

# CLINICAL THYROIDOLOGY

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## Editor-in-Chief

**Robert D. Utiger, M.D.**

Thyroid Division  
Department of Medicine  
Brigham & Women's Hospital  
77 Avenue Louis Pasteur  
Boston, MA 02115  
(617) 525-5171 Telephone  
(617) 731-4718 Fax  
editorclinthy@thyroid.org

## Founding Editor

Ridha Arem, M.D.

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Diane P. Miller  
American Thyroid Association  
55 Old Nyack Turnpike, Suite 611  
Nanuet, NY 10954-2454  
(845) 623-1800 Telephone  
(845) 623-3736 Fax  
admin@thyroid.org

## Published By

Saratoga Graphics  
7 Kaatskill Way  
Ballston Spa, NY 12020  
(518) 583-0243  
Art Direction: Kandra L. Files  
kanlynn@sprynet.com

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## A New *Clinical Thyroidology*

This issue marks a new beginning for *Clinical Thyroidology*. It is now a publication of the American Thyroid Association, and it has a new appearance and a new editor. Now beginning its 13th year of publication, this journal was launched by Dr. Ridha Arem for the purpose of informing endocrinologists about the best clinical studies in thyroidology - wherever published - and providing commentary about those studies. As founding editor, Dr. Arem nourished the journal wisely, so that it has become a valuable source of information about new studies in the field.

The purpose of this format is not only to inform readers of interesting and useful new studies of thyroid pathophysiology and disease (the summaries), but also to put the studies in perspective and offer editorial opinion about them (the commentaries). Ideally, readers will be stimulated to look further. Journals such as this do not take the place of those that contain reports of original research, indeed they are totally dependent upon reports of original research for their existence. What you will get here is only a summary and commentary, and no matter how carefully an article is summarized or how good (or bad) the commentary may be, you will not see all the data you ought to see before drawing your own conclusions about the value of a particular study and whether it is applicable to your work or practice.

The focus of *Clinical Thyroidology* will continue to be on clinical studies, and the search for such studies will be broad, extending beyond journals of endocrinology as it has in the past. In addition, I think that there is a place for summaries and commentary about preclinical studies. As examples, there is in this issue a summary of an article describing the identification of thyroid hormone receptors in the brain of fetuses and another of an article describing the effects of a new thyroid hormone analogue in mice and rats.

This journal was supported initially by the Daniels Pharmaceutical Company, and the support continued when Daniels was bought by Jones Pharma, Inc. That company has in effect given the journal to the association, and has generously agreed to provide support for it for five years. I have no financial or other relationships with Jones Pharma.

*Clinical Thyroidology* is the second scientific publication, after *Thyroid*, of the American Thyroid Association. It will be distributed three times yearly to all members of the association, other endocrinologists, and anyone else who requests a copy, and it will be available soon on the association's Web site. It is my hope that it will complement *Thyroid* well.

I am pleased to be the editor of this journal. I think it will be fun, informative and stimulating. You may not find the contents fun, but I hope you will find them informative and stimulating, and will let me know if they are not.

Robert D. Utiger, M.D.

## ATA News & Upcoming Events

### *Clinical Thyroidology*

The journal is available without charge. Those who wish to be added to the mailing list should e-mail the administrative office (admin@thyroid.org), including your full name, institution, address, telephone and fax numbers, and e-mail address.

### 73rd Annual Meeting of the Association

The annual meeting will be held at the Omni Shoreham Hotel in Washington, DC from September 12 to 16, 2001. The deadline for submission of abstracts is Wednesday, May 9, 2001. All abstracts must be submitted electronically using the form on the ATA web site.

Pre-registration material for the meeting will be mailed in May 2001.

The preliminary scientific program for 2001 is available online (www.thyroid.org).

## Approximately half of patients with hyperthyroidism or hypothyroidism have neuromuscular dysfunction

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Duyff RF, Van den Bosch J, Laman DM, Potter van Loon B-J, Linssen WHJP. Neuromuscular findings in thyroid dysfunction: a prospective clinical and electrodiagnostic study. *J Neurol Neurosurg Psychiatry* 2000;68:750-5.

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### SUMMARY

**Background** Patients with either hyperthyroidism or hypothyroidism may have symptoms and signs of neuromuscular dysfunction, but there have been few systematic studies of neuromuscular function in these patients.

**Methods** Comprehensive clinical and electrodiagnostic studies were done in 24 consecutive patients with hyperthyroidism (mean age 48 years) and 21 patients with hypothyroidism (mean age 43 years) before and after treatment. The studies included detailed assessment of muscle strength and sensation and electrodiagnostic studies (electromyography and measurements of nerve conduction times).

**Results** Among the 24 patients with hyperthyroidism, 67 percent had complaints of muscle weakness, 62 percent had objective muscle weakness, mainly in the proximal muscles of the legs, 19 percent had symmetric distal sensory abnormalities and depressed distal tendon reflexes, 38 percent had generalized hyperreflexia and 76 percent had tremor. During or after treatment (an antithyroid drug or radioiodine) the muscle weakness resolved in an average of 4 months and the sensory abnormalities resolved in an average of 7 months.

Among the 21 patients with hypothyroidism, 79 percent had symptoms of muscle dysfunction (weakness 54 percent, fatigability, muscle cramps, pain or stiffness 42 percent). Muscle weakness was detected in 38 percent, largely in proximal muscles, symmetric distal sensory abnormalities and depressed reflexes in 42 percent and the carpal tunnel syndrome in 29 percent. Seven patients had high serum creatine kinase concentrations, which did not correlate with muscle weakness. During treatment the muscle symptoms resolved in most patients in an average of 7 months.

**Conclusion** The majority of patients with hyperthyroidism or hypothyroidism have symptoms and signs of neuromuscular dysfunction.

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### COMMENTARY

These 45 patients were seen in a medical outpatient department in the Netherlands, and their age (mean 46 years), sex (80 percent women) and biochemical abnormalities were characteristic of the two thyroid disorders. The study has several limitations. The patients were recruited from a larger group of 141 patients (most of the others declined to participate because of the electrodiagnostic studies). Those who participated may have had more, or more severe, symptoms, and therefore the study patients may not be representative of all patients with these disorders.

Also, similar studies were not done simultaneously in a group of normal subjects of the same age and sex.

Whatever the limitations of the study, there is considerably more information in the article than summarized above. It includes detailed summaries of different symptoms and signs, the results of systematic grading of muscle strength and of measurements of muscle strength by dynamometry, the results of the electrodiagnostic studies and the relationships between neuromuscular symptoms and the overall duration of thyroid disease. The results thus provide a useful picture of the breadth of neuromuscular symptoms

and signs that occur in patients with hyperthyroidism and hypothyroidism and the extent to which they are reversible.

Robert D. Utiger, M.D.

## Radiation therapy in children and adolescents is associated with risk for all types of thyroid disease

Sklar C, Whitton J, Mertens A, Stovall M, Green D, Marina N, Greffe B, Wolden S, Robison L. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor study. *J Clin Endocrinol Metab* 2000;85:3227-32.

