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# Thyroid Iodine Content and Serum Thyroid Hormone Levels in Autoimmune Thyroiditis: Effect of Iodide Supplementation

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The relationship between thyroid iodine content (TIC) measured by x-ray fluorescence and serum TSH, T<sub>4</sub>, and T<sub>3</sub> levels was investigated under iodide supplementation (0.5 mg/day for 1 to 9 mo). In five euthyroid control patients, whose TIC ranged from 2.5 to 14 mg, the TIC increased from 1.5 to 4 mg after 4 wk of treatment and had a tendency to plateau when the treatment was pursued. No significant changes in serum T<sub>4</sub>, T<sub>3</sub>, and TSH levels have been observed in these control subjects. Fourteen patients with autoimmune thyroiditis with low TIC (0–5 mg) were also studied. In six patients, the TIC increased significantly (3–10 mg over initial value after 3–7 mo of treatment). In parallel, there was a significant increase in serum T<sub>4</sub> levels (35–150% over initial value) while T<sub>3</sub> levels were modified in only two patients. In five patients serum TSH level decreased and was two- to seven-fold lower than before treatment whatever was its initial value; however, the spectrum of changes varied among patients from slight increase to a complete normalization in hormonesynthesis. In the eight other patients, iodide supplementation aggravated the thyroid disorders during the first months of treatment. The thyroid hormone blood levels dropped significantly in six patients (percent decrease below initial value: 20–100%) and was unchanged in the two others. An increase in the TSH blood level (X2–6) was observed in all patients except one. Concomitantly, the iodine stores were progressively depleted in three patients, unchanged in three and increased in two. When iodide treatment was pursued, an escape from this organification block was observed in two patients.

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**I**ntroduction of the x-ray fluorescence method 15 yr ago enabled *in vivo* assay of the thyroid iodine content (TIC) (1–7). Patients with autoimmune thyroiditis have low TIC and Jonckheer et al. (5) have suggested that circulating T<sub>4</sub> values are abnormally low when the TIC is less than 3 mg. The question arose whether chronic supplementation with low dose of iodide (0.5 mg/day) would be beneficial for these patients, as it is in endemic goiter (8,9) or some congenital goiter (10).

This study was performed on 14 patients with autoimmune thyroiditis and five euthyroid control subjects

in order to assess the effect of iodine supplementation on TIC as measured by x-ray fluorescence as well as on thyroid serum hormone (TSH) and thyroid hormone blood levels.

## MATERIALS AND METHODS

### Patients

Fourteen patients with autoimmune thyroiditis were studied. All of them had high titers of antimicrosomal antibodies (titers:  $3 \times 10^3$ – $6 \times 10^6$ ). Table 1 shows for each subject thyroid status as assessed by 2.5 hr radioiodine uptake (2.5 hr RAIU) and/or serum T<sub>4</sub>, T<sub>3</sub>, TSH blood levels measured by radioimmunoassay before the beginning of iodide treatment. Serum TSH levels were elevated in eight of these patients and were within

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**TABLE 1**  
Examined Patients: Biological Data Before Treatment

Case No.	Sex	Age (yr)	2.5 hr RAIU (%)	TIC (mg)	T <sub>4</sub> (μg/dl)	T <sub>3</sub> (ng/dl)	TSH (μU/ml)		Antibodies against	
							0	20 min*	Tg	Microsomal (titers)
<b>Autoimmune thyroiditis</b>										
1	F	40	–	UD†	2.6	74	60	–	2 × 10 <sup>3</sup>	6 × 10 <sup>6</sup>
2	F	30	6	1	6.6	82	20	–	1 × 10 <sup>5</sup>	6 × 10 <sup>6</sup>
3	F	20	38	UD	8.2	175	29	–	6 × 10 <sup>6</sup>	6 × 10 <sup>6</sup>
4	F	72	–	3.3	2.7	177	48	–	N‡	6 × 10 <sup>6</sup>
5	F	52	–	UD	2.7	91	60	–	6 × 10 <sup>6</sup>	6 × 10 <sup>6</sup>
6	F	34	31	UD	1	80	97	–	N	6 × 10 <sup>6</sup>
7	F	34	–	4.1	7.1	84	15	–	3 × 10 <sup>4</sup>	1 × 10 <sup>5</sup>
8	F	53	–	UD	3.2	32	80	–	N	6 × 10 <sup>6</sup>
9	F	42	11	2.4	5.8	64	6.5	47	N	6 × 10 <sup>6</sup>
10	F	33	14	1.3	6.7	185	4	44	N	3 × 10 <sup>5</sup>
11	F	35	–	2.8	10.4	179	2.2	30.5	N	6 × 10 <sup>6</sup>
12	F	73	–	5	6.9	107	6.3	–	N	3 × 10 <sup>5</sup>
13	F	43	–	2.8	9.6	174	4	39	N	3 × 10 <sup>3</sup>
14	F	45	8	3.6	6.2	75	7	37.4	N	6 × 10 <sup>6</sup>
<b>Control</b>										
15	M	42	15	2.5	10.5	132	3.2	–	N	N
16	M	32	17	15	11	152	3.1	–	N	N
17	F	44	10	7.8	10.5	251	3.2	–	N	N
18	F	54	–	8.4	10	100	2	–	N	N
19	F	32	19	4.9	9.0	127	4	–	N	N

\* After TRH injection.

† UD: undetectable.

‡ N: negative.

the normal range for the others, the TSH response to thyrotropin-releasing hormone (TRH) being increased in five of the latter patients.

Five euthyroid subjects were studied as control (Table 1). They had no familial or personal history of thyroid disease and none of them had detectable antithyroid antibodies.

#### Protocol

Informed consent was obtained from each patient. Iodide solution (0.5 mg/day) was administered during 1 to 9 mo. The 0.5 mg/day daily intake under iodide supplementation is similar to the intake from the normal diet in the USA, but in clear excess of normal iodide intake in France (approximately 0.1 mg/day) (11,12). After withdrawal of this treatment, patients were followed up for 1–12 mo. The thyroid function was assessed by clinical examination and T<sub>4</sub>, T<sub>3</sub>, TSH serum level assays. Sequential x-ray fluorescence measurements were performed during this period of time. The 2.5 hr RAIU which is correlated with the iodide clearance (13) was measured in seven patients during and/or after withdrawal of iodide therapy.

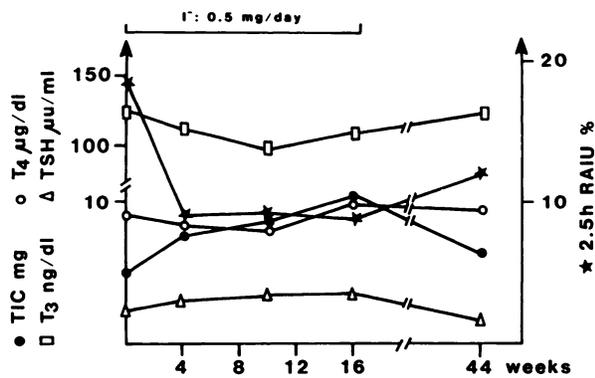
#### Methods

The iodine content of the thyroid gland was measured by x-ray fluorescence. The instrument, which was previously described (14), consists of an x-ray fluorescence

unit (80 kV x-ray excitation beam plus Si(LI) semiconductor) mounted on the arm of a scinti-scanner. The detector axis was vertical and at a 24° angle with the axis of the x-ray beam. Scintigraphic data were digitalized on a data processing unit.\* The images were visualized on a color T.V. monitor. Quantification was performed only when the image corresponded to the shape of the thyroid, otherwise it was considered to be undetectable. Determinations of TIC were obtained from a calibration curve established on assays performed with a thyroid phantom. Using the phantom, the smallest detectable content of iodine was less than 1 mg. The coefficient of variation over weeks was 5%. In France, as previously reported, the TIC measured with this system ranged

**TABLE 2**  
Control Subjects, Effect of Iodide Supplementation on Thyroid Iodine Content

Case No.	Thyroid iodine content (mg)	
	Before 4 wk I <sup>-</sup>	After 4 wk I <sup>-</sup>
15	2.5	4
16	15	17
17	8.5	11.5
18	8.5	11.5
19	4.5	8.5



**FIGURE 1**  
Effect of iodide supplementation on thyroid function in one euthyroid patient (Case 19). Horizontal line indicates duration of treatment

from 2.5 to 27 mg in control euthyroid subjects without goiter (7).

Serum T<sub>4</sub> was measured with an RIA<sup>†</sup> with a normal range of 3–10.3 µg/dl. Serum T<sub>3</sub> was evaluated with the Behring T<sub>3</sub> RIA kit in which the normal range is 90–250 ng/dl. Serum TSH was measured with an RIA<sup>‡</sup>; the normal range is lower than 7 µU/ml. For the TRH stimulation test, 200 µg of TRH<sup>§</sup> were injected i.v. and serum TSH level was measured 20 min before and after

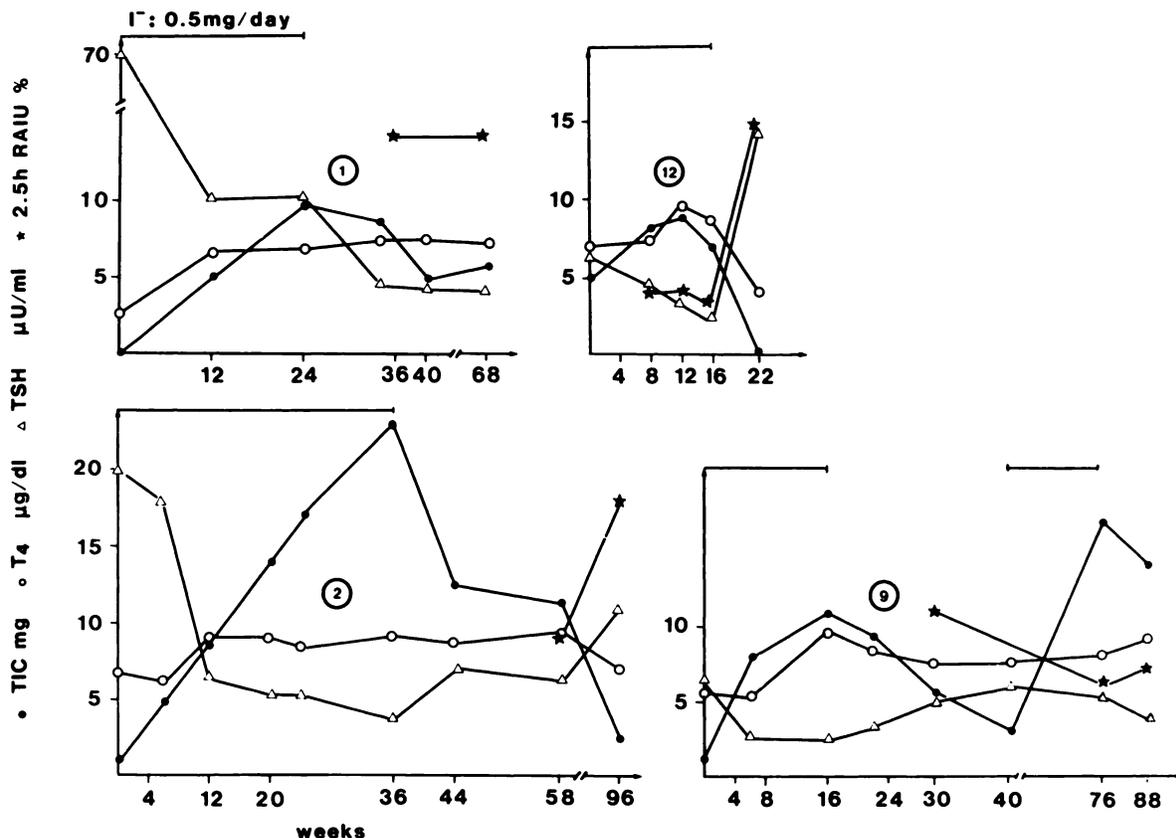
injection. In euthyroid control patients, the highest increment is 15 µU/ml. Circulating antithyroglobulin and antimicrosomal antibodies were assayed by the tanned red cell agglutination technique.<sup>¶</sup>

After oral administration of 5 µCi of <sup>131</sup>I, 2.5 hr RAIU was measured. In France, the normal range is 16 ± 8% (11).

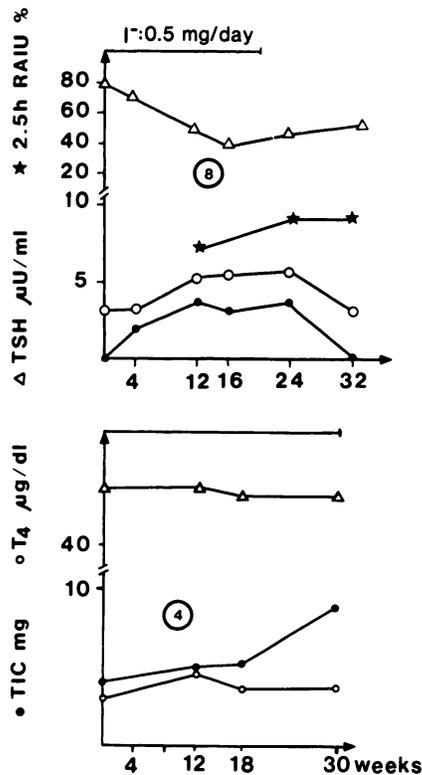
## RESULTS

In control subjects, TIC ranged from 2.5 to 14 mg before the iodide administration (Table 2). After 4 wk of iodide supplementation, the TIC increased from 1.5 to 4 mg over initial value. Therefore it leveled off or slightly increased until the end of the treatment. During iodide administration 2.5 RAIU significantly decreased (Fig. 1). After withdrawal of iodide treatment, the TIC decreased to their initial values. In these control subjects, no significant changes of T<sub>4</sub>, T<sub>3</sub>, and TSH blood levels were found although the overall picture of the time course changes suggested a slight decrease of the hormonal secretion in agreement with the data obtained on ten volunteers by Jonckheer et al. (15). This demonstrates the presence of autoregulatory mechanisms which prevent intrathyroidal iodine excess (16).

All the patients with autoimmune thyroiditis, had a



**FIGURE 2**  
Improvement of thyroid function during iodide treatment in four patients with autoimmune thyroiditis. Circle numbers refer to patient numbers of Table 1



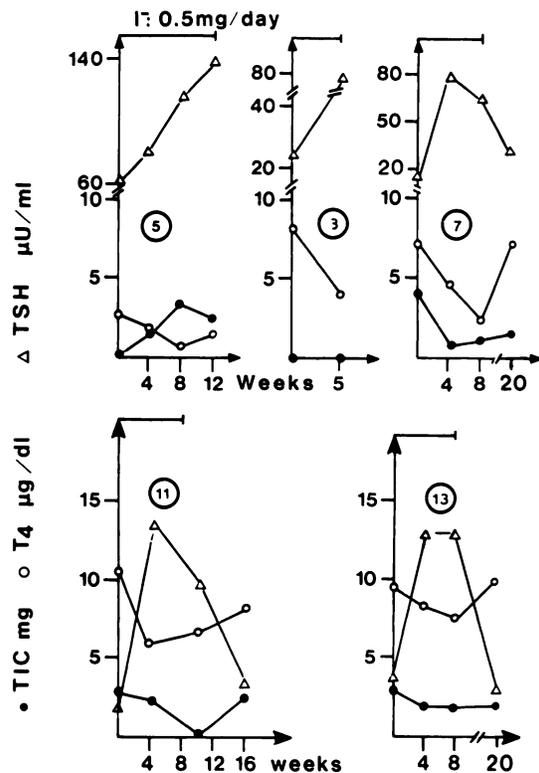
**FIGURE 3**  
Little changes in thyroid function during iodide treatment in two patients with autoimmune thyroiditis

low TIC before treatment (range 0–5 mg). However, the average TIC were 2.5-fold higher in patients with normal serum TSH level than in patients with elevated TSH. Under iodide treatment, different types of evolution were observed, irrespective of the basal serum TSH level.

1. In six patients thyroid function was improved and the TIC rose during iodide administration but to a variable extent from one patient to another (Figs. 2 and 3). After 3–4 mo of treatment, the increase over initial value of iodine stores ranged from 3 to 10 mg in five patients. In Patient 4, the effect was delayed and TIC rose only after 7.5 mo of treatment from 3 to 8 mg.

The serum T<sub>4</sub> level increased in all the patients by 35 to 150% over initial value; serum T<sub>3</sub> increased significantly in Patients 1 and 8 from 74 to 108 ng/ml and from 63 to 83 ng/dl, respectively, while its level was unmodified in the four other patients. In three patients, TSH levels dropped from frankly hypothyroid range to normal range (Case 2), its upper limit (Case 1) or remained in the hypothyroid range (Case 8). In two other patients (Cases 9, 12) with initial normal serum, TSH level was 2–2.5-fold lower at the end of the treatment. In only one patient (Case 4) TSH did not decrease.

In two patients (Cases 1, 2), when iodide was given for a long period of time (6–9 mo) the TIC continued to increase linearly but the other thyroid function parameters did not undergo further changes.



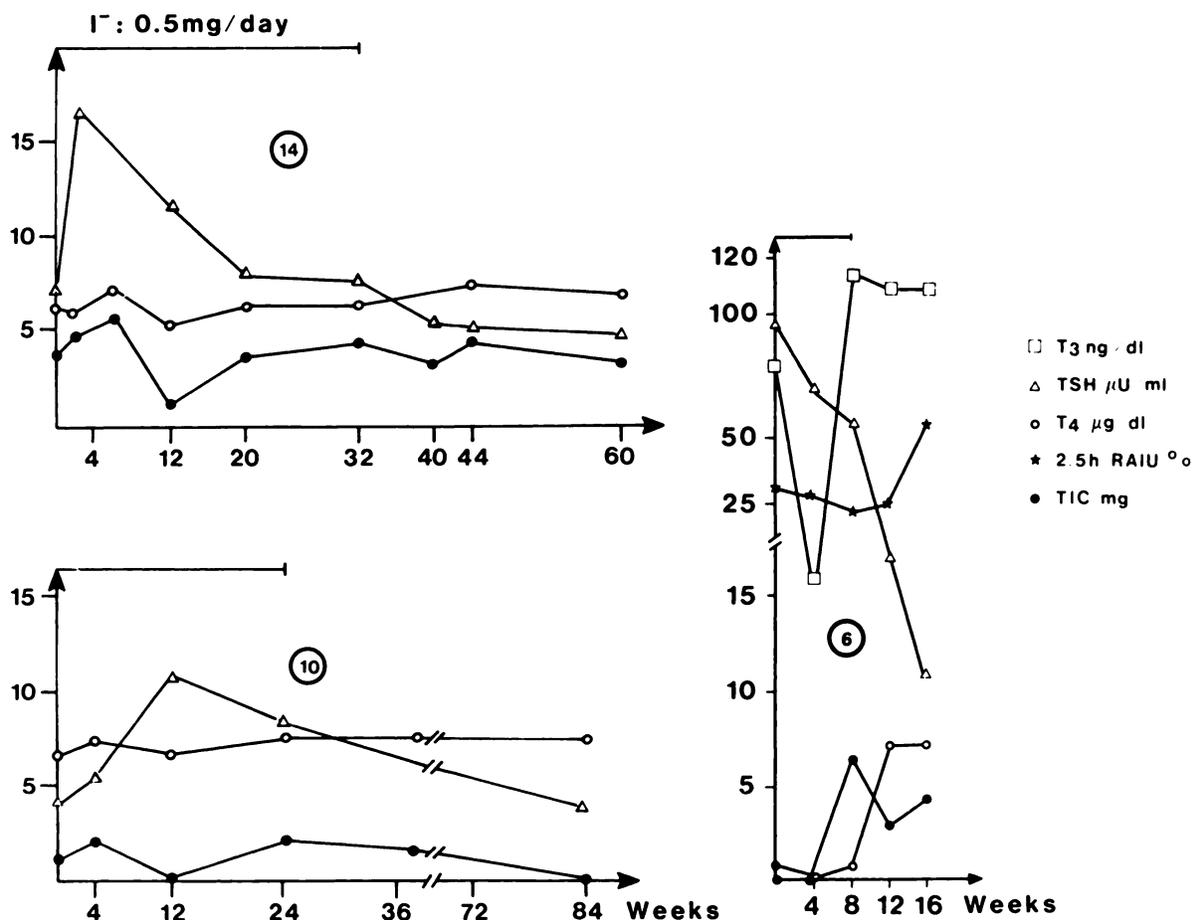
**FIGURE 4**  
Aggravation of thyroid function during iodide treatment in five patients with autoimmune thyroiditis

After withdrawal of iodide, the TIC generally decreased rapidly. Despite a 2.5 hr RAIU within the normal range after withdrawal of therapy, iodine depletion was observed in three patients (Cases 2, 8, 12) and thyroid function became worse.

2. In eight patients thyroid function was aggravated during the first 3 mo of iodide administration (Figs. 4 and 5).

In five patients (Fig. 4), after 1–2 mo of treatment, the T<sub>4</sub> level dropped significantly and were 20 to 66% below their initial values. The decrease in serum T<sub>3</sub> level was of the same magnitude except in Patient 7 in whom the T<sub>3</sub> level did not vary. In all the patients the serum TSH level increased dramatically (×2–6) whatever its initial value. The TIC increased from undetectable value to 3 mg in Patient 5 while it remained unchanged in two patients (Cases 3, 13) and decreased in two patients (Cases 7, 11). In these patients iodide had to be withdrawn between the fourth and tenth week. Substitutive therapy was prescribed in two patients; in the other three patients, thyroid function recovered spontaneously.

In two patients (Fig. 5), iodide administration was pursued during 24 and 32 wk, respectively, and the aggravation of the thyroid function appeared to be only transitory during iodide administration. They had a normal serum TSH level, before treatment. Their serum T<sub>4</sub>-T<sub>3</sub> levels did not change significantly during the first



**FIGURE 5**  
Transient aggravation of thyroid function during iodide treatment in patients with autoimmune thyroiditis

2 mo of treatment, but their serum TSH levels transiently increased to the hypothyroid range. When iodide treatment was pursued, TSH levels decreased to the normal range. These two patients had a transient fall in their TIC.

In Patient 6 (Fig. 5) with high initial TSH blood level,  $T_4$  and  $T_3$  levels decreased also during the first 4 wk of treatment and TIC remained undetectable. Therefore the TIC increased to a value of 7 mg while  $T_3$  level dramatically increased and  $T_4$  level returned to its initial value. After withdrawal of the iodide treatment, serum TSH,  $T_4$ , and  $T_3$  levels returned within the normal range while the TIC remained above its initial value. Spontaneous remission cannot be excluded in this patient who was examined within 3–10 mo postpartum (17–18).

## DISCUSSION

In patients with autoimmune thyroiditis our data stress two main findings.

1. The thyroid hormonosynthesis generally becomes deficient when the iodine content falls below 1 mg. This is in agreement with the results of Jonckheer et al. (5)

and Schlumberger et al. (19) who found an inverse relationship between the log basal TSH and the log TIC in patients with asymptomatic thyroiditis (5) or with Graves' disease treated with radioiodine (19).

2. The thyroid function response to diet supplementation with low doses of iodide is not uniform. In approximately one third of the patients the thyroid function improved, while it worsened in the other two thirds, at least during the first 2–4 mo of treatment. This difference could not be predicted on the basis of the thyroid function parameters studied: high TSH blood level and iodine depletion were observed in both groups.

Among the six patients who were improved, 3 mo of iodide supplementation induced a significant increase of the TIC in five of them. Moreover the hormonosynthesis became more effective, since the average  $T_4$  levels were significantly higher after 3 mo of treatment. However, the spectrum of changes varied among patients, from a slight increase in  $T_4$  level without significant change in TSH level to a complete normalization of all functional parameters. This improvement was probably in relation with a restoring of the iodine concentration at a level which permits  $T_4$  synthesis with a

normal yield and it was obtained after a variable time of treatment (2–7 mo). In some of these patients the daily increment in the thyroid stores remained unchanged until the end of the treatment, conversely to what was observed in control patients. Although T<sub>4</sub> and T<sub>3</sub> levels remained unmodified, this suggests a defect of the autoregulation mechanisms of iodine concentration which could lead to thyroid iodide overload and perhaps thyrotoxicosis (12,20,21). However, the duration of the study has been too short to allow a final conclusion and further investigations are going on.

After withdrawal of therapy, the iodine content decreased. Despite a 2.5-hr RAIU in the normal range, iodine depletion was again observed in most of these patients with autoimmune thyroiditis leading to lower T<sub>3</sub> and T<sub>4</sub> serum levels. This suggests that a large proportion of the trapped iodide, leaked from the thyroid gland before hormonesynthesis. Thus a large supply of iodine in the diet might make this disorder inapparent as demonstrated for patients with an iodotyrosine deiodination defect (22).

Conversely, a large proportion of the patients with autoimmune thyroiditis drastically increased their TSH blood levels. This was probably due to a block of iodine organification and hormonesynthesis rather than to an inhibition of the iodine release since a concomitant decrease of the TIC occurred in half of the patients. These data are in agreement with the unusually high susceptibility to inhibition of the thyroid function resulting from high doses of iodide in Hashimoto's thyroiditis (23). In five of the patients this inhibition was so pronounced that iodide treatment had to be withdrawn. In two patients, iodide treatment was pursued for 6 to 8 mo: an escape of the Wolff-Chaikoff effect had been observed and TSH blood levels decreased to the normal range. The hormonal secretion started to increase again when the TIC were above 1 mg. These data underline the effectiveness of the regulation of thyroid iodine stores in these patients who have a high susceptibility to iodide.

Thus, determination of TIC by x-ray fluorescence allows in vivo study of autoregulation of thyroid response to iodide in man. The present data underline the broad and varied spectrum of response in patients with autoimmune thyroiditis which can lead to hypothyroidism or hyperthyroidism (24,25). In some patients the autoregulatory mechanisms are effective, in others they do not work.

## FOOTNOTES

\* Informatek Simis 9.

† Clinical assay T<sub>4</sub> RIA kit.

‡ C.E.A. (France) TSH kit.

§ Hoffman LaRoche, Nutley, NJ.

¶ Burroughs-Wellcome Research, Triangle Park, NC.

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