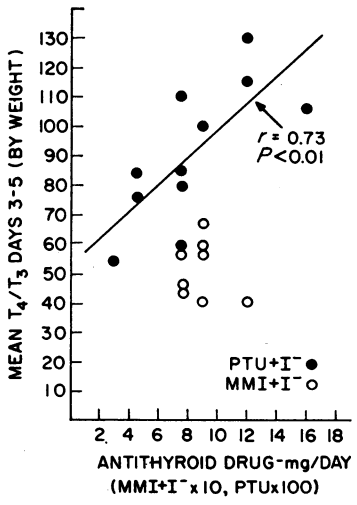

FIGURE 5 Correlation between the mean serum T_4/T_3 ratios on days 3–5 of therapy in individual patients and the dose of PTU or MMI. Linear regression was determined by least squares analysis.

TABLE I

T_3 and T_4 during Treatment of Hyperthyroidism with PTU or MMI in Combination with Iodide

Subject	T_3 Day of therapy 0	1	2	3	4	5	T_4 Day of therapy 0	1	2	3	4	5	Daily dose
	ng/100 ml						*μg/100 ml*						*mg**
						PTU + Iodide							
F. B.	935	635	239	256	216	254	25.6	24.4	23.1	21.7	19.6	20.2	750
W. K.	913	294	268	255	275	—	40.0	29.6	29.7	29.8	25.9	—	1,600
C. H.	700	512	—	—	266	—	24.3	24.3	—	—	15.6	—	750
B. R.	659	211	194	—	—	158	24.6	21.8	19.2	—	—	18.2	1,200
M. F.	584	309	237	215	—	—	27.2	24.1	24.5	21.4	—	—	900
K. P.	570	326	255	238	—	—	20.4	21.0	18.0	18.0	—	—	450
E. J.	529	415	382	370	331	313	24.9	27.6	27.9	25.2	24.6	22.9	450
E. C.	495	271	236	261	245	263	24.1	21.8	20.8	21.0	20.2	19.6	750
C. O.	414	260	243	198	194	190	15.2	11.9	11.7	11.2	10.4	9.6	300
T. K.	353	164	163	114	149	—	18.6	16.5	17.1	16.6	16.9	16.4	1,200
M. B.	326	236	—	203	130	166	18.3	17.7	—	18.5	18.9	15.6	750
Mean	586	326	248	231	221	214	23.9	21.9	21.3	20.4	19.0	17.5	827
SEM	61	41	21	20	21	19	2.0	1.5	1.9	1.8	1.7	1.6	115
						MMI + Iodide							
M. P.	965	839	586	586	410	373	31.7	30.6	24.5	22.9	19.7	20.3	75
E. H.	923	653	575	463	—	—	31.1	34.1	27.8	26.5	—	—	90
W. K.	829	885	849	—	694	679	28.2	—	27.5	28.3	28.2	—	120
B. B.	778	600	432	343	230	368	20.0	21.1	19.3	18.9	16.4	19.8	90
M. C.	490	394	309	237	252	282	20.2	17.3	17.9	18.6	16.9	15.8	90
J. M.	451	585	336	313	334	236	14.1	19.8	14.5	11.6	14.7	10.0	90
C. G.	413	310	311	243	244	209	18.2	15.7	15.9	14.1	13.5	12.3	75
S. P.	314	278	207	218	206	198	12.6	11.3	9.6	9.0	9.6	9.1	75
Mean	645	568	452	344	339	335	22.0	21.4	19.6	18.7	17.0	14.6	88
SEM	90	81	73	51	65	63	2.6	3.1	2.3	2.5	2.2	2.0	5
P‡	NS	<0.025	<0.025	NS§	NS§	NS§	NS	NS	NS	NS	NS	NS	

* Iodide was given as SSKI, 5 gtt. q. 8 h except as follows: B. R. received NaI i.v., 1 g for 2 days; E. H. received 3 ml SSKI per day; and M. C. received KI 750 mg q. 8 h.