### SUMMARY

**Background** Most patients with Hodgkin's disease receive radiation therapy to the neck, which may subsequently affect thyroid function and cause thyroid tumors. The types of thyroid disease and the risk factors for them have not been evaluated in a large cohort followed for many years.

**Methods** The Childhood Cancer Survivor Study is a cohort study of children, adolescents and young adults (age <21 years) treated for cancer between 1970 and 1986 at 25 centers in the United States who survived for at least 5 years after diagnosis. This study focused on the 1791 patients (959 males and 82 females) with Hodgkin's disease in the cohort for whom follow-up data were obtained. The median age at diagnosis was 14 years (range 2 to 20), and the median age at follow-up was 30 years (range 12 to 47).

Follow-up data were obtained by mail questionnaire containing specific questions about thyroid dysfunction and tumors; diagnoses of thyroid cancer were verified by review of pathology reports. The same questionnaire was sent to 348 siblings (150 males and 198 females, median age 25 years) of the patients with Hodgkin's disease.

**Results** The incidence of hyperthyroidism, hypothyroidism and thyroid nodules was significantly higher in the patients with Hodgkin's disease than their siblings ( $P < 0.001$  for all comparisons) (table).

**Hyperthyroidism.** The mean interval between diagnosis of Hodgkin's disease and hyperthyroidism was 8 years (range 0 to 22). Factors associated with increased risk were time after diagnosis of Hodgkin's disease and higher radiation doses.

Table. Incidence of Thyroid Disease in Surviving Patients with Hodgkin's Disease.

Disease	Survivors		Siblings		Relative Risk*
	Cases	Rate/1000 py**	Cases	Rate/1000 py	
Hyperthyroidism	82	1.6	13	0.2	8.0 (4.6-15.1)
Hypothyroidism	456	9.6	39	0.6	17.1 (12.5-24.3)
Nodule(s)	146	2.9	7	0.1	27.0 (13.6-63.9)

\*95 percent confidence intervals in parenthesis.  
\*\*py denotes person years.

**Hypothyroidism.** Hypothyroidism was diagnosed a mean of 7 years (range 0 to 27 years) after diagnosis of Hodgkin's disease. Hypothyroidism was more common in females, and was associated with older age at and increasing time after diagnosis of Hodgkin's disease. Among patients who received 3500 to 4499 cGy and those who received  $\geq 4500$  cGy or more, the actuarial risks of hypothyroidism at 20 years were 30 percent and 50 percent, respectively.

**Thyroid Nodules.** Thyroid nodules were detected on average 14 years (range 0 to 27) after diagnosis of Hodgkin's disease. Factors associated with increased risk were female sex, time after diagnosis of Hodgkin's disease and radiation doses  $\geq 2500$  cGy. The actuarial risk of a thyroid nodule in a female 20 years after radiation therapy was 20 percent.

**Thyroid Cancer.** Among the 146 patients who had thyroid nodules, 11 (7.5 percent) had thyroid cancer; 9 other patients reported having thyroid cancers but not thyroid nodules.

**Conclusion** Thyroid diseases of all types are common in patients with Hodgkin's disease who receive radiation therapy.

### COMMENTARY

Thyroid nodular disease, including thyroid cancer, is a complication of both low- and high-dose radiation therapy to the head and neck region in young people. Hypothyroidism is a complication of high-dose radiation therapy to this region in patients of any age, not only in patients with Hodgkin's disease but also in those who receive radiation therapy for cancer of the larynx or other head

and neck structures.

That patients with Hodgkin's disease who receive radiation therapy have an increased risk of hyperthyroidism is less well known. There is no information about the causes of hyperthyroidism in this study, but it was probably Graves' disease in most of the patients. Presumably, in some patients who are genetically susceptible to Graves' disease radiation therapy injures the T cells that maintain the patient's tolerance to their

own thyroid antigen(s). Perhaps hypothyroidism in radiation-treated patients is due not to a direct destructive effect of radiation on thyroid cells, but rather radiation-induced injury of T cells that maintain tolerance to the thyroid antigen(s) involved in thyroid-cell cytotoxicity or antibody-mediated thyroid-cell injury.

Robert D. Utiger, M.D.



## Subclinical hyperthyroidism causes symptoms and has deleterious cardiovascular effects

Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Sacca L, Filetti S, Lombardi G, Perticone F. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. *J Clin Endocrinol Metab* 2000;85:4701-5.

### SUMMARY

**Background** Subclinical hyperthyroidism is defined as a low serum thyrotropin (TSH) concentration in an otherwise biochemically euthyroid patient. The extent to which it causes symptoms or affects organ function is debated.

**Methods** The presence of symptoms and cardiovascular function were determined in 23 patients (20 women and 3 men, mean [ $\pm$ SD] age  $40 \pm 10$  years) with subclinical hyperthyroidism caused by a solitary thyroid adenoma or a multinodular goiter and 23 age- and sex-matched normal subjects. All the patients had subclinical hyperthyroidism for at least 6 months. Symptoms were assessed using a Hyperthyroid Symptom Scale and the Short Form 36 Health Survey. Cardiac function was assessed by electrocardiography and echocardiography.

**Results** The mean symptom score was 10 in the patients and 4 in the normal subjects ( $P < 0.001$ ) (compared with  $\geq 20$  in patients with overt hyperthyroidism). The scores on both the mental and physical scales of the Short Form 36 were lower in the patients, indicating more disability. The

mean 24-hour heart rates were 70 and 82 beats/minute in the normal subjects and the patients ( $P < 0.01$ ), but there were no differences in the frequency of atrial or ventricular premature beats. Echocardiography revealed a greater ventricular mass (162 g versus 132 g) and end-systolic diameter, increased systolic contractility and decreased diastolic relaxation in the patients, as compared with the normal subjects.

**Conclusion** Patients with subclinical hyperthyroidism caused by thyroid nodular disease have some symptoms of hyperthyroidism, are less healthy, and have abnormal cardiac function.

### COMMENTARY

Some notable features of this study were that the patients had endogenous subclinical hyperthyroidism, they had no changes in serum free  $T_4$  and free  $T_3$  concentrations in the six months before they were studied and the study included use of the Short Form 36 to assess well being. The overall findings are similar to those found in patients with subclinical hyperthyroidism caused by exogenous thyroxine ( $T_4$ ) therapy by the same investigators (1); the Short Form 36 scores provide further evidence that subclinical hyperthyroidism may be associated with some disability. In another study of  $T_4$ -treated patients, however, the patients had substantially lower scores on the Hyperthyroid Symptom Scale (2). Unfortunately, none of these studies included a group of patients with overt hyperthyroidism.

When subclinical hyperthyroidism is

caused by too much  $T_4$ , the cardiovascular changes, and presumably the risk of overt cardiovascular problems, can be reduced by reducing the dose of  $T_4$  (3) or giving a  $\beta$ -adrenergic antagonist drug. Symptoms should improve too. There is no reason to doubt that similar improvement would occur in patients with subclinical hyperthyroidism caused by thyroid nodular disease, but the study hasn't been done. It should be a controlled study with methimazole or placebo, or possibly radioiodine and placebo, and last at least six months.

Robert D. Utiger, M.D.

#### References

1. Biondi B, Fazio S, Palmieri EA, et al. Effects of chronic subclinical hyperthyroidism from levothyroxine on cardiac morphology and function. *Cardiologia* 1999;44:443-9.

2. Shapiro LE, Sievert R, Ong L, et al. Minimal cardiac effects in asymptomatic athyreotic patients chronically treated with thyrotropin-suppressive doses of L-thyroxine. *J Clin Endocrinol Metab* 1997;82:2592-5.

3. Mercurio M, Panzuto MG, Bina A, et al. Cardiac function, physical exercise capacity, and quality of life during long-term thyrotropin-suppressive therapy with levothyroxine: effect of individual dose tailoring. *J Clin Endocrinol Metab* 2000;85:159-64.

## High serum triiodothyronine concentrations are a risk factor for coronary events

Peters A, Ehlers M, Blank B, Exler D, Falk C, Kohlmann T, Fruehwald-Schultes B, Welhoener P, Kerner W, Fehm HL. Excess triiodothyronine as a risk factor for coronary events. *Arch Intern Med* 2000;160:1993-9.

### SUMMARY

**Background** Hyperthyroidism alters cardiovascular function in ways that may be detrimental, but the relationships between hyperthyroidism and angina pectoris and myocardial infarction are unclear.

**Methods** Serum free thyroxine (T<sub>4</sub>), free triiodothyronine (T<sub>3</sub>) and thyrotropin (TSH) were measured in all 1049 patients aged 40 years or older (median age 70 years, 51 percent men) seeking care in a university hospital emergency department during a 4-month period in 1995. Among the 185 patients who had angina or a myocardial infarction at this time, 181 (98 percent) were reevaluated three years later.

**Results** There were 76 patients in the myocardial infarction group, 109 patients in the angina group, and 864 other patients. Serum free T<sub>3</sub> concentrations were high in 10.5 percent, 8.2 percent and 5.0 percent, respectively. Serum free T<sub>4</sub> concentrations were high in 10.5 percent, 8.2 percent and 9.5 percent, respectively. Serum TSH concentrations were low in 7.9 percent, 7.3 percent and 10.9 percent, respectively. Among the patients with low serum TSH values, most had high serum free T<sub>3</sub> or T<sub>4</sub> values. Considering serum free T<sub>3</sub> concentrations as a continuous variable, the odds ratio for coronary artery disease at the time of hospitalization in those patients who had a high serum free T<sub>3</sub>

concentration was 2.6 (95 percent confidence interval, 1.3 to 5.2, P=0.007).

Among the 181 patients with coronary artery disease who were evaluated 3 years later, 22 had some subsequent coronary event. As compared with the patients who had no coronary event, more patients in the coronary-event group had high baseline serum free T<sub>3</sub> concentrations (22.7 percent vs. 6.9 percent, odds ratio 4.0) and low baseline serum TSH concentrations (22.7 percent vs. 12.6 percent, odds ratio 3.3); the proportion with high baseline serum free T<sub>3</sub> concentrations was similar (9.1 percent and 9.4 percent).

**Conclusion** More patients hospitalized for angina or myocardial infarction have biochemical evidence of hyperthyroidism, especially high serum free T<sub>3</sub> concentrations, than do other patients seeking emergency care. Among the angina-myocardial infarction group, high serum free T<sub>3</sub> and low serum TSH concentrations are risk factors for coronary events during follow-up.

### COMMENTARY

It is difficult to know how to interpret these results. The measurements were done only once, no actual hormonal values are given, and unexplained (and unexplainable) abnormalities are common in acutely ill patients. The finding that high serum free T<sub>3</sub> concentrations were associated with angina or myocardial infarction at the time of admission (10.5 percent of patients) may be because the proportion of patients without angina or myocardial infarction who had high serum free T<sub>3</sub> concentrations was low (5.0 percent), since the proportions of patients in the two groups with high serum free T<sub>4</sub> and low TSH concentrations were similar. If more patients in the latter group had been sick longer, were sicker, or were taking drugs that inhibit extrathyroidal conversion of T<sub>4</sub> to T<sub>3</sub>, then more of them would

have normal or even low serum free T<sub>3</sub> concentrations (no data regarding low values are given).

Looked at broadly, these results do not suggest that abnormalities compatible with hyperthyroidism are more common in patients presenting to emergency departments with angina or myocardial infarction. Possibly relevant to this conclusion is the fact that in patients with coronary artery disease a high dose of T<sub>3</sub> given immediately after bypass surgery does not precipitate coronary events (1,2). The follow-up data in the angina-myocardial infarction group are more suggestive of a relationship between hyperthyroidism and future coronary events, but this conclusion is weakened substantially by the problems mentioned above.

Robert D. Utiger, M.D

### References

1. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary bypass surgery. *N Eng J Med* 1995;333:1522-7.
2. Bennett-Guerrero E, Jimenez JL, White WD, et al. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo-controlled trial. *JAMA* 1996;275:687-92.

## Liver dysfunction in patients with hyperthyroidism

Biscoveanu M, Hasinski S. Abnormal results of liver function tests in patients with Graves' disease. *Endocr Pract* 2000;6:367-9.

### SUMMARY

**Background** Hyperthyroidism has been associated with abnormalities in tests of liver function, but only rarely with liver disease. Whether the frequency of these abnormalities has changed as more sensitive tests for identifying patients with hyperthyroidism is not known.

**Methods** Serum total alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase and bilirubin were measured at the time of diagnosis in 30 consecutive ambulatory patients with hyperthyroidism caused by Graves' disease. There were 27 women and 3 men, ranging in age from 25 to 60 years. Not all patients had all tests, and the isoforms of serum alkaline phosphatase were not measured separately.

**Results** Overall, 15 patients (50 percent) had high serum concentrations of one or more of the enzymes or bilirubin. Four patients had only high serum alkaline phosphatase concentrations.

The results of the individual tests are shown in the table.

Serum Test	Values in Patients	Normal Range	No. Abnormal /Tested (%)
Alkaline phosphatase (IU/L)	124-283	0-117	10/30 (33)
Aspartate aminotransferase (U/L)	36-71	0-35	5/30 (17)
Alanine aminotransferase (U/L)	45-157	0-40	6/23 (26)
γ-Glutamyl transferase (U/L)	69-331	0-68	6/25 (24)
Total bilirubin (mg/dL)	2.5	0.1-0.5	2/24 (8)

To convert serum bilirubin values to μmol/L multiply by 17.1.

**Conclusion** Minor abnormalities in hepatic function tests are present in approximately one third of patients with hyperthyroidism.

### COMMENTARY

The frequency of abnormalities in liver function in these 30 patients, as assessed by these tests and excluding serum alkaline phosphatase because it has several sources, was very similar to that found in two similar studies in the 1970s and 1980s (1,2). No details were provided about the severity of the hyperthyroidism or the presence of other factors that might contribute to liver dysfunction in these 30 patients, but it seems reasonable to assume that they had what might be called 'typical' hyperthyroidism as encountered among outpatients in the 1990s. If one assumes that it was easier to identify patients with hyperthyroidism in the 1990s and that hyperthyroidism alone caused the abnormalities, then a lower frequency of abnormalities might have been expected.

Liver dysfunction in patients with

hyperthyroidism has been explained on the basis of hypoxia (increased need for oxygen but no increase in splanchnic blood flow), hepatic congestion secondary to cardiac dysfunction (the frequency of abnormal tests is indeed higher in hyperthyroid patients who also have congestive heart failure [2]), and - in patients with Graves' hyperthyroidism - autoimmune hepatitis. The abnormalities are reversible (1).

There is no evidence that the presence of these minor abnormalities predicts the occurrence of hepatotoxicity in patients treated with an antithyroid drug, so there is no reason to assess liver function in patients with hyperthyroidism. When the tests are done, for whatever reason, and minor abnormalities are found, no further action need be taken until the patient's hyperthyroidism has been treated.

Robert D. Utiger, M.D.

### References

1. Thompson P Jr, Strum D, Boehm T, et al. Abnormalities of liver function tests in thyrotoxicosis. *Mil Med* 1978; 143:548-51.
2. Fong T-L, McHutchinson JG, Reynolds TB. Hyperthyroidism and hepatic dysfunction. A case series analysis. *J Clin Gastroenterol* 1992;14:240-4.

## Propylthiouracil, but not methimazole, is associated with antineutrophil cytoplasmic antibodies

Sera N, Ashizawa K, Ando T, Abe Y, Ide A, Usa T, Tominaga T, Ejima E, Yokoyama N, Eguchi K. Treatment with propylthiouracil is associated with appearance of antineutrophil cytoplasmic antibodies in some patients with Graves' disease. *Thyroid* 2000;10:595-9.

### SUMMARY

**Background** Occasional patients with hyperthyroidism treated with an antithyroid drug develop vasculitis with antineutrophil cytoplasmic antibodies, but the frequency with which these antibodies can be detected in patients with hyperthyroidism before and during treatment with propylthiouracil or methimazole is not known.

**Methods** Serum antineutrophil cytoplasmic antibodies (ANCA) were measured in three groups of patients with hyperthyroidism caused by Graves' disease. One group consisted of 42 patients who had not received any treatment, a second group of 56 patients who had received propylthiouracil for 3 to 138 months (mean 57), and a third group of 21 patients who had received methimazole for 6 to 146 months (mean 44). The patients' serum was tested for ANCA reacting with both myeloperoxidase (MPO) and proteinase-3 using immunoassay kits. These antibodies stain the perinuclear (P-ANCA) and cytoplasmic (C-ANCA) region of neutrophils, respectively, when tested by immunofluorescence.

**Results** Using two different immunoassay kits, high serum MPO-ANCA concentrations were found in 18 (32 percent) and 13 (23 percent) of the 56 patients treated with

propylthiouracil, but none of the untreated patients and none of the patients treated with methimazole. Among the patients treated with propylthiouracil, the results of the two assays were correlated ( $P < 0.001$ ). The frequency of high concentrations increased with the duration of propylthiouracil treatment; the mean ( $\pm$ SD) duration of treatment was  $78 \pm 48$  months in the patients with high serum MPO-ANCA concentrations and  $46 \pm 34$  months in those with normal concentrations.

Two of the patients with high serum MPO-ANCA concentrations had been tested before treatment, and were normal. Nine of the patients in this group had myalgia, arthralgia, purpura and recurrent influenza-like symptoms, but none had proteinuria.

Approximately 65 percent of the patients in each group had high serum antithyroid peroxidase antibody concentrations, and no patient in any group had a high serum concentration of the proteinase-3 ANCA.

**Conclusion** A substantial proportion of patients with Graves' hyperthyroidism who are treated with propylthiouracil have high serum MPO-ANCA concentrations, and some of them have symptoms consistent with vasculitis.

### COMMENTARY

Vasculitis - a better term is microscopic polyangiitis - with the symptoms listed above, fever, glomerulonephritis and high serum concentrations of MPO-ANCA is a reasonably well-defined syndrome. It is a known although infrequent complication of antithyroid drug therapy. A 1999 summary identified 27 patients with hyperthyroidism treated with an antithyroid drug who developed vasculitis with high serum ANCA concentrations (nearly all the antibodies were MPO-ANCA) (1). Among them all but three were taking propylthiouracil. The cause of hyperthyroidism was Graves' disease in 9 patients, a multinodular goiter in 1 and unstated in 17; 48 percent were Japanese.

Japanese patients with hyperthyroidism seem to be more likely to have not only vasculitis but also high serum ANCA concentrations. Evidence for the

latter comes from both this study by Sera et al and another study of 51 Japanese children and adolescents with Graves' hyperthyroidism (age range 3 to 15 years at the time of diagnosis) (2). Among these 51 patients, high serum MPO-ANCA concentrations were found in 1 of 16 untreated patients (6 percent), 16 of 25 patients treated with propylthiouracil (64 percent) (mean duration of treatment  $4.0 \pm 3.6$  years) and 0 of 10 patients treated with methimazole (mean duration  $2.1 \pm 2.8$  years). However, no surveys of comparable size from elsewhere have been reported.

Given the apparent rarity of vasculitis, the results of these two studies might be interpreted to mean that MPO-ANCA are necessary but not sufficient to cause vasculitis. Whether true or not, the association of both the antibodies and the disease with propylthiouracil is striking, and another reason - in addition to ease of administration, rapidity of action and probably lower frequency of

other side effects - to prefer methimazole for patients with hyperthyroidism who choose to be treated with an antithyroid drug for a prolonged period.

Robert D. Utiger, M.D.

#### References

1. Gunton JE, Stiel J, Caterson RJ, et al. Anti-thyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis. A case report and review of the literature. *J Clin Endocrinol Metab* 1999; 84:13-6.
2. Sato H, Hattori M, Fujieda M, et al. High prevalence of antineutrophil cytoplasmic antibody positivity in childhood onset Graves' disease treated with propylthiouracil. *J Clin Endocrinol Metab* 2000;85:4270-3.



## Mothers taking methimazole can nurse their infants safely

Azizi F, Khoshniat M, Bahrainian M, Hedayati M. Thyroid function and intellectual development of infants nursed by mothers taking methimazole. *J Clin Endocrinol Metab* 2000;85:3233-8.

### SUMMARY

**Background** Pregnant women taking an antithyroid drug are usually advised not to nurse their infants after delivery because their milk might contain sufficient amounts of the drug to cause hypothyroidism in the infant. However, the data to support this advice are sparse.

**Methods** Serum thyrotropin (TSH), free thyroxine ( $T_4$ ) index and free triiodothyronine ( $T_3$ ) index were measured monthly for 6 months in 51 mothers taking 5 mg methimazole daily after delivery and their breast-fed infants. All these women had received methimazole during pregnancy. The same measurements were done before and serially for 12 months during methimazole treatment in 88 mothers who developed hyperthyroidism 2 to 8 months after delivery. 46 of the mothers were treated with 10 mg daily for 2 months and 5 or 10 mg daily thereafter, and 42 were treated with 20 mg daily for 1 month, 10 mg for 1 month and 5 to 10 mg daily thereafter. Fourteen of the infants whose mothers had received methimazole and 17 other infants of similar sex, age and socioeconomic status had tests of intellectual development at age 48 to 74 months.

**Results** The 51 infants who were nursed from the time of delivery had normal serum TSH concentrations and free  $T_4$

index and free  $T_3$  index values at all times. Among the 88 mothers in whom treatment was begun after pregnancy, most had normal serum free  $T_4$  index and free  $T_3$  index values after treatment for 2 months and all had normal values after 3 months. The infants of these 88 mothers had normal values for all tests before and at all times during treatment of their mothers. This includes the tests done in 6 infants at a time when their mothers had transient hypothyroidism.

There were no differences in the full-scale, verbal and performance intelligence quotient (IQ) scores (mean IQ score 103 in both groups) or the subscales of the verbal and performance IQ tests, for example the information, vocabulary, sentences, picture completion and mazes subscales.

**Conclusion** Thyroid function is normal in breast-fed infants whose mothers are taking low or moderate doses of methimazole, as is their intellectual development at 48 to 74 months of age.

### COMMENTARY

The still-widespread recommendation (1) that women who take an antithyroid drug not nurse their infants seems to be based primarily on the presumption that any amount of drug would be harmful for infants. With respect to drug concentrations in milk, the little evidence that is available suggests that breast milk contains relatively more of a dose of methimazole than of propylthiouracil (milk to plasma ratio 1 versus <0.1), but the amount of either drug a breast-fed infant receives is very small. Further, small studies have revealed no deleterious effects of either drug in breast-fed infants, even infants whose mothers were taking 750 mg propylthiouracil daily (2,3).

This study, the largest yet reported, provides further evidence that breast-fed infants of mothers who are taking small or moderate doses of methimazole have no changes in thyroid function or in intellectual development. Parallel studies

were not done in infants of mothers with hyperthyroidism taking methimazole who were not breast fed, but it is very hard to believe their thyroid function would have been more normal. The results of the studies of intellectual development, albeit of relatively few infants, are consistent with the findings of normal thyroid function during breast-feeding in these infants.

Women with hyperthyroidism who are taking moderate doses of either methimazole or propylthiouracil can be encouraged to breast feed their infants, like other women.

Robert D. Utiger, M.D.

#### References

1. Lee A, Moretti E, Collantes A, et al. Choice of breastfeeding and physician's advice: a cohort study of women receiving propylthiouracil. *Pediatrics* 2000; 106:27-30.

2. Lamberg B-A, Ikonen E, Osterlund K, et al. Antithyroid treatment of maternal hyperthyroidism during lactation. *Clin Endocrinol* 1984;21:81-7.

3. Momotani N, Yamashita R, Makino F, et al. Thyroid function in wholly breast-feeding infants whose mothers take high doses of propylthiouracil. *Clin Endocrinol* 2000;53:177-81.

## Surgical and radiation therapy lowers intraocular pressure in patients with Graves' ophthalmopathy

Danesh-Meyer HV, Savino PJ, Deramo V, Sergott RC, Smith AF. Intraocular pressure changes after treatment for Graves' orbitopathy. *Ophthalmology* 2001;108:145-50.

### SUMMARY

**Background** Some patients with Graves' ophthalmopathy have high intraocular pressures, which may be caused by orbital venous congestion, compression of the eye by enlarged or fibrotic extraocular muscles, or orbital inflammation, or it may be coincidental. There is little information about the effect of orbital decompression, extraocular-muscle surgery and orbital radiation therapy on intraocular pressure.

**Methods** The study subjects were patients with Graves' ophthalmopathy who underwent decompression of the medial and inferior orbital walls (80 patients, 116 eyes) or recession of the inferior and medial rectus muscles (24 patients, 32 eyes), or who received orbital radiation therapy (2000 cGy in 10 daily fractions) (28 patients, 56 eyes). Intraocular pressure was measured just before treatment and 2 to 6 weeks after surgery or 6 to 12 weeks after the last radiation treatment. Patients taking a glucocorticoid or medication for glaucoma were not excluded unless their therapy was changed during the observation period.

**Results** The preoperative and postoperative intraocular pressure results in the three groups are shown in the table.

	Decompression Surgery mm Hg	Extraocular Muscle Surgery mm Hg	Radiation Therapy mm Hg
Pretreatment	21.6	18.5	19.4
Post-treatment	17.5	16.1	18.4
Difference (%)	-4.1 (-18.9)	-2.4 (-13.3)	-1.0 (-5.1)

The decreases in intraocular pressure on forward gaze and also on upward gaze in the decompression and extraocular muscle surgery groups were highly statistically significant ( $P < 0.01$ ). Among the 116 patients in the decompression group, the fall in intraocular pressure was greater in the 65 patients who had values  $\geq 21$  mm Hg before surgery and in the 35 patients who were receiving topical therapy for glaucoma.

**Conclusion** In patients with Graves' ophthalmopathy orbital decompression surgery and extraocular muscle surgery reduces intraocular pressure.

### COMMENTARY

Most if not all patients with Graves' ophthalmopathy who undergo orbital decompression or extraocular muscle surgery have severe ophthalmopathy, however that is defined, usually with considerable inflammation and edema of the extraocular muscles and adipose tissue and therefore venous congestion within the orbit. These changes raise episcleral pressure, which in turn slows removal of fluid by the trabecular network of the eye and raises intraocular pressure. It is reassuring that the two operations resulted in a fall in intraocular pressure, but unfortunate that the patients were not followed longer. It is perhaps surprising that orbital radiation therapy did not lower intraocular pressure, since it can reduce retrobulbar inflammation. There was no control

group in this study to determine the effect of time alone on intraocular pressure, but given the characteristics of the patients assembling a control group might be difficult.

The frequency of intraocular hypertension, usually defined as intraocular pressure greater than 20 or 22 mm Hg, is increased in patients with Graves' ophthalmopathy, at least in those patients who are referred to ophthalmologists. For example, in a survey of 500 consecutive patients with Graves' ophthalmopathy, 120 (24 percent) had intraocular pressure values greater than 22 mm Hg but less than 30 mm Hg (1); the frequency in the general population was 5 percent in one study (2). It is important to note that intraocular hypertension is not synonymous with glaucoma; that diagnosis is based on the presence of a high cup-to-disk ratio and progressive visual

field deficits and not on the intraocular pressure alone. Glaucoma is not often mentioned in studies of Graves' ophthalmopathy, but the possibility of its occurrence is one reason why patients with more than minimal Graves' ophthalmopathy should be evaluated by an ophthalmologist.

Robert D. Utiger, M.D.

#### References

1. Cockerham KP, Pal C, Jani B, et al. The prevalence and implications of ocular hypertension and glaucoma in thyroid-associated orbitopathy. *Ophthalmology* 1997;104:914-7.
2. Sommer A. Intraocular pressure and glaucoma. *Am J Ophthalmol* 1989; 107:186-8.

## Thyroxine therapy lowers serum cholesterol concentrations in patients with subclinical hypothyroidism

Danese MD, Ladenson PW, Meinert C, Powe NR. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab* 2000;85:2993-3001.

### SUMMARY

**Background** Patients with mild thyroid failure, defined the same way as is subclinical hypothyroidism (high serum thyrotropin (TSH) and normal serum free thyroxine (T<sub>4</sub>) concentrations), may have high serum total and low-density-lipoprotein (LDL) cholesterol concentrations. However, the extent to which the values fall when the patients are treated with T<sub>4</sub> has varied considerably in different studies.

**Methods** In an extensive review of the literature the authors identified 13 studies in which serum total cholesterol was measured prospectively in a total of 247 patients with subclinical hypothyroidism before and during treatment with T<sub>4</sub>. Serum LDL cholesterol and high-density-lipoprotein (HDL) cholesterol and other lipids also were measured in some of the studies. The studies were evaluated using 13 criteria of validity, including randomized controlled design, treatment for at least 3 months, mean serum TSH concentration <2 mU/L during treatment, individual dosing of T<sub>4</sub>, and recruitment from a population-based sample.

**Results** No study fulfilled all 13 of the criteria of validity. For example, only 3 were randomized trials, in only 6 was the mean serum TSH concentration <2 mU/L at the time of follow-up, and in only 1 were the study subjects drawn from a population-based sample.

The mean baseline serum total cholesterol concentration in the 13 studies was 241 mg/dL (6.2 mmol/L). During T<sub>4</sub> treatment it decreased in 11 studies and increased in 2 studies. The overall mean decrease was 7.9 mg/dL (0.2 mmol/L), and it was greater in patients with higher initial values. The baseline serum LDL cholesterol concentration, measured in 9 studies, was 158 mg/dL (4.1 mmol/L). During T<sub>4</sub> treatment it decreased in 7 studies and increased in 2; the overall mean decrease was 10 mg/dL (0.3 mmol/L). The mean baseline serum HDL cholesterol concentration, measured in 10 studies, was 51 mg/dL (1.3 mmol/L). During T<sub>4</sub> treatment; it increased in 5 of the studies; the overall mean increase was 3.1 mg/dL (0.1 mmol/L). The 95 percent confidence intervals for the overall change excluded 0 (no change) for the 3 measurements. There was no change in serum triglyceride concentrations, measured in 12 studies.

**Conclusion** T<sub>4</sub> therapy lowers serum total and LDL cholesterol concentrations slightly in patients with subclinical hypothyroidism.

### COMMENTARY

Whether patients with subclinical hypothyroidism should be treated with T<sub>4</sub> is debated. That treatment might lower serum total and LDL cholesterol concentrations is one argument in favor of treatment, but its efficacy in this regard has been debated. This article describes a systematic review of the literature on the effect of T<sub>4</sub> treatment on serum lipid concentrations in these patients. The criteria used to evaluate the validity of the studies might be considered utopian, so it is perhaps not surprising that no study met all of them.

This study focused on changes during treatment, not the baseline values. The baseline values in the different stud-

ies ranged from 196 to 310 mg/dL (5.1 to 8.0 mmol/L) for serum total cholesterol and from 123 to 204 mg/dL (3.2 to 5.3 mmol/L) for serum LDL cholesterol. The values on the whole were higher than would be expected in normal subjects. However, many patients with subclinical hypothyroidism have normal values. As an example, in a recent study in Austria, the mean serum cholesterol concentration in 4866 normal subjects was 217 mg/dL (5.6 mmol/L) and it was 219 mg/dL (5.7 mmol/L) in 1055 patients with subclinical hypothyroidism, the largest group ever reported (1). So one cannot prescribe T<sub>4</sub> for patients with subclinical hypothyroidism on the assumption that they have high serum cholesterol con-

centrations, but if the concentrations are high T<sub>4</sub> treatment will lower them slightly.

Robert D. Utiger, M.D.

#### References

1. Vierhapper H, Nardi A, Grosser A, et al. Low-density lipoprotein cholesterol in subclinical hypothyroidism. *Thyroid* 2000;10:981-4.

## Hypothyroidism caused by rapid thyroid hormone destruction in an infant with hepatic hemangiomas

Huang SA, Tu HM, Harney JW, Venihaki M, Butte A, Kozakewich HPW, Fishman SJ, Larsen PR.. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med* 2000;343:185-9.

### SUMMARY

**Background** Thyroid hormone degradation is not thought to be an important determinant of thyroid hormone production. When changes in degradation do occur compensation by the pituitary-thyroid system usually maintains thyroid secretion within the normal range. The infant described in this report had multiple hepatic hemangiomas that degraded thyroid hormone so rapidly that the infant had hypothyroidism.

**Care Report** A 6-week-old boy developed abdominal distension, and was found to have hepatomegaly. Liver biopsy revealed hemangioma. The infant's serum thyrotropin (TSH) concentration was 156 mU/L and his serum free thyroxine ( $T_4$ ) concentration was low. He was treated with prednisolone and  $T_4$ .

At age 3 months, he was hospitalized for increasing abdominal distension and respiratory distress. He had bradycardia, hypothermia and massive hepatomegaly; the thyroid gland was not enlarged. The liver contained multiple large hemangiomas. Serum  $T_4$  was 2.5  $\mu\text{g/dL}$  (32 nmol/L), triiodothyronine ( $T_3$ ) <15 ng/dL (0.23 nmol/L), reverse  $T_3$  413 ng/dL (6.4 nmol/L), TSH 177 mU/L and thyroglobulin 1014 ng/mL (normal 6 to 87).

The infant was treated with mechanical ventilation, 6-methylprednisolone, interferon-2 alfa and intravenous  $T_3$ . His clinical condition improved, and his serum TSH concentration 27 hours later was 79 mU/L. In the next 18 days, he received intravenous  $T_3$  continuously in doses up to 96  $\mu\text{g/day}$ , and intravenous and then jejunal  $T_4$  in doses up to 50  $\mu\text{g/day}$ . This treatment raised the infant's serum  $T_3$  concentration to normal in 5 days and lowered his serum TSH

concentration to normal in 17 days; both remained normal thereafter. Serum  $T_4$  concentrations remained low. Serum reverse  $T_3$  concentrations initially declined when  $T_3$  was given, but then increased to near the baseline value when  $T_4$  was added.

The hepatic hemangiomas were treated by embolization. Staphylococcal bacteremia was diagnosed on hospital day 19. The infant's clinical condition continued to deteriorate, and he died 40 days after admission

**Special Studies** Studies of hemangioma tissue from the infant revealed a very high level of type 3 deiodinase activity. The maximal velocity of deiodination of  $T_3$  was 0.78 nmol/mg protein, 7.5 times higher than is found in placenta, the normal tissue with the highest activity. The tissue also contained a large quantity of mRNA for this deiodinase; in situ hybridization studies revealed the mRNA to be in the hemangioma cells.

A review of hospital records revealed that, among 1555 children with hemangiomas, serum TSH had been measured in 92. Two of them had values two or more times the upper limit of normal for age and low serum  $T_4$  concentrations; both had massive hepatic hemangiomas. No tissue from these children was available for study.

Assays of hemangioma tissue from 5 other children revealed type 3 deiodinase activity in amounts comparable to that in placental tissue in 3.

**Conclusion** Some hemangiomas contain large amounts of type 3 iodothyronine deiodinase activity, which in one infant with a large tumor deiodinated both  $T_4$  and  $T_3$  sufficiently rapidly to cause hypothyroidism.

### COMMENTARY

Infants with congenital hypothyroidism are usually treated with  $T_4$  in a dose of 25  $\mu\text{g/kg/day}$ , about 35 percent of which is converted to  $T_3$ . Thus, this infant's requirement for thyroid hormone was vastly greater than expected. Furthermore, this treatment did not raise the infant's serum  $T_4$  concentration, it raised his serum  $T_3$  concentration much less than expected, and it raised his serum reverse  $T_3$  concentration to well above normal. Another factor undoubtedly contributing to the low serum  $T_3$  concentrations was the infant's severe nonthyroidal illness.

The results pointed to rapid destruction of both  $T_4$  and  $T_3$ , and thus to an increase in the activity of type 3 deiodinase, which catalyzes inner ring deiodination (5-deiodination) of each hormone to form, respectively, reverse  $T_3$  and 3,3-diiodothyronine. This was confirmed by the invitro studies. The presence of a high level of type 3 deiodinase activity in the hemangioma tissue of this and several other children is a unique finding.

The infant's thyroidal secretion was certainly highly stimulated, witness the high serum TSH and thyroglobulin concentrations, but was unable to produce sufficient quantities of  $T_4$  and  $T_3$  to pre-

vent hypothyroidism. No other situation in which  $T_4$  and  $T_3$  are so rapidly degraded that a person who has normal pituitary-thyroid function does not remain euthyroid has been described. This study will undoubtedly stimulate more studies of pituitary-thyroid function in patients with not only hemangiomas but also other tumors. It may be that hypothyroidism due to rapid tumor-mediated degradation of  $T_4$  and  $T_3$  is not so rare.

Robert D. Utiger, M.D.



## Fetal loss is increased in pregnant women with hypothyroidism

Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ. Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screening* 2000;7:127-30.

### SUMMARY

**Background** Hypothyroidism in pregnant women has been associated with several maternal and fetal complications of pregnancy in observational studies. However, there have been no population-based studies in which the outcome of pregnancy was related to the presence of hypothyroidism during the pregnancy.

**Methods** Serum thyrotropin (TSH) was measured between 15 and 18 weeks gestation and the outcome of pregnancy was determined from state records in 9403 women with singleton pregnancies undergoing screening for neural tube defects and Down's syndrome in Maine between 1990 and 1992. Serum free thyroxine ( $T_4$ ) was measured in the women with serum TSH concentrations  $\geq 6$  mU/L and twice that number of women with serum TSH concentrations  $< 6$  mU/L.

**Results** Among the 9403 pregnant women, 209 (2.2 percent) had serum TSH concentrations  $\geq 6$  mU/L. The values were 6 to 9.9 mU/L in 172 women (1.8 percent) and  $\geq 10$  mU/L in 37 women (0.4 percent). The two groups of women with high serum TSH concentrations had lower mean serum free  $T_4$  concentrations than the women who

had normal serum TSH concentrations, although their mean values were within the normal range. In addition, more of the women with high serum TSH concentrations had high serum antithyroid peroxidase antibody concentrations (60 percent versus 9 percent).

Among the 9194 women with normal serum TSH values, there were 83 fetal deaths (0.9 percent), as compared with 8 fetal deaths among the 209 women with serum TSH values  $\geq 6$  mU/L (3.8 percent) (odds ratio 4.4, 95 percent confidence interval, 1.9 to 9.5). The frequency of fetal death was higher in the women with serum TSH values  $\geq 10$  mU/L (8.1 percent) than in those with values of 6 to 9.9 mU/L (2.9 percent). There were no differences in the frequency of gestational hypertension, abruptio placenta or cesarean delivery in the women in the three groups, or in gestational age at delivery, mean birth weight, Apgar scores at 5 minutes or neonatal deaths.

**Conclusion** The rate of fetal death but not other maternal or fetal outcomes is increased in women who have high serum TSH concentrations during the second trimester of pregnancy.

### COMMENTARY

Most of the women with high serum TSH concentrations had subclinical hypothyroidism, and they were studied only once, so it might have been transient. Nonetheless, the finding of an increasing rate of fetal loss as a function of the degree of elevation in serum TSH concentration (and decrease in serum free  $T_4$  concentration) suggests that mild hypothyroidism has a deleterious effect on fetuses.

The lack of an increased frequency of gestational hypertension, abruptio placenta, premature birth and low birth-weight, as reported in observational studies of women with hypothyroidism (1), may be due to differences in severity of hypothyroidism or to differences in ascertainment of the complications of pregnancy. Overt hypothyroidism is associated with increased peripheral vascular resistance, and might be expected to reduce placental blood flow, but whether the same change occurs in sub-

clinical hypothyroidism is not known.

The evidence from this study that hypothyroidism in pregnant women is associated with decreased fetal survival complements the results of a study of an earlier cohort of women in Maine (2). That study revealed that the infants of women who were hypothyroid at 15 to 18 weeks gestation had slightly lower scores on intelligence tests at age 7 years than the infants of normal women. These new results may strengthen the argument for screening all pregnant women for hypothyroidism, but it would seem prudent to determine if intervention is beneficial before widespread screening is undertaken.

Robert D. Utiger, M.D.

#### References

1. Leung AS, Millar LK, Koonings PP, et al. Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol* 1993; 81:349-53.

2. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent psychological development in the child. *N Engl J Med* 1999;341:549-55.

## Iodine-123 is superior to iodine-131 in detecting thyroid remnants in patients with differentiated thyroid carcinoma

Mandel SJ, Shankar LK, Benard F, Yamamoto A, Alavi A. Superiority of iodine-123 compared with iodine-131 scanning for thyroid remnants in patients with differentiated thyroid carcinoma. *Clin Nucl Med* 2001;26:6-9.

### SUMMARY

**Background** Iodine-123 is considered the radionuclide of choice for studying patients with thyroid nodular disease, but has not been widely used in patients with thyroid carcinoma.

**Methods** Total body scans were done in 14 consecutive patients with differentiated thyroid carcinoma within 7 weeks after near-total thyroidectomy. All the patients were hypothyroid (serum thyrotropin concentrations greater than 40 mU/L) and had eaten a low-iodine diet for 1 week. The first scan was done 5 hours after oral administration of 48 to 56 MBq (1.3 to 1.5 mCi) iodine-123 (I-123). The patients then were given 111 MBq (3 mCi) iodine-131 (I-131) and another scan was done 42 to 44 hours later. The patients who had uptake in the neck were given 3700 to 5500 MBq (100 to 150 mCi) I-131 and a third scan was done 7 days later.

**Results** Thirteen patients had at least one focus of uptake in the thyroid bed or neck on the diagnostic scans, and overall 35 foci were seen. All 35 foci were seen on the I-123 scans, as compared with 32 foci on the I-131 scans. The 3 foci not seen on the latter scans were in different patients. The scans done after I-131 therapy were similar in 11 patients. In 1 patient a new focus of uptake was seen in the

lateral neck; this focus was not seen on either diagnostic scan and proved to be carcinoma. In another patient uptake in the left thyroid bed on the diagnostic scans was no longer seen. The I-123 scans were judged to be of better quality.

**Conclusion** Iodine-123 is superior to iodine-131 for imaging the neck in patients with differentiated thyroid carcinoma.

### COMMENTARY

The strength of this small study is that the diagnostic I-123 and I-131 scans were done in the same patients. The results therefore add in a unique way to the existing evidence that diagnostic scanning in patients with thyroid carcinoma should be done with I-123. As compared with I-131 scans, I-123 scans reveal a few more foci of uptake. Furthermore, I-123 does not damage ('stun') thyroid tissue so that it becomes more difficult to destroy with a high dose of I-131 (1), it is safer, and it yields better-quality scans. It is also about twice as expensive and less readily available than I-131.

The 'stunning' phenomenon seems to apply more to thyroid remnants than carcinoma. Therefore, the benefit of I-123 for scanning may be greatest for the first scan. Of course, the risk of stunning can be avoided entirely by not doing a scan before I-131 is given to destroy thyroid remnants, but this means some patients would be treated unnecessarily.

Robert D. Utiger, M.D.

### References

1. Park HM, Park YH, Zhou XH. Detection of thyroid remnant/metastasis without stunning: an ongoing dilemma. *Thyroid* 1997;7:277-80.

## Presence of PAX8-PPAR $\gamma$ 1 gene translocation distinguishes follicular carcinoma from other follicular lesions

Kroll TG, Sarraf P, Pecciarini L, Chen C-J, Mueller E, Spiegelman BM, Fletcher JA. PAX8-PPAR $\gamma$ 1 fusion in oncogene human thyroid carcinoma. *Science* 2000;289:1357-60.

### SUMMARY

**Background** It is not possible to distinguish between benign and malignant follicular tumors of the thyroid gland on the basis of cytology and it may be difficult to distinguish between them by histology. Molecular analysis for a chromosomal translocation that has been identified in follicular carcinomas may be useful in distinguishing between benign and malignant follicular tumors. This translocation, (t(2;3)(q13;p25), results in fusion of part of the DNA binding region of the PAX8 gene to the peroxisome proliferator-activator  $\gamma$ 1 (PPAR $\gamma$ 1) gene. PAX8 is a transcription factor that plays an important role in the development and function of thyroid follicular cells, and PPAR $\gamma$ 1 is a transcription factor that stimulates cell differentiation and inhibits cell growth.

**Methods** The presence of PAX8-PPAR $\gamma$ 1 DNA and protein was studied in sections of 8 follicular carcinomas, 20 follicular adenomas, 10 papillary carcinomas and 10 hyperplastic nodules by molecular and immunochemical methods. In addition, the biological activity of the fusion pro-

tein was evaluated by determining its ability to activate response elements in DNA that are activated by wild-type PPAR $\gamma$ 1 in the presence of troglitazone.

**Results** PAX8-PPAR $\gamma$ 1 DNA was detected by reverse transcriptase-polymerase chain reaction analysis in 5 of the 8 follicular carcinomas (62 percent), but in none of the follicular adenomas, papillary carcinomas or hyperplastic nodules. Two of the other follicular carcinomas contained a different rearrangement of the two genes. Immunochemical studies using a monoclonal antibody against PPAR $\gamma$ 1 revealed strong diffuse staining of the nuclei of 7 of the 8 follicular carcinomas, but only faint focal staining of the nuclei of the follicular adenomas, papillary carcinomas and hyperplastic nodules. In transfection studies in cultured cells, PAX8-PPAR $\gamma$ 1 was biologically inactive and blocked the activity of PPAR $\gamma$ 1, an effect that would be expected to block cell differentiation and promote cell growth.

**Conclusion** Many follicular carcinomas of the thyroid contain a PAX8-PPAR $\gamma$ 1 fusion oncogene.

### COMMENTARY

Approximately 10 to 20 percent of fine-needle aspiration biopsies of thyroid nodules are assigned terms such as follicular tumor, follicular lesion, and follicular neoplasm (1,2). The major cytological characteristics of these nodules are a large number of follicular cells, the presence of microfollicles, and little or no colloid. The term "suspicious" is applied to biopsy results having these characteristics in some studies, but that term is also applied to biopsies that have cells with some but not all of the characteristics of papillary carcinomas. In short, the terminology used to categorize the cytological findings in fine-needle aspiration biopsies is not standardized.

From 10 to 25 percent of follicular tumors prove to be follicular carcinomas and follicular variants of papillary carcinoma when removed surgically and examined histologically (1,2). The remainder are follicular adenomas and

hyperplastic nodules. In some patients who undergo surgery the nodule is thought to be benign by the surgeon and pathologist on the basis of examination of frozen sections, and therefore only a thyroid lobectomy is done, but subsequent pathological examination reveals follicular carcinoma (3). Then, a second operation to remove the contralateral thyroid lobe is necessary.

Given this background, a reliable procedure that allowed cells of follicular carcinomas to be identified in thyroid cells obtained by fine-needle aspiration biopsy would be very useful. Although this study was done using tissue sections, it should be feasible to detect the fusion oncogene in isolated cells, by expansion of the DNA with the polymerase chain reaction, in situ hybridization or immunocytochemistry. The practical question is whether the findings will be confirmed when many more follicular tumors are studied.

Robert D. Utiger, M.D.

### References

1. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. *Ann Intern Med* 1993; 118:282-89.
2. Ravetto C, Colombo L, Dottorini ME. Usefulness of fine-needle aspiration in the diagnosis of thyroid carcinoma. A retrospective study in 37,895 patients. *Cancer (Cancer Cytopathol)* 2000;90:357-63.
3. Chen H, Nicol TL, