

## DISAPPEARANCE OF THYROTROPIN-BLOCKING ANTIBODIES AND SPONTANEOUS RECOVERY FROM HYPOTHYROIDISM IN AUTOIMMUNE THYROIDITIS

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**Abstract Background.** Hypothyroidism may result from the production of antibodies that block the actions of thyrotropin. How often these thyrotropin-blocking antibodies are a cause of hypothyroidism and whether their production may cease, causing hypothyroidism to disappear, have not been extensively studied.

**Methods.** We determined the frequency with which thyrotropin-blocking antibodies were present in 172 hypothyroid patients with goitrous autoimmune thyroiditis (Hashimoto's disease) and 64 hypothyroid patients with atrophic autoimmune thyroiditis (idiopathic primary hypothyroidism). For 6 to 11 years we then followed 21 of these patients who were found to have thyrotropin-blocking antibodies. They received levothyroxine therapy for 3.5 to 8 years, after which it was discontinued. At frequent intervals during this time we measured the patients' serum concentrations of thyroxine, triiodothyronine, thyrotropin, and thyrotropin-blocking antibodies (measured as immunoglobulins that inhibit thyrotropin binding and immunoglobulins that inhibit thyrotropin bioactivity).

**Results.** Thyrotropin-blocking antibodies were detected in 9 percent of the patients with goitrous autoimmune thyroiditis and in 25 percent of those with atrophic autoimmune thyroiditis. Among the 21 patients studied serially while receiving levothyroxine, thyrotropin-blocking antibodies disappeared in 15 (group 1), 7 of whom had goiter initially, and persisted in 6 (group 2), none of whom had goiter initially. Levothyroxine therapy was subsequently discontinued in these 21 patients. Six of those in group 1 (four with goiter) remained euthyroid (mean follow-up after discontinuation of therapy, 2.1 years), and nine became hypothyroid again within 3 months. All six patients in group 2 remained hypothyroid.

**Conclusions.** Hypothyroidism in some patients with autoimmune thyroiditis may be due to thyrotropin-blocking antibodies. The production of thyrotropin-blocking antibodies may subside, producing remissions of hypothyroidism. Chronic autoimmune thyroiditis may therefore cause transient as well as permanent hypothyroidism. (N Engl J Med 1992;326:513-8.)

THERE are two forms of autoimmune thyroiditis — atrophic autoimmune thyroiditis (idiopathic primary hypothyroidism) and goitrous autoimmune thyroiditis (Hashimoto's disease).<sup>1</sup> Hypothyroidism is a major feature of both disorders, thought to be due to the destruction of the thyroid gland by the autoimmune process and therefore to be permanent.<sup>2-4</sup> In recent years it has become evident that hypothyroidism may also occur as a result of the production of autoantibodies that block the action of thyrotropin.<sup>1,5,6</sup> These thyrotropin-blocking antibodies have been found in patients with atrophic autoimmune thyroiditis and in patients with goitrous autoimmune thyroiditis,<sup>1</sup> their frequency ranging from 0 to 75 percent and from 0 to 44 percent, respectively, in different studies.<sup>1,5-16</sup> Much less is known about the extent to which they persist and whether they alone are responsible for the hypothyroidism in these patients, although in several patients thyrotropin-blocking antibodies disappeared and thyroxine therapy could be discontinued.<sup>17-19</sup> This outcome suggests not only that thyrotropin-blocking antibodies are the predominant cause of hypothyroidism in some patients with chronic autoimmune thyroiditis, but also that the functional antibodies disappear and therapy may be discontinued — i.e., that spontaneous remissions occur, as in Graves' disease.<sup>2,20</sup> We undertook this study to determine the frequency with which thyrotropin-blocking antibodies were present in a large number of patients with chronic autoimmune thyroiditis. We also sought

to determine the natural history of the disorder in a subgroup of patients who had thyrotropin-blocking antibodies initially, and to determine whether the absence or presence of the antibodies during follow-up correlated with the need for continued thyroxine therapy.

### METHODS

#### Subjects

We measured thyrotropin-blocking antibodies in 172 consecutive patients with hypothyroidism due to goitrous autoimmune thyroiditis (155 women and 17 men with a mean [ $\pm$ SD] age of  $44 \pm 16$  years) and 64 consecutive patients with hypothyroidism due to atrophic autoimmune thyroiditis (52 women and 12 men with a mean age of  $40 \pm 14$  years). The diagnosis of hypothyroidism was made on the basis of history, physical examination, and the finding of serum concentrations of thyrotropin above 10 mU per liter and thyroxine below 77 nmol per liter. The diagnosis of goitrous autoimmune thyroiditis was based on the finding of palpable goiter, and that of atrophic autoimmune thyroiditis on the absence of goiter. All the patients had positive tests for antithyroid autoantibodies (antithyroid peroxidase antibodies, antithyroglobulin antibodies, or thyrotropin-blocking antibodies). Patients who had thyroid-stimulating autoantibodies were excluded from the study, as were patients with high values for the uptake of radioactive iodine, since patients with goitrous autoimmune thyroiditis who have high levels of iodine uptake may have iodine-induced reversible hypothyroidism.<sup>21-24</sup> None of the patients took any drugs that might affect thyroid function or ate large quantities of iodine-rich foods, such as seaweed, either before or during the study.

We followed 21 of these patients who had thyrotropin-blocking antibodies at the time of their first visit and who agreed to be examined at regular intervals. The group included 18 women and 3 men; 7 had goitrous autoimmune thyroiditis and 14 atrophic autoimmune thyroiditis. The duration of follow-up was 6 to 11 years. All 21 patients were treated with levothyroxine in doses (75 to 150  $\mu$ g per day) sufficient to ameliorate their symptoms and return their serum thyroxine and thyrotropin concentrations to normal; they were followed at intervals of two to four weeks during treatment and

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after. The 15 patients in whom thyrotropin-blocking antibodies disappeared during follow-up (group 1) had the antibodies for at least 0.5 year (mean, 2; range, 0.5 to 5) after treatment was begun and continued to receive levothyroxine for at least 1.5 years (mean, 3.4; range, 1.5 to 6.5) after the antibodies had disappeared. The six patients who continued to have thyrotropin-blocking antibodies during follow-up (group 2) were treated with levothyroxine for at least 3.5 years (mean, 6; range, 3.5 to 7) before treatment was discontinued. In all 21 patients, the levothyroxine was discontinued abruptly, and the patients were then examined at intervals of two to four weeks for one to five years, until the end of the study. Levothyroxine therapy was resumed in patients who were subsequently found to have serum thyrotropin concentrations of more than 10 mU per liter.

The study plan was reviewed and approved by our institutional review committee, and consent was obtained from all the patients.

### Laboratory and Statistical Analysis

Serum thyroxine, triiodothyronine, and thyrotropin concentrations were determined by radioimmunoassay with commercially available kits. The ranges for serum thyroxine and triiodothyronine in 507 normal subjects were 77 to 155 nmol per liter and 1.2 to 2.8 nmol per liter, respectively, and that for serum thyrotropin was 0.2 to 5 mU per liter. The uptake of radioactive iodine by the thyroid was measured 24 hours after the administration of  $^{131}\text{I}$  (normal uptake, 15 to 40 percent). Antithyroid peroxidase (microsomal) antibodies and antithyroglobulin antibodies were measured with commercial kits (Fuji Zoki, Tokyo, Japan). Antibodies were considered to be present when positive reactions were obtained in serum dilutions of 1:40 or higher. Thyrotropin-blocking antibodies were measured as immunoglobulins that inhibit thyrotropin binding (TBII) and as immunoglobulins that inhibit the thyrotropin-stimulated response of cyclic AMP (TSII). TBII are antibodies that block the binding of thyrotropin to its receptor, and TSII are those that block the action of thyrotropin on thyroid cells. TBII was measured in serum by radioreceptor assay with a commercial kit (R.S.R., Cardiff, United Kingdom),<sup>25</sup> as described elsewhere.<sup>1</sup> The assay results were expressed in terms of the ability of the patients' serum to inhibit the binding of [ $^{125}\text{I}$ ]thyrotropin to thyroid plasma membranes as compared with the ability of pooled serum from normal subjects. The values in 115 normal subjects ranged from 15 percent to -15 percent; a positive test for TBII was defined as a value >15 percent, and a negative test a value of  $\leq 15$  percent. The assay was performed every four weeks. TSII was measured in IgG fractions of serum as described elsewhere.<sup>1</sup> In brief, IgG (1 g per liter) was incubated with porcine-thyroid cells in the presence of 100 mU of bovine thyrotropin per liter for two hours, and cyclic AMP was measured in the cells and the medium by radioimmunoassay.<sup>1</sup> Results were expressed as the percent inhibition of thyrotropin-stimulated production of cyclic AMP, as compared with production in a pool of IgG from normal subjects. The values in 52 normal subjects ranged from 22 percent to -22 percent; a positive test for TSII was defined as a value >22 percent, and a negative test as a value of  $\leq 22$  percent. TSII was measured in the patients in five different assays with triplicate samples; the results in the different assays were the same. The intraassay and interassay coefficients of variation were <3 percent and <8 percent, respectively. The IgG fractions were prepared by Protein A affinity chromatography.<sup>26</sup> Porcine-thyroid cells were isolated and cultured as previously described.<sup>27,28</sup> Thyrotropin was obtained from Armour Pharmaceutical (Phoenix, Ariz.). All other chemicals were of the highest purity availa-

Table 1. Detection of TBII and TSII in Patients with Goitrous or Atrophic Autoimmune Thyroiditis.

TEST RESULT	GOITROUS AUTOIMMUNE THYROIDITIS (N = 172)	ATROPHIC AUTOIMMUNE THYROIDITIS (N = 64)	$\chi^2$	P VALUE
	no. (%)			
TBII				
Positive	14 (8)	16 (25)	12.0	<0.01
Negative	158 (92)	48 (75)		
TSII				
Positive	17 (9)	16 (25)	8.9	<0.01
Negative	155 (91)	48 (75)		

ble commercially. We found a good correlation between the results of the TBII and TSII assays in individual patients and normal subjects.<sup>1</sup>

Statistical analysis was performed by the  $\chi^2$  test. P values of less than 0.05 were considered to indicate significance.

### RESULTS

#### Thyrotropin-Blocking Antibodies in Hypothyroid Patients with Goitrous or Atrophic Autoimmune Thyroiditis

Table 1 shows the frequency of positive tests for TBII and TSII in the 172 patients with goitrous autoimmune thyroiditis and the 64 with atrophic autoimmune thyroiditis. Among the patients with goitrous autoimmune thyroiditis, 14 (8 percent) were positive for TBII and 17 (10 percent) for TSII; 14 were positive for both. Among the patients with atrophic auto-

Table 2. Clinical Findings in the 21 Patients with Thyrotropin-Blocking Antibodies Who Were Followed at Frequent Intervals.

PATIENT NO.	SEX/AGE*	IODINE UPTAKE†	GOITER		FOLLOW-UP	RECOVERY FROM HYPOTHYROIDISM‡				
			INI-TIALLY	END OF STUDY		THYROX-INE	TRIODO-THYRONINE	THYROTROPIN	TBII	TSII
		%			yr	nmol/liter	mU/liter		%	
<b>Group 1 (antibodies disappeared)</b>										
<b>Reversible hypothyroidism</b>										
1	F/44	2.4	No	No	6	112	1.6	1.2	2	8
2	M/72	0.8	No	No	7	120	1.7	0.8	5	6
3	F/32	3.2	No	Yes	6	102	1.8	1.5	2	4
4	F/27	5.9	Yes	Yes	9	98	1.9	1.0	0	5
5	F/57	2.3	Yes	Yes	10	106	1.5	0.9	2	9
6	F/28	6.5	Yes	Yes	6	102	1.8	1.3	0	10
<b>Irreversible hypothyroidism</b>										
7	F/42	2.3	No	No	9					
8	F/32	3.5	No	No	6					
9	F/27	—	Yes	Yes	11					
10	F/19	—	No	No	10					
11	F/59	4.2	Yes	Yes	10					
12	F/33	—	No	No	9					
13	M/28	—	No	No	7					
14	F/42	—	Yes	Yes	6					
15	F/31	7.6	Yes	Yes	11					
<b>Group 2 (antibodies remained)</b>										
16	F/26	2.6	No	No	7					
17	F/25	0.7	No	No	11					
18	F/28	1.2	No	No	11					
19	M/12	2.6	No	No	11					
20	F/29	0.6	No	No	6					
21	F/32	2.2	No	No	11					

\*The age shown is that at which the patient was found to be hypothyroid.

†The uptake of radioactive iodine by the thyroid was measured 24 hours after the administration of  $^{131}\text{I}$  (given at the initial visit).

‡Values were determined one year after the discontinuation of levothyroxine therapy. None of the patients in group 1 whose hypothyroidism was irreversible and none of the patients in group 2 recovered.

immune thyroiditis, 16 (25 percent) were positive for both TBII and TSII and none for either alone. TBII and TSII were detected significantly more frequently in the patients with atrophic autoimmune thyroiditis than in those with goitrous autoimmune thyroiditis.

The mean ( $\pm$ SD) serum thyroxine, triiodothyronine, and thyrotropin levels before the initiation of levothyroxine therapy in the patients with goitrous autoimmune thyroiditis and those with atrophic autoimmune thyroiditis were  $16.8 \pm 4.9$  and  $12.2 \pm 3.2$  nmol per liter,  $0.84 \pm 0.12$  and  $0.58 \pm 0.14$  nmol per liter, and  $128 \pm 32$  and  $156 \pm 52$  mU per liter, respectively.

#### Follow-up Study in the Patients with Thyrotropin-Blocking Antibodies

We followed 21 patients who had thyrotropin-blocking antibodies when their hypothyroidism was diagnosed (Table 2). They were divided into two groups according to whether the antibodies disappeared or persisted after levothyroxine treatment. In 15 patients (group 1) the antibodies disappeared, and in 6 patients (group 2) they persisted. In group 1, six patients remained euthyroid for more than 1 year after levothyroxine was discontinued (mean follow-up, 2.1 years; range, 1 to 4.5); the results of their thyroid tests at 1 year are shown in Table 2. The other nine patients became hypothyroid (serum thyrotropin level,  $>10$  mU per milliliter) within three months after levothyroxine therapy was discontinued. Of the 15 patients in group 1, 7 initially had goiter and 8 did not. Among the patients in group 1 who remained euthyroid, three had initially had goiter and three had not; a small goiter developed in one patient five months after levothyroxine was discontinued. None of the six patients who continued to have thyrotropin-blocking antibodies (group 2) recovered from hypothyroidism (none had had goiter initially or at any time thereafter). Levothyroxine therapy was resumed in all the patients in group 2 and in all those in group 1 who had become hypothyroid when treatment was discontinued.

Figure 1 shows the sequential changes in serum TBII and TSII values in these 21 patients. The values for the two antibodies were always comparable in individual patients. The initially positive tests for both

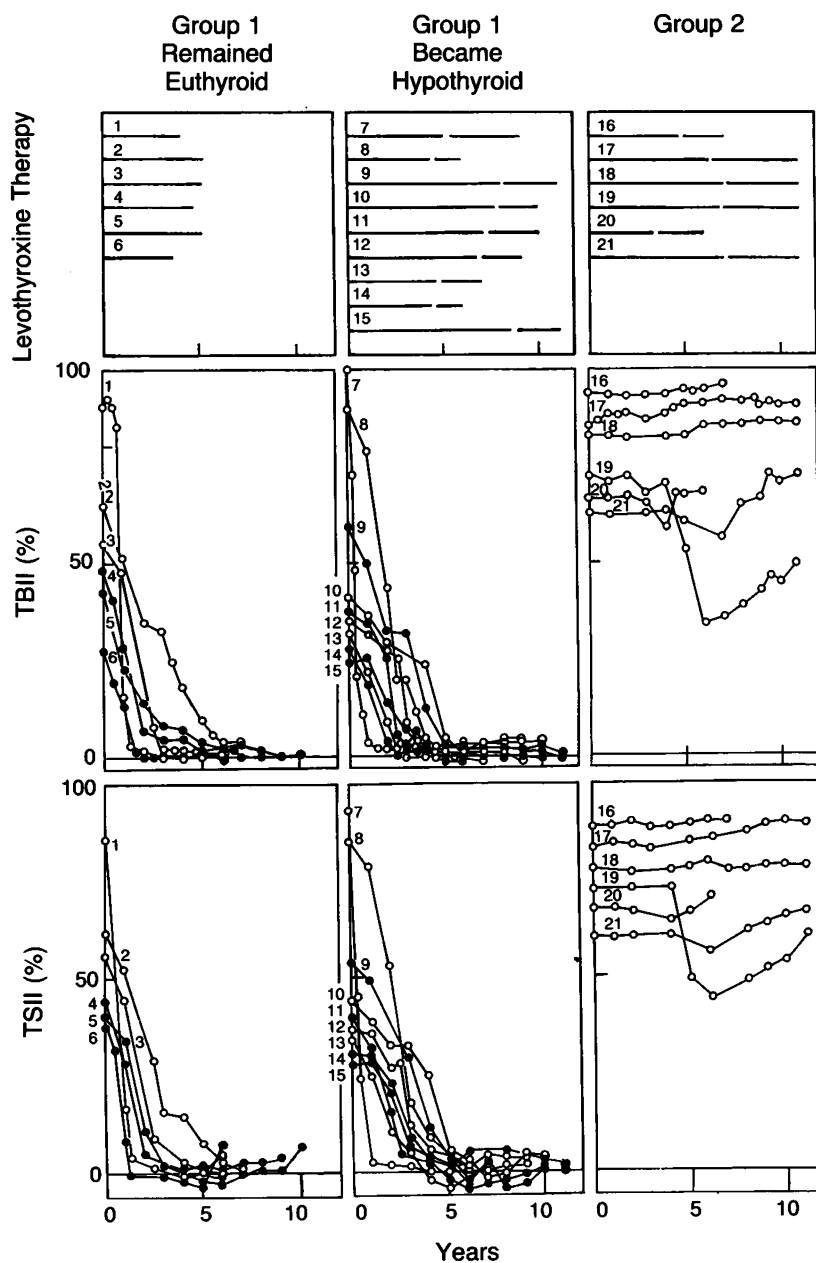


Figure 1. Results of Serial Measurements of TBII and TSII in 21 Patients with Chronic Autoimmune Thyroiditis.

Solid symbols represent patients with goiter, and open symbols those without. The bars in the top panel indicate the periods during which the patients were taking levothyroxine. The numbers are patient numbers.

TBII and TSII in the 15 patients in group 1 became negative after 0.5 to 5 years, and there were no differences between the values in the patients who remained euthyroid after levothyroxine therapy was discontinued and those in the patients who became hypothyroid again. In contrast, the values in the six patients in group 2 changed little.

The serum thyroxine, triiodothyronine, and thyrotropin concentrations in these 21 patients before levothyroxine therapy and one to three months after therapy was discontinued are shown in Figure 2. All 21 patients initially had hypothyroidism, low serum

thyroxine and triiodothyronine levels, and high thyrotropin levels. The six patients in group 1 who remained clinically euthyroid after levothyroxine was discontinued had normal thyroxine, triiodothyronine, and thyrotropin concentrations three months later and remained euthyroid (Table 2). The other nine patients in group 1 and the six in group 2, however, all had not only symptoms of hypothyroidism, but also low thyroxine and triiodothyronine and high thyrotropin levels after levothyroxine was discontinued (Fig. 2).

The titers of antithyroid peroxidase antibody and antithyroglobulin antibody at the initial visit and after the discontinuation of levothyroxine therapy are shown in Figure 3. During the study period, the antibody titers changed in some of the patients in group 1 but in none of those in group 2, in whom they were always very low or negative.

### DISCUSSION

There are two forms of autoimmune thyroiditis — atrophic and goitrous.<sup>1</sup> Early studies<sup>5,6</sup> indicated that thyrotropin-blocking antibodies were present almost exclusively in patients with atrophic autoimmune thy-

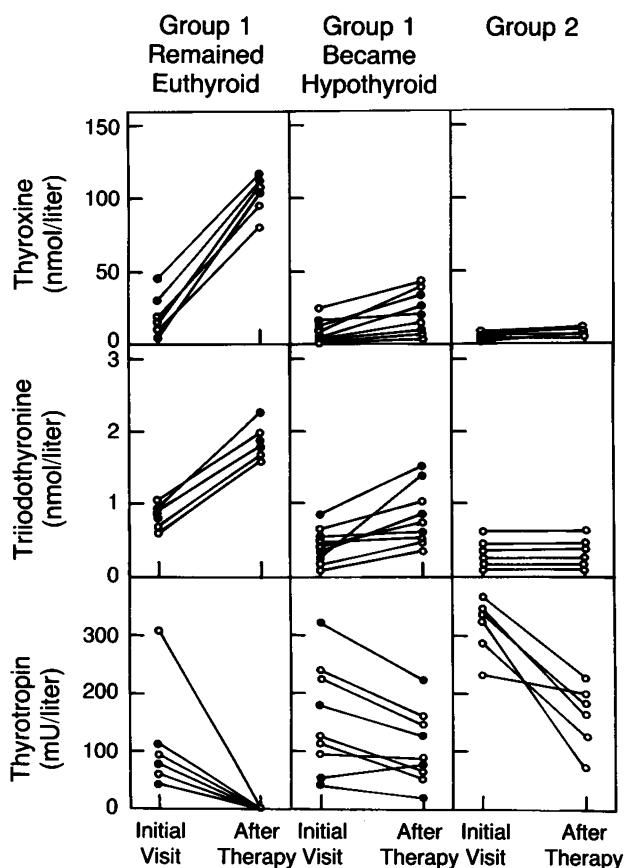


Figure 2. Serum Thyroxine, Triiodothyronine, and Thyrotropin Concentrations at the Initial Visit and One to Three Months after the Discontinuation of Levothyroxine Therapy in 21 Patients with Chronic Autoimmune Thyroiditis.

Solid symbols represent patients with goiter, and open symbols those without.

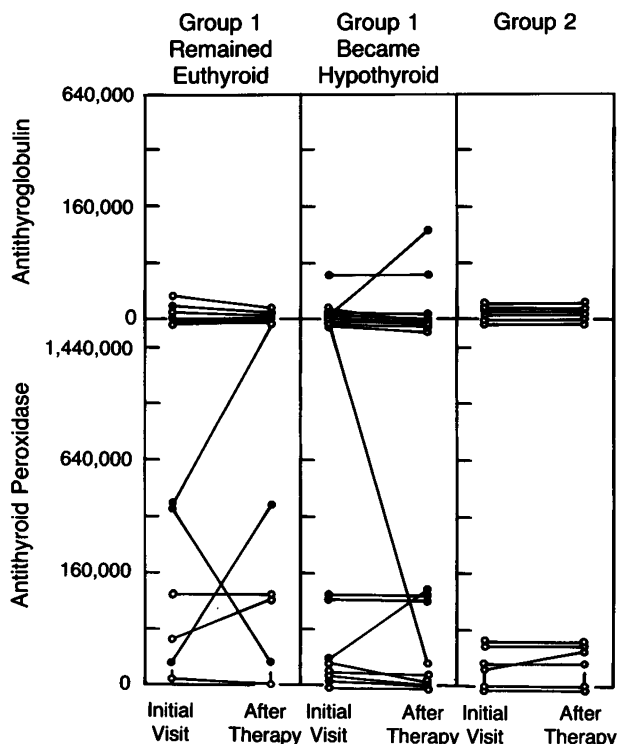


Figure 3. Titers of Antithyroglobulin and Antithyroid Peroxidase Antibodies at the Initial Visit and One to Three Months after the Discontinuation of Levothyroxine Therapy in 21 Patients with Chronic Autoimmune Thyroiditis.

Solid symbols represent patients with goiter, and open symbols those without.

roiditis and that they contributed to the pathogenesis of hypothyroidism in such patients, but not in patients with goitrous autoimmune thyroiditis. We and others have since demonstrated, however, that some patients with goitrous autoimmune thyroiditis also have thyrotropin-blocking antibodies.<sup>1,12,15,16,29,30</sup> We confirmed those results in this study, although the frequency of the presence of thyrotropin-blocking antibodies in the patients with goitrous autoimmune thyroiditis was lower than reported previously.<sup>1</sup> These results suggest that the antibodies may have a role in the pathogenesis of hypothyroidism independently of the presence or absence of goiter.

Among 21 patients who were hypothyroid and had thyrotropin-blocking antibodies at the initial study visit, the inhibitory immunoglobulins disappeared in 15, and 6 of them remained euthyroid after levothyroxine therapy was discontinued. These results indicate that the production of thyrotropin-blocking antibodies may cease or at least decline greatly. The change is presumably spontaneous, although it is possible that levothyroxine contributed to it. Our results also indicate that thyrotropin-blocking antibodies alone may be responsible for hypothyroidism in some patients. It has been assumed that autoimmune thyroiditis results in permanent hypothyroidism,<sup>2-4,31,32</sup> although remissions have been reported in some patients.<sup>19,33-38</sup> In some cases they were spontaneous,<sup>19,33-38</sup> whereas in others they were associated

with glucocorticoid therapy.<sup>17,18</sup> Presumably, remissions do not occur in most patients who have hypothyroidism due to autoimmune thyroiditis, because of the destruction of thyroid tissue, whether it is replaced by lymphocytic infiltration and fibrosis or not. Such destruction may be due to cell-mediated autoimmune mechanisms, cytotoxic autoantibodies, or both. Spontaneous recovery is known to occur in transient neonatal hypothyroidism,<sup>39,40</sup> a classic example of transient hypothyroidism mediated by thyrotropin-blocking antibodies that affects infants whose mothers have autoimmune thyroiditis.

Although we think the remission of hypothyroidism in the six patients in group 1 who remained euthyroid after treatment was due to the cessation of production of thyrotropin-blocking antibodies, the possibility that the remission had another basis should be considered. Several forms of reversible hypothyroidism have been described in patients with autoimmune thyroiditis, among them iodine-induced reversible hypothyroidism<sup>21-24</sup> and postpartum transient hypothyroidism.<sup>41</sup> None of our patients had a history of excess iodine intake, and all had low values for radioiodine uptake, whereas high uptake values have been reported in patients with iodine-induced reversible hypothyroidism.<sup>21-24</sup> Furthermore, in none of our female patients did the hypothyroidism appear during the postpartum period.<sup>41</sup>

We measured thyrotropin-blocking antibodies as TBII and TSII. The levels of the two antibodies were always comparable in individual patients, indicating that the antibodies probably inhibited thyroid secretion by blocking the binding of thyrotropin to its receptors and suggesting that the two activities reside in the same immunoglobulin molecules.

We conclude that hypothyroidism in some patients may be due entirely to thyrotropin-blocking antibodies and that the production of such antibodies may spontaneously decline, so that thyroid secretion is no longer inhibited and levothyroxine therapy is no longer needed. Thus, autoimmune thyroiditis, like Graves' disease, need not be lifelong.

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*Club Foot*

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