

## COMPARISON OF ADMINISTRATION OF RECOMBINANT HUMAN THYROTROPIN WITH WITHDRAWAL OF THYROID HORMONE FOR RADIOACTIVE IODINE SCANNING IN PATIENTS WITH THYROID CARCINOMA

PAUL W. LADENSON, M.D., LEWIS E. BRAVERMAN, M.D., ERNEST L. MAZZAFERRI, M.D., FRANÇOISE BRUCKER-DAVIS, M.D., DAVID S. COOPER, M.D., JEFFREY R. GARBER, M.D., FREDRIC E. WONDISFORD, M.D., TERRY F. DAVIES, M.D., LESLIE J. DEGROOT, M.D., GILBERT H. DANIELS, M.D., DOUGLAS S. ROSS, M.D., AND BRUCE D. WEINTRAUB, M.D.

### ABSTRACT

**Background** To detect recurrent disease in patients who have had differentiated thyroid cancer, periodic withdrawal of thyroid hormone therapy may be required to raise serum thyrotropin concentrations to stimulate thyroid tissue so that radioiodine (iodine-131) scanning can be performed. However, withdrawal of thyroid hormone therapy causes hypothyroidism. Administration of recombinant human thyrotropin stimulates thyroid tissue without requiring the discontinuation of thyroid hormone therapy.

**Methods** One hundred twenty-seven patients with thyroid cancer underwent whole-body radioiodine scanning by two techniques: first after receiving two doses of thyrotropin while thyroid hormone therapy was continued, and second after the withdrawal of thyroid hormone therapy. The scans were evaluated by reviewers unaware of the conditions of scanning. The serum thyroglobulin concentrations and the prevalence of symptoms of hypothyroidism and mood disorders were also determined.

**Results** Sixty-two of the 127 patients had positive whole-body radioiodine scans by one or both techniques. The scans obtained after stimulation with thyrotropin were equivalent to the scans obtained after withdrawal of thyroid hormone in 41 of these patients (66 percent), superior in 3 (5 percent), and inferior in 18 (29 percent). When the 65 patients with concordant negative scans were included, the two scans were equivalent in 106 patients (83 percent). Eight patients (13 percent of those with at least one positive scan) were treated with radioiodine on the basis of superior scans done after withdrawal of thyroid hormone. Serum thyroglobulin concentrations increased in 15 of 35 tested patients: 14 after withdrawal of thyroid hormone and 13 after administration of thyrotropin. Patients had more symptoms of hypothyroidism ( $P < 0.001$ ) and dysphoric mood states ( $P < 0.001$ ) after withdrawal of thyroid hormone than after administration of thyrotropin.

**Conclusions** Thyrotropin stimulates radioiodine uptake for scanning in patients with thyroid cancer, but the sensitivity of scanning after the administration of thyrotropin is less than that after the withdrawal of thyroid hormone. Thyrotropin scanning is associated with fewer symptoms and dysphoric mood states. (N Engl J Med 1997;337:888-96.)

©1997, Massachusetts Medical Society.

THYROID carcinoma is diagnosed in 14,000 people each year in the United States.<sup>1</sup> Most are effectively treated by surgery, followed often by radioiodine therapy and always by thyroid hormone therapy to suppress the secretion of thyrotropin. These patients require monitoring for recurrence of tumor, which can occur decades later.<sup>2,3</sup> In some patients, monitoring includes periodic discontinuation of thyroid hormone therapy for radioiodine scanning<sup>4,5</sup> and measurement of serum thyroglobulin<sup>6,7</sup> to detect residual or recurrent thyroid carcinoma. As a consequence of discontinuing thyroid hormone therapy, patients typically have symptomatic hypothyroidism, some may not have a sufficient increase in thyrotropin secretion for optimal imaging,<sup>8</sup> and a few patients have accelerated tumor growth.<sup>9-11</sup>

A solution to these problems is the administration of thyrotropin to stimulate remaining thyroid tissue.<sup>12,13</sup> Recombinant human thyrotropin has the properties and actions of native thyrotropin.<sup>14-17</sup> In a preliminary study, thyrotropin stimulated the uptake of radioiodine by residual thyroid and thyroid-cancer tissue in patients who had previously been oper-

---

From the Division of Endocrinology and Metabolism and the Thyroid Tumor Center, Johns Hopkins University School of Medicine, Baltimore (P.W.L.); the Division of Endocrinology and Metabolism, University of Massachusetts Medical Center, Worcester (L.E.B.); the Department of Internal Medicine, Ohio State University, Columbus (E.L.M.); the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Md. (F.B.-D., B.D.W.); the Division of Endocrinology and Metabolism, Sinai Hospital of Baltimore, Baltimore (D.S.C.); the Division of Endocrinology and Metabolism (J.R.G.) and the Thyroid Unit (F.E.W.), Beth Israel Hospital, Boston; the Division of Endocrinology and Metabolism, Mount Sinai Medical Center, New York (T.F.D.); the Thyroid Study Unit, University of Chicago Medical Center, Chicago (L.J.D.); and the Thyroid Unit, Massachusetts General Hospital, Boston (G.H.D., D.S.R.). Address reprint requests to Dr. Ladenson at the Division of Endocrinology and Metabolism, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287-4904.

Other authors were Jan D. Hay, M.D., Ph.D. (Division of Endocrinology, Mayo Clinic and Foundation, Rochester, Minn.), Silvina Levis, M.D. (Division of Endocrinology, University of Miami School of Medicine, Miami), James C. Reynolds, M.D. (National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md.), Jacob Robbins, M.D. (National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md.), David V. Becker, M.D. (New York Hospital, Cornell Medical Center, New York), Ralph R. Cavalieri, M.D. (Veterans Affairs Medical Center, San Francisco), Harry R. Maxon, M.D. (University of Cincinnati Medical Center, Cincinnati), Kevin McEllin (Genzyme Corporation, Cambridge, Mass.), and Richard Moscicki, M.D. (Genzyme Corporation, Cambridge, Mass.).

ated on for thyroid carcinoma.<sup>18</sup> The current study was designed to assess the efficacy and side effects of the administration of thyrotropin as compared with the withdrawal of thyroid hormone therapy in a larger group of patients with previously treated thyroid carcinoma.

**METHODS**

**Study Patients**

The subjects were 152 patients (mean age, 44 years; range, 20 to 84) with differentiated thyroid cancer for whom radioiodine scanning was indicated according to their treating physicians. The patients gave written informed consent to participate in the study, which was approved by the institutional review committee at each center. All but one patient had undergone total or subtotal thyroidectomy, and most had received radioiodine therapy. None had received drugs or radiographic contrast agents that interfere with the uptake of iodine by thyroid tissue. Twenty-five patients did not complete the study or were excluded: 14 because of protocol deviations, 4 because of adverse reactions, 4 for personal reasons, and 3 because of the inability of the independent reviewers who evaluated the radionuclide images to reach consensus. Consequently, the findings in the remaining 127 patients make up the final results of the study.

**Recombinant Thyrotropin**

Recombinant thyrotropin (Thyrogen, Genzyme, Cambridge, Mass.) was produced as previously described.<sup>14,19</sup> Its biologic potency was 10 U per milligram of protein (Second World Health Organization International Reference Preparation, thyrotropin, Human, for Bioassay, 84/703).

**Study Design**

Two whole-body scans with iodine-131 were obtained in each patient, and the uptake of radioiodine was measured quantitatively in foci of activity thought to be normal thyroid tissue or thyroid carcinoma. The first scan was performed after administration of thyrotropin while the patient continued thyroid hormone therapy, and the second was performed after withdrawal of thyroid hormone therapy (Fig. 1). Thyroid hormone treatment consisted of thyroxine in 97 patients, triiodothyronine in 6 patients, and both in 49 patients, in doses sufficient to reduce serum thyrotropin concentrations to less than 0.5 mU per liter. Thyrotropin was given intramuscularly at a dose of 0.9 mg once a day for two days. Twenty-four hours after the second dose, each patient was given

2 to 4 mCi (74 to 148 MBq) of iodine-131 orally. The first whole-body scan was obtained 48 hours later. Thyroid hormone therapy was continued for at least two weeks, and was then discontinued for at least two weeks until the serum thyrotropin concentration was greater than 25 mU per liter. The patient was then given a quantity of iodine-131 within 20 percent of that previously administered, and whole-body scanning was performed again 48 hours later.

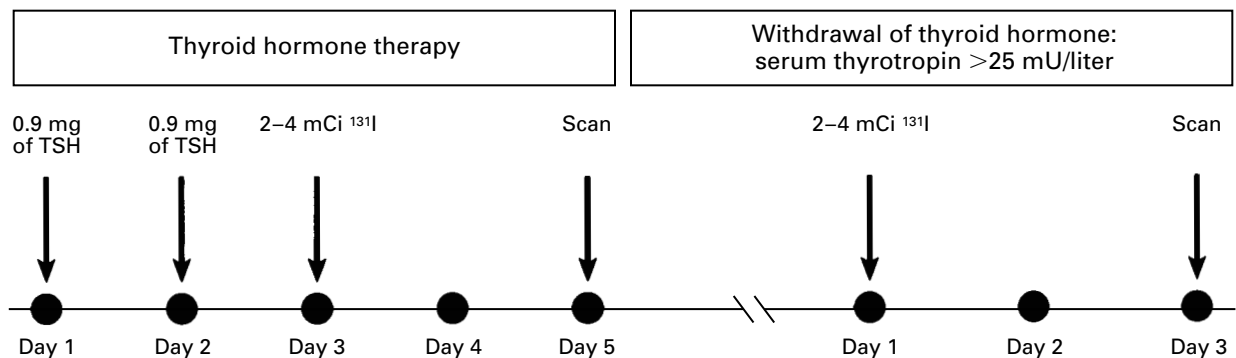
**Interpretation of Radioiodine Scans and Measurement of Uptake**

The radioiodine scans were evaluated by three reviewers who were not aware of the identity of the patient, the center, or the sequence of the scans. The reviewers initially categorized the technical quality of the scans, identified physiologic and abnormal sites of activity and potential artifacts, and stratified the apparent extent of disease on the basis of the presence of uptake in the thyroid bed or abnormal activity elsewhere in the neck, the lungs or mediastinum, or other distant sites. The numbers and locations of the foci of uptake were compared within each pair of scans to classify the two scans as concordant or discordant. If a pair of scans was discordant, the scan with the greater number of foci or the more widespread distribution of foci was considered superior. In 55 patients, the fractional radioiodine uptake in cervical foci was determined with a thyroid probe, by computerized region-of-interest analysis with a digital gamma camera, or both.

**Other Measurements**

Before each scan was obtained, the patient's vital signs; serum cholesterol, triglyceride, uric acid, creatinine, thyrotropin, and thyroglobulin concentrations; and urinary iodine<sup>20</sup> and creatinine concentrations were measured. In 35 patients, serum samples were obtained for thyroglobulin assay before and 48, 72, and 96 hours after the administration of thyrotropin and on the day of radioiodine administration after withdrawal of thyroid hormone therapy when the serum thyrotropin concentration was at least 25 mU per liter. Serum thyrotropin was measured by an immunoassay with a sensitivity of 0.1 mU per liter. Serum thyroglobulin was measured by a radioimmunoassay (Kronus, San Clemente, Calif.) with a sensitivity of 1 µg per liter. Antithyroglobulin antibodies were also measured by radioimmunoassay (Thymune-T, Murex Diagnostics, Dartford, United Kingdom); samples with values greater than 1 U per milliliter were not analyzed for thyroglobulin. Serum samples obtained one week after the second scanning were tested for antithyrotropin antibodies.

Each patient's clinical status was assessed by the Billewicz Scale and the short-form Profile of Mood States on entry to the study



**Figure 1.** The Study Design. TSH denotes intramuscular recombinant human thyrotropin.

and each time that radioiodine was administered. The Billewicz Scale is an observer-rated evaluation of 14 symptoms and signs of hypothyroidism.<sup>21</sup> The short-form Profile of Mood States is a self-administered assessment of six mood states (fatigue-inertia, depression-dejection, vigor-activity, confusion-bewilderment, tension-anxiety, and anger-hostility).<sup>22</sup>

### Statistical Analysis

The numbers of superior scans obtained by the two techniques were compared by the McNemar chi-square test. The differences in prescanning serum thyrotropin concentrations, absolute and fractional uptake of radioiodine, and prevalences of symptoms and disordered mood states, as assessed by the Billewicz Scale and the Profile of Mood States, were analyzed by the Wilcoxon signed-rank test. All statistical tests were two-sided.

## RESULTS

The characteristics of the 127 patients who completed the study are shown in Table 1.

### Serum Thyrotropin Concentrations

The mean ( $\pm$ SD) serum thyrotropin concentrations rose from a base line of  $0.2 \pm 0.3$  mU per liter to  $101 \pm 60$  and  $132 \pm 89$  mU per liter 24 hours after the first and second doses of thyrotropin, respectively. Seventy-two hours after the second dose of thyrotropin, the mean serum thyrotropin concentration was  $16 \pm 12$  mU per liter. In comparison, the mean serum thyrotropin concentration on the day of radioiodine administration after withdrawal of thyroid hormone was  $101 \pm 77$  mU per liter.

**TABLE 1. CHARACTERISTICS OF 127 PATIENTS WITH THYROID CARCINOMA.\***

CHARACTERISTIC	No. (%)
Female sex	90 (71)
Type of cancer	
Papillary	112 (88)
Follicular	12 (9)
Hürthle cell	3 (2)
Treatment status	
Previous thyroidectomy and radioiodine therapy	98 (77)
Previous thyroidectomy only	28 (22)
Previous radioiodine therapy only	1 (1)†
Sites of radioiodine-concentrating tissue after most recent surgery	
No uptake	3
Thyroid bed	75
Other cervical	34
Intrathoracic	10
Skeletal	5

\*None of the characteristics of the 127 patients completing the study protocol were significantly different from those of the remaining patients in the cohort of 152 patients initially enrolled. Because of rounding, not all percentages total 100.

†This patient had received previous radioiodine therapy for hyperthyroid Graves' disease and had never undergone thyroid surgery.

### Whole-Body Radioiodine Scanning after Thyrotropin Administration and after Thyroid Hormone Withdrawal

In 65 patients (51 percent), both the scan obtained after administration of thyrotropin and the scan obtained after withdrawal of thyroid hormone were negative. Among the 62 patients who had a positive scan with one or both techniques, 45 had radioiodine uptake limited to the thyroid bed, 10 had cervical activity consistent with local metastases, 4 had apparent intrathoracic metastases, 2 had skeletal or hepatic metastases, and 1 had activity interpreted as intrathoracic by one reviewer and as cervical by another.

The two scans were equivalent in 41 of the 62 patients (66 percent) who had at least one positive scan (Fig. 2 and Table 2). The scan obtained after administration of thyrotropin was superior (positive) in 3 patients (5 percent), and the scan obtained after withdrawal of thyroid hormone was superior in 18 patients (29 percent) ( $P=0.001$ ) (Table 3). On the assumption that all activity outside the thyroid bed actually represented tumor, the staging of thyroid cancer would be similar in 40 of the 62 patients (65 percent), including 6 of the 11 patients with cervical activity outside the thyroid bed, 3 of the 4 patients with intrathoracic activity, and the 2 patients with radioiodine uptake in other distant regions.

Among all 127 patients, including those who had concordant negative scans, the reviewers rated the scans obtained after administration of thyrotropin as equivalent (in 106 patients) or superior (in 3 patients) to those obtained after withdrawal of thyroid hormone in 86 percent and as inferior in 14 percent. The rates of concordant and discordant pairs of scans were similar whether or not the patient had received iodine-131 therapy previously.

There were no significant differences between patients with concordant scans and those with discordant scans in any of the following features: age, sex, weight, tumor type or extent of disease, previous radioiodine therapy, time since surgery or last iodine-131 treatment, activity of iodine-131 administered for scanning, serum thyrotropin concentrations or estimated urinary iodine excretion (data not shown) before administration of radioiodine for the two scans, time after withdrawal of thyroid hormone therapy, or investigational site.

Of the 18 patients for whom the scan obtained after withdrawal of thyroid hormone was superior, 10 were subsequently treated with iodine-131. Five received iodine-131 to ablate thyroid remnants and three to ablate cervical activity outside the thyroid bed that was seen only on the scan obtained after withdrawal of thyroid hormone. The serum thyroglobulin concentrations had increased after administration of thyrotropin in three of these patients. In the remaining two radioiodine-treated patients for whom the scans obtained after withdrawal of thyroid

hormone were superior, both scans showed uptake in the thyroid bed, but the scans were categorized as discordant because one additional focus was identified on the scan obtained after withdrawal of thyroid hormone. Of the eight patients with a superior scan after withdrawal of thyroid hormone who were not treated with iodine-131, only thyroid-bed activity was seen in five patients, and a single focus outside the thyroid bed was seen in three patients, who were not treated because their serum thyroglobulin concentration was low (one patient) or an artifact was suspected (two patients).

#### Radioiodine Uptake after Thyrotropin Administration and after Thyroid Hormone Withdrawal

Among the 126 patients who had undergone thyroidectomy, the mean thyroid-bed uptake of iodine-131 was higher after withdrawal of thyroid hormone than after administration of thyrotropin according to thyroid-probe analysis ( $0.4 \pm 0.7$  percent vs.  $0.3 \pm 0.7$  percent,  $P=0.004$ ) in 47 patients and region-of-interest analysis ( $0.5 \pm 0.9$  percent vs.  $0.3 \pm 0.6$  percent,  $P=0.02$ ) in 30 patients. When the mean thyroidal uptake of radioiodine was corrected for the differences in whole-body retention of iodine-131, however, the average fractional-uptake value did not differ in scans obtained after administration of thyrotropin and scans obtained after withdrawal of thyroid hormone (data not shown).

#### Serum Thyroglobulin after Thyrotropin Administration and after Thyroid Hormone Withdrawal

Serum thyroglobulin was measured in 35 patients before administration of thyrotropin and at various intervals after their first dose of thyrotropin and after withdrawal of thyroid hormone. The serum thyroglobulin concentration increased to  $5 \mu\text{g}$  per liter or more at some time in 15 patients. The increase occurred after thyrotropin administration in 13 patients and after withdrawal of thyroid hormone in 14 patients. The serum thyroglobulin concentration was higher after withdrawal of thyroid hormone in 11 patients and after administration of thyrotropin in 3 patients, and it was not precisely quantified by dilution studies in 1 patient. The serum thyroglobulin concentrations were highest 72 or 96 hours after the first dose of thyrotropin in the 33 patients studied at these times.

#### Clinical and Biochemical Changes after Thyrotropin Administration and after Thyroid Hormone Withdrawal

The patients had more symptoms after withdrawal of thyroid hormone than after administration of thyrotropin. There were statistically significant differences between the two study periods for all 14 symptoms and signs of hypothyroidism on the Billewicz Scale (weight gain, constipation, cold intolerance, slow movement, paresthesias, deafness, diminished

sweating, hoarseness, dry skin, coarse skin, cold skin, puffiness, slowed ankle jerk, and decreased pulse rate) ( $P<0.001$ ) and all 6 states of the Profile of Mood States ( $P<0.001$ ).

The mean heart rate was slower after withdrawal of thyroid hormone than after administration of thyrotropin ( $78 \pm 12$  vs.  $68 \pm 11$  beats per minute,  $P<0.001$ ). The patients had significantly higher mean serum concentrations of cholesterol (by 66 percent), triglycerides (by 70 percent), uric acid (by 24 percent), and creatinine (by 44 percent) after withdrawal of thyroid hormone than after administration of thyrotropin ( $P<0.001$  for all).

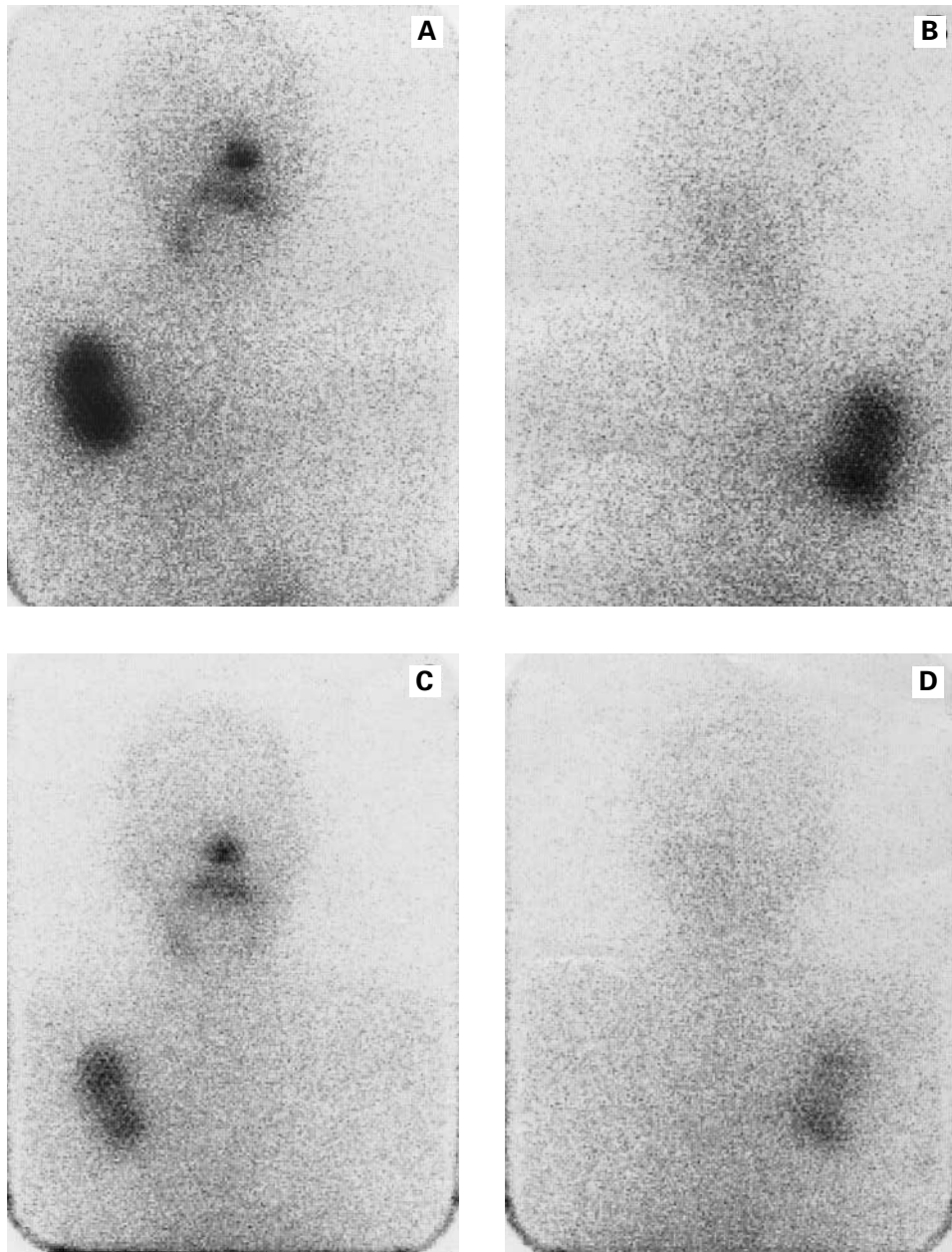
#### Adverse Effects and Assessment of Antithyrotropin Antibodies

Of the 152 patients enrolled in the study, 48 (32 percent) had adverse events, which were interpreted by their treating physicians as definitely caused by thyrotropin in 6 patients, probably caused by it in 20, and possibly caused by it in 22. The only common adverse event was nausea, which occurred in 25 patients (16 percent), but was usually mild and short-lived. One patient with recurrent invasive thyroid carcinoma died of an apparent pulmonary embolus six days after administration of thyrotropin. No patient had detectable serum antithyrotropin antibodies, including seven who had received thyrotropin 7 to 16 months earlier.

## DISCUSSION

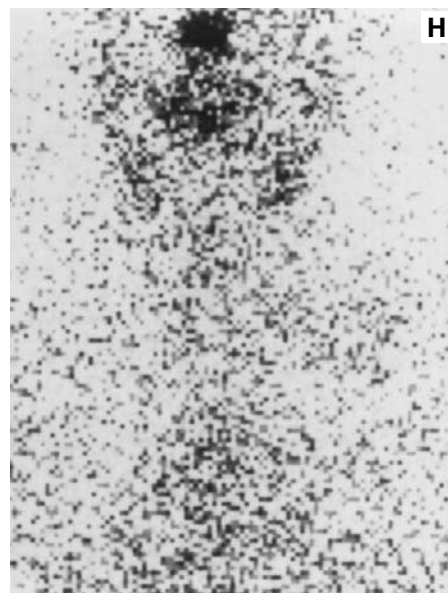
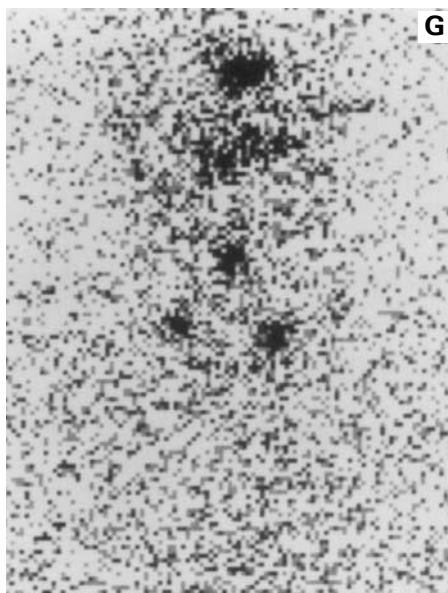
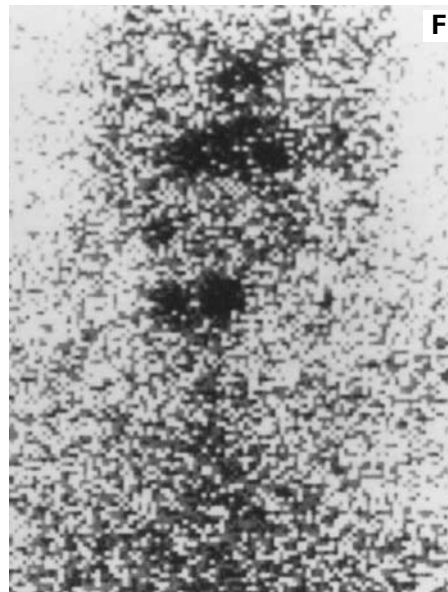
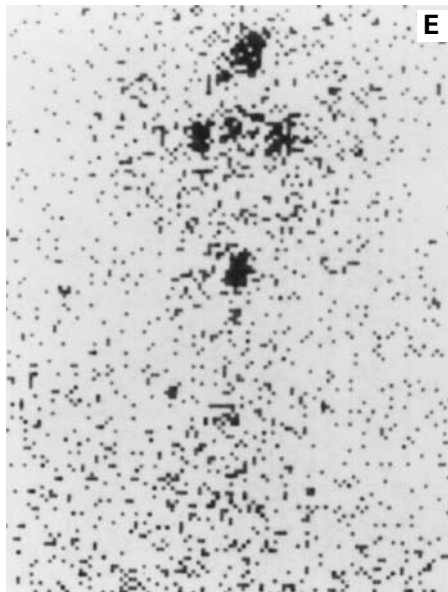
We found that recombinant thyrotropin was efficacious and safe for stimulating the uptake of radioiodine in patients with thyroid carcinoma who continued thyroid hormone therapy, but not as effective as withdrawal of thyroid hormone. Treatment with thyrotropin averted the hypothyroid symptoms and mood disorders that occur after withdrawal of thyroid hormone. In 71 percent of patients with a positive scan obtained by one or both techniques, the scan obtained after the administration of thyrotropin was equivalent or superior to the one obtained after withdrawal of thyroid hormone, whereas the latter was superior in the remaining 29 percent. Conversely, the scans obtained after withdrawal of thyroid hormone were equivalent or superior to those obtained after administration of thyrotropin in 95 percent of the patients with a positive scan. When patients with negative scans — the finding most commonly encountered in patients who have previously received radioiodine therapy — were included, the scans obtained after administration of thyrotropin were equivalent or superior to those obtained after withdrawal of thyroid hormone in 86 percent of the patients.

Although the scans obtained after withdrawal of thyroid hormone were rated superior by the independent reviewers in more than one quarter of the



**Figure 2.** Radioiodine Scans in Patients with Thyroid Cancer after Administration of Thyrotropin and after Withdrawal of Thyroid Hormone Therapy.

Panels A, B, C, and D show paired concordant whole-body scans. Panels A (anterior view) and B (posterior view) show scans in a patient with metastatic thyroid carcinoma after thyrotropin administration; Panels C (anterior view) and D (posterior view) show scans in this patient after withdrawal of thyroid hormone. Both sets of scans show abnormal foci of iodine-131 activity in the right superior thorax. Physiologic nasopharyngeal activity is seen in the anterior views and in all the scans shown in Panels E, F, G, and H. Panels E and F show paired discordant scans of the head, neck, and upper chest. The scan obtained after administration of thyrotropin shows a single focus of thyroid-bed activity (Panel E), and a superior scan obtained after thyroid hormone withdrawal shows two additional foci in the right thyroid bed and right cervical region (Panel F). Panels G and H show paired discordant scans of the head, neck, and upper chest in another patient. The scan obtained after administration of thyrotropin shows three foci of cervical activity (Panel G), and an inferior scan obtained after thyroid hormone withdrawal (Panel H) shows no abnormal foci. All scans were performed 48 hours after the administration of 2 to 4 mCi of iodine-131.



patients, the clinical importance of the difference is uncertain. Of 12 patients with uptake in the thyroid bed on the post-withdrawal scan alone, 5 were treated with radioiodine, a difference that reflects the variability in practice with regard to radioiodine therapy in this circumstance. Of the six patients with additional iodine-avid lesions outside the thyroid bed demonstrated only by the post-withdrawal scan, three were treated with radioiodine. Both scans were positive in the seven patients with other metastases subsequently treated with radioiodine. The additional information provided by the withdrawal of thyroid hormone must be balanced against the symptoms

that occur in most patients when they are hypothyroid for several weeks.

There are two possible explanations for the discordant scans. First, radioiodine clearance is decreased in hypothyroidism, resulting in higher bioavailability of radioiodine for imaging after withdrawal of thyroid hormone.<sup>23</sup> Second, the degree and duration of stimulation by thyrotropin produced by the dosing regimen in this study may not be optimal. Protocols producing more prolonged stimulation by thyrotropin, mimicking more closely that which follows withdrawal of thyroid hormone, might be superior.

A limitation of the study design was that the se-

**TABLE 2.** CORRELATION OF POSITIVE AND NEGATIVE RADIOIODINE SCAN FINDINGS AFTER ADMINISTRATION OF THYROTROPIN AND AFTER WITHDRAWAL OF THYROID HORMONE IN 127 PATIENTS WITH THYROID CARCINOMA.\*

POST-THYROTROPIN SCAN	POST-WITHDRAWAL SCAN	
	POSITIVE	NEGATIVE
Positive	41	3
Negative	18	65

\*P=0.001 for the comparison of scanned findings with the two techniques.

quence of the two scans was not randomized. It would have been inappropriate if a patient for whom radioiodine therapy was indicated by a positive scan on withdrawal of thyroid hormone or by an elevated serum thyroglobulin concentration had been required to resume thyroid hormone therapy so that another scan could be obtained after administration of thyrotropin, because this second scanning would delay radioiodine therapy. It is possible that the radioiodine administered for the first scan might have “stunned” residual iodine-avid thyroid tissue, decreasing the sensitivity of the scanning after withdrawal of thyroid hormone. However, this seems unlikely, because 96 percent of the post-withdrawal

**TABLE 3.** CANCER STAGE, SCAN CLASS, AND SERIAL SERUM THYROGLOBULIN CONCENTRATIONS IN THE 21 PATIENTS WITH DISCORDANT RADIOIODINE SCANS AFTER THYROTROPIN ADMINISTRATION AND AFTER WITHDRAWAL OF THYROID HORMONE THERAPY.

PATIENT NO.	CANCER STAGE*	CLASS OF RADIOIODINE SCANT		SERUM THYROGLOBULIN CONCENTRATION†			RADIOIODINE THERAPY
		AFTER THYROTROPIN	AFTER WITHDRAWAL	DURING THYROID HORMONE THERAPY	AFTER THYROTROPIN§	AFTER WITHDRAWAL	
						µg/liter	
1	II	1	0	2	3	3	Yes
2	I	1	0	1	1	2	No
3	II	1	1	NA	2	7	No
4	I	0	2	2	134	233	Yes
5	I	0	2	2	2	3	Yes
6	I	1	2	NA	NA	NA	Yes
7	I	0	1	1	1	1	Yes
8	I	0	1	15	27	98	Yes
9	II	0	1	2	3	5	Yes
10	II	0	1	26	78	ND	Yes
11	III	0	1	2	2	7	Yes
12	III	1	1	2	5	ND	Yes
13	III	1	1	57	55	124	Yes
14	I	0	1	3	6	5	No
15	I	0	1	NA	NA	NA	No
16	III	0	2 or 3	2	4	7	No
17	I	1	2	3	2	3	No
18	I	1	1	3	4	4	No
19	II	0	1	10	7	3	No
20	II	0	3	4	4	3	No
21	I	0	1	2	2	2	No

\*The tumor–node–metastasis staging system of the American Joint Commission on Cancer was used, with I denoting tumor localized to the thyroid gland or local spread in patients less than 45 years old, or primary tumor less than 1 cm in diameter and no spread in patients 45 or older; II, distant metastases in patients less than 45 years old, or tumor greater than 1 cm in diameter and no spread in patients 45 or older; III, local cervical invasion or lymph-node involvement by tumor in patients 45 or older; and IV, tumor with distant metastases in patients 45 or older.

†The scans were classified as follows: 0, no abnormal uptake; 1, uptake in thyroid bed; 2, uptake in neck outside thyroid bed; 3, pulmonary or mediastinal uptake; and 4, other distant uptake.

‡NA denotes not available because of interference by antithyroglobulin antibodies, and ND not done.

§The serum thyroglobulin concentrations shown were measured at the sole sampling time, 24 hours after the second dose of thyrotropin, except in Patients 1, 9, and 16, in whom serial samples were obtained (see the Methods section) and for whom 48- or 96-hour values are shown.

scans proved to be positive in patients with preceding positive thyrotropin scans, the fractional radioiodine uptake in thyroid tissue was actually higher after radioiodine dosing for the second scan, and "stunning" occurs more often with higher doses of radioiodine for scanning than were used in this study.<sup>24</sup>

Measurement of serum thyroglobulin is a valuable technique for detecting residual or recurrent thyroid carcinoma.<sup>6,7</sup> Although assessment of thyrotropin-mediated thyroglobulin stimulation was not a primary end point of this study, the results in a subgroup of patients demonstrate that exogenous thyrotropin is capable of stimulating the release of thyroglobulin. This finding suggests that administration of thyrotropin may increase the sensitivity of serum thyroglobulin as a tumor marker.

The fact that with radioiodine scanning after the administration of thyrotropin one can avert the hypothyroidism that occurs after the withdrawal of thyroid hormone therapy is potentially clinically important. The consequences of even short-term hypothyroidism — in terms of impaired work performance, personal safety, and interpersonal relations — are familiar to physicians who have cared for patients requiring periodic discontinuation of thyroid hormone therapy for radioiodine scanning. Although a recent small study<sup>25</sup> suggested that partial withdrawal of thyroid hormone can facilitate scanning while minimizing symptoms, this approach will require more evaluation. Furthermore, after withdrawal of thyroid hormone, the prolonged rise in serum thyrotropin, which has tropic effects on residual thyroid-cancer tissue, can promote tumor progression, with potentially serious clinical consequences, particularly in patients with central nervous system metastases.<sup>9-11</sup>

Thyrotropin was well tolerated by most patients in this study. The side effects were limited to nausea, which was short-lived and mild in most patients. An antithyrotropin immunoglobulin response was not detected, even among patients who had previously received thyrotropin.

In conclusion, thyrotropin was effective in stimulating the uptake of radioiodine for scanning in patients who had been treated for thyroid cancer. Thyrotropin-mediated diagnostic scans were as sensitive as those obtained after withdrawal of thyroid hormone in the majority of patients, but 29 percent of the patients with positive scans had superior scans after withdrawal of thyroid hormone. This resulted in more advanced tumor staging in 6 percent of the patients and led to radioiodine treatment of 13 percent of the patients. Thyrotropin also stimulates the production of thyroglobulin by residual thyroid tissue, which may increase the usefulness of this tumor marker in patients treated with thyroid hormone who have had thyroid tissue ablated. The patients

had significantly fewer symptoms when they were taking thyrotropin and continuing thyroid hormone therapy than when they discontinued thyroid hormone therapy.

*We are indebted to Juan Francisco Fierro, M.D., Colum A. Gorman, M.D., Gregory A. Ledger, M.D., S.-G. Park, M.D., Gregory Randolph, M.D., Christine Schmeier, M.D., Monica Skarulis, M.D., Irini Veronikis, M.D., Steven Tollin, M.D., Maralyn Valentine, M.D., Karen M. Auwaerter, R.N., Craig Cochran, R.N., Sheryl M. Ness, R.N., Roxanne Schock, R.N., Naomi Walpert, R.N., M.S., Millie Whatley, N.M.T., and Bernadette White, R.N., who skillfully contributed to these studies and to the care of the patients; and to Ms. Deirdre Maxted for assistance with study coordination and data analyses.*

## REFERENCES

1. Cancer facts and figures. Atlanta: American Cancer Society, 1995.
2. Robbins J, Merino MJ, Boice JD Jr, et al. Thyroid cancer: a lethal endocrine neoplasm. *Ann Intern Med* 1991;115:133-47.
3. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 1994; 97:418-28. [Erratum, *Am J Med* 1995;98:215.]
4. Maxon HR III, Smith HS. Radioiodine-131 in the diagnosis and treatment of metastatic well differentiated thyroid cancer. *Endocrinol Metab Clin North Am* 1990;19:685-718.
5. Goldman JM, Line BR, Aamodt RL, Robbins J. Influence of triiodothyronine withdrawal time on I31I uptake postthyroidectomy for thyroid cancer. *J Clin Endocrinol Metab* 1980;50:734-9.
6. Ozata M, Suzuki S, Miyamoto T, Liu RT, Fierro-Renoy F, DeGroot LJ. Serum thyroglobulin in the follow-up of patients treated with differentiated thyroid cancer. *J Clin Endocrinol Metab* 1994;79:98-105.
7. Pacini F, Pinchera A, Giani C, Grasso L, Baschieri L. Serum thyroglobulin concentrations and I31I whole body scans in the diagnosis of metastases from differentiated thyroid carcinoma (after thyroidectomy). *Clin Endocrinol (Oxf)* 1980;13:107-10.
8. Ringel MD, Ladenson PW. Diagnostic accuracy of I31I scanning with recombinant human thyrotropin versus thyroid hormone withdrawal in a patient with metastatic thyroid carcinoma and hypopituitarism. *J Clin Endocrinol Metab* 1996;81:1724-5.
9. Maloof F, Vickery AL, Rapp B. An evaluation of various factors influencing the treatment of metastatic thyroid carcinoma with I31I. *J Clin Endocrinol Metab* 1956;16:1-27.
10. Sfakianakis GN, Skillman TG, George JM. Thyroxine withdrawal in thyroid cancer. *Ohio State Med J* 1975;71:79-82.
11. Goldberg LD, Ditchek NT. Thyroid carcinoma with spinal cord compression. *JAMA* 1981;245:953-4.
12. Sturgeon CT, Davis FE, Catz B, Petit D, Starr P. Treatment of thyroid cancer metastases with TSH and I31I during thyroid hormone medication. *J Clin Endocrinol Metab* 1953;13:1391-407.
13. Benua RS, Sonenberg M, Leeper RD, Rawson RW. An 18 year study of the use of beef thyrotropin to increase I31I uptake in metastatic thyroid cancer. *J Nucl Med* 1964;5:796-801.
14. Szkudlinski MW, Thotakura NR, Bucci I, et al. Purification and characterization of recombinant human thyrotropin (TSH) isoforms produced by Chinese hamster ovary cells: the role of sialylation and sulfation in TSH bioactivity. *Endocrinology* 1993;133:1490-503.
15. Thotakura NR, Desai RK, Bates LG, Cole ES, Pratt BM, Weintraub BD. Biological activity and metabolic clearance of a recombinant human thyrotropin produced in Chinese hamster ovary cells. *Endocrinology* 1991; 128:341-8.
16. Huber GK, Fong P, Concepcion ES, Davies TF. Recombinant human thyroid-stimulating hormone: initial bioactivity assessment using human fetal thyroid cells. *J Clin Endocrinol Metab* 1991;72:1328-31.
17. Braverman LE, Pratt BM, Ebner S, Longcope C. Recombinant human thyrotropin stimulates thyroid function and radioactive iodine uptake in the Rhesus monkey. *J Clin Endocrinol Metab* 1992;74:1135-9.
18. Meier CA, Braverman LE, Ebner SA, et al. Diagnostic use of human recombinant thyrotropin in patients with thyroid carcinoma (phase I/II study). *J Clin Endocrinol Metab* 1994;78:188-96.
19. Cole ES, Lee K, Lauziere K, et al. Recombinant human thyroid stimulating hormone: development of a biotechnology product for detection of metastatic lesions of thyroid carcinoma. *Biotechnology* 1993;11:1014-24.

- 20.** Benotti J, Benotti N, Pino S, Gardyna H. Determination of total iodine in urine, stool, diets, and tissue. *Clin Chem* 1965;11:932-6.
- 21.** Billewicz WZ, Chapman RS, Crooks J, et al. Statistical methods applied to the diagnosis of hypothyroidism. *Q J Med* 1969;38:255-66.
- 22.** Shacham S. A shortened version of the Profile of Mood States. *J Pers Assess* 1983;47:305-6.
- 23.** Park S-G, Reynolds JC, Brucker-Davis F, et al. Iodine kinetics during I-131 scanning in patients with thyroid cancer: comparison of studies with recombinant human TSH (rhTSH) vs. hypothyroidism. *J Nucl Med* 1996;37:Suppl:15P abstract.
- 24.** Park H-M, Perkins OW, Edmondson JW, Schnute RB, Manatunga A. Influence of diagnostic radiiodines on the uptake of ablative dose of iodine-131. *Thyroid* 1994;4:49-54.
- 25.** Guimaraes V, DeGroot LJ. Moderate hypothyroidism in preparation for whole body <sup>131</sup>I scintiscans and thyroglobulin testing. *Thyroid* 1996;6:69-73.