‡ Unpaired t test for PTU vs. MMI groups. NS = $P > 0.05$.

§ For days 3–5 combined, mean T3 levels are lower in PTU group ($P < 0.025$).

value of 52±3 were all significantly lower than the values in the former group ($P < 0.005$ for day 1; $P < 0.001$ for day 2, and $P < 0.001$ for days 3–5). These results suggest that the larger acute decreases in serum T_3 on days 1 and 2 during PTU + iodide therapy cannot be explained adequately either by inhibition of thyroid hormone secretion by iodide or by the antithyroid effect of PTU alone. The abrupt increase in the T_4/T_3 ratio suggests that there is inhibition of peripheral deiodination of T_4.

Correlation of the "plateau" T_4/T_3 ratio and dose of antithyroid agent. If PTU inhibits peripheral T_3 production, then a dose-response relationship might be anticipated between the amount of drug given and the T_4/T_3 ratio. As mentioned above, after the acute increases in the first 2 days, there was no significant change in these ratios in either group during days 3–5 (Fig. 4). Therefore, it seemed reasonable to use the average value of T_4/T_3 during this period as an index of the maximum acute response of the individual patients to the antithyroid therapy. When the "plateau" T_4/T_3 ratios were plotted for each individual against the corresponding dosage, a significant direct correlation was observed between this ratio and the dose of PTU (Fig. 5). This relationship was not apparent with MMI. A similar relationship is observed in PTU-treated patients when the percentage decrease in serum T_3 on day 1 is plotted against the dose of PTU given ($r = 0.78$, $P < 0.01$, not shown). Again, there was no such correlation in the patients receiving MMI. The results in the PTU-treated

group could not be explained on the basis of higher initial serum T_3 concentrations in the patients receiving larger doses of this drug since the initial T_3 values in the groups receiving different doses of PTU were essentially the same. Specifically, the mean initial T_3 concentrations were 504±47, 614±132, and 627±115 in patients receiving daily doses of 300–450 mg (three), 750 mg (four), and 900–1,600 mg (four), respectively (Table I).

DISCUSSION

The significant inverse correlation of T_4/T_3 ratios with serum T_3 concentrations in untreated hyperthyroidism indicates that greater increases in circulating T_3 relative to T_4 are consistently observed in this condition. This relative excess of T_3 could be due either to relatively smaller increases in the metabolic clearance of T_3 than in the metabolic clearance of T_4 or to a disproportionate increase in the production rate of this hormone. Studies by Nicoloff, Low, Dussault, and Fisher in hyperthyroid subjects suggest that the former possibility is unlikely since parallel increases in the disappearance rates of both labeled T_3 and T_4 were observed in this condition (13). The study further estimated that there was a 7-fold increase in the daily production of T_3 whereas production of T_4 was increased only 3.5-fold. The relative overproduction of T_3 in turn could be a result of either increased thyroidal T_3 secretion or increased quantities of T_3 arising from peripheral deiodination of T_4 or both. Review of recent studies by several laboratories suggests that this latter pathway is the major source of circulating T_3 in euthyroid subjects (2). If one assumes that the fraction of T_4 which is converted to T_3 per day remains constant in hyperthyroidism, then rough estimates of the relative contribution of the two pathways to the peripheral T_3 pool can be made. While the precise proportion of the peripheral T_3 pool deriving from T_4 is a matter of debate, a recent review of the literature suggests that a minimum of about two-thirds comes from this source (2). This would amount to about 80 ng/100 ml of the normal serum T_3 concentration of about 120 ng/100 ml. If peripheral T_3 production were increased 3.5-fold as is total T_4 production in hyperthyroidism (i.e., if the fractional T_4 to T_3 conversion remains constant) an increase to a serum T_3 concentration of 280 ng/100 ml would be anticipated. This amounts to 46% (280/610) of the mean serum T_3 level in 19 patients examined in detail in this study. These approximations would indicate that the thyroid and the periphery contribute about equally to the T_3 pool in hyperthyroidism and that the acute inhibition of either pathway would cause similar initial decreases in serum T_3 concentrations.

The observation that iodide alone caused a rapid fall in circulating T_3 is evidence substantiating the acute inhibition of thyroid hormone secretion produced by this agent in hyperthyroid subjects. The acute inhibition of release of ^{131}I from prelabeled glands was first demonstrated by Goldsmith and Eisele (14) using epithyroid counting techniques and more recently verified in studies by Wartofsky, Ransil, and Ingbar by analysis of the changes in stable and labeled serum T_4 concentrations during iodide administration (7). The latter reported a mean decrease of 74% in T_4 secretion rate. Since the half-life of T_3 is short relative to T_4, changes in the concentration of this hormone are more abrupt than changes in the latter. Since some decreases in T_4 were present during iodide therapy, peripheral T_3 production was presumably decreased as well and contributed to the overall changes observed. The effect of an agent such as MMI on T_3 levels is more difficult to analyze. It is apparent that despite the presence of effective inhibition of T_4 and T_3 synthesis, release of these hormones will continue until the preformed stores are depleted. The duration of continued T_3 and T_4 secretion will be a function of the amount of colloid and the thyroidal release rate in each individual. Thus, a heterogeneous response might be expected in any group of hyperthyroid patients. This was observed in the three patients receiving MMI (Fig. 2). A similar type of response would be anticipated in patients treated with PTU if its only mechanism of action was to inhibit thyroidal hormone production. However, in our preliminary studies, the decreases in serum T_3 during therapy with PTU alone appeared to be both more acute and more consistent than those seen with MMI. This effect was different from that obtained with iodide alone in that simultaneous decreases in T_4 concentration were minimal. Consequently, the increases in T_4/T_3 ratios were greater with PTU than with either MMI or iodide. The consistency of the response pattern during PTU therapy argued against the chance occurrence of low intrathyroidal pools of T_3 relative to T_4 in the patients treated with this drug. Alternatively, it suggested that perhaps the acute decrease in serum T_3 in the absence of significant changes in serum T_4 could result from inhibition of peripheral T_3 production from T_4.

The evidence that PTU inhibits deiodination of T_4 in the experimental animal has been extensively reviewed by Morreale de Escobar and Escobar del Rey (15). Recent studies by Oppenheimer, Schwartz, and Surks have further documented that PTU administration to rats results in a decrease in the generation of labeled T_3 from labeled T_4 (10). Other studies have reported evidence of inhibition of T_4 deiodination in hyperthyroid subjects (8, 16). More recently, Nicoloff reported that PTU caused an acute inhibition of T_4 deiodination in euthyroid subjects (12). This effect was not shared by either MMI or iodide.

To our knowledge, there are no previous studies of the effect of PTU-induced inhibition of T_4 deiodination on peripheral T_3 production in either hyperthyroid or euthyroid subjects. It was apparent from the preliminary studies that the comparison of the effects of MMI and PTU on peripheral T_3 production in hyperthyroidism would be complicated by the previously discussed differences in thyroidal stores in different individuals. To overcome this problem, PTU and MMI were combined with iodide. Under these circumstances, the release of both thyroid hormones would be expected to be decreased to approximately 25% of the initial rate. Acute changes in circulating T_3 would, then, better reflect primary effects on peripheral T_3 production. The gradual decrease in circulating T_3 observed in the patients receiving MMI + iodide did not appear substantially different from the effects of iodide alone in the preliminary studies. The serum T_3 concentration appeared to plateau at about 340 ng/100 ml or 53% of the control level at about 3 days, consistent with the approximations outlined previously. The abrupt decrease of the serum T_3 to 56% of control on day 1 and to 42% of control on day 2 in the PTU group indicates that both pathways for T_3 production are inhibited. The decreasing T_4 levels in both groups was presumably a result of the iodide therapy. While there was no significant difference in the serum T_4 values between the two groups, this disappearance slope appeared shallower in the PTU-treated group as would be anticipated if T_4 deiodination were inhibited. While circulating T_4 might then tend to be higher in this group, it was primarily the significant decreases in circulating T_3 which resulted in the marked elevations in the serum T_4/T_3 ratio. Since the drugs were given in roughly the accepted potency ratio, namely, 10:1 for PTU versus MMI, it is probable that the inhibition of thyroid hormone synthesis induced by these agents was also equivalent. Because of the substantial acute inhibition of thyroidal release rate produced by iodide, small differences in the inhibition of thyroid hormone synthesis in the two groups would play little role in the observed responses.

However, the concomitant administration of iodide and antithyroid drugs requires one further comment. If inhibition of thyroid hormone formation were incomplete with these amounts of PTU and MMI, then the additional amounts of iodide could lead to the synthesis of greater amounts of hormones than would be formed in the presence of the antithyroid drugs alone. Since PTU is perhaps less than 10% as potent as MMI by weight (17), one could speculate that the T_4/T_3 ratio of newly synthesized hormones in PTU-treated patients would be greater than in MMI-treated patients, since greater restriction of iodine organification could result from the more efficient blockade by the latter drug. The situation might be analogous to studies in rats where iodine deficiency results in a decrease in the T_4/T_3 ratio of synthesized hormones (18). However, absolute T_3 production during the apparent plateau period (days 3–5) appears to be about 50% greater during MMI therapy than during treatment with PTU. It thus seems difficult to explain the higher total T_3 production rate in MMI-treated patients as due to a greater absolute rate of thyroidal T_3 secretion resulting from more complete inhibition of organification. It is perhaps more likely, at least acutely, that the high iodide levels, in addition to inhibiting hormone release, also caused intracellular iodide concentrations sufficiently elevated to cause further inhibition of the organification process in both groups through the Wolff-Chaikoff effect (19). The similarity of the pattern of response in the PTU-treated patients, whether or not added iodide was given, would add support to these theoretical arguments.

The previous studies in animals and man, as well as the present results, point to inhibition of T_4 deiodination as the best explanation for the acute decreases in circulating T_3 resulting from PTU therapy. Further support for this interpretation is found in the dose-response relationships between the "plateau" T_4/T_3 ratio (or the T_3 decrement on day 1) and the dose of PTU administered (Fig. 5). A similar dose-response relationship over a range of 100–1,000 mg was demonstrated for PTU inhibition of T_4 deiodination in euthyroid subjects by Nicoloff (12). Previous investigations suggest that the maximum inhibition of T_4 deiodination by PTU in the rat is approximately 50% (15). If there is a similar limit in man, a plateau in this curve should eventually occur which was not evident in our studies nor in the above mentioned studies in euthyroid subjects (12).

Certain clinical implications of this study deserve further comment. If T_3 is the active form of thyroid hormone and serum concentrations are an accurate reflection of the availability of this hormone to the cells, then the acute response of patients to treatment with PTU + iodide is clearly superior to the results with MMI + iodide. Whether the chemical improvements will be paralleled by more rapid clinical improvement is currently under investigation. Unfortunately, the present series of patients was not objectively evaluated from a clinical standpoint. However, these results are sufficiently impressive to make PTU (as opposed to MMI) in combination with iodide, our drug-of-choice in the treatment of patients with thyroid storm. In patients with less severe manifestations of thyrotoxicosis, the potential benefits of more rapid decreases in T_3 levels with PTU + iodide (or MMI + iodide) must be weighed against the risks of giving two drugs simultaneously. The peripheral effects of PTU might also be therapeutically advantageous in the treatment of exogenous thyroxine in-

toxication or in postsurgical or ^{131}I therapy-induced thyroid storm where minimal effects of any agents on thyroid hormone release are anticipated. In addition, the present studies are acute and may, therefore, have limited applicability to the effects of chronic PTU or MMI therapy on circulating T_3 and T_4 concentrations.

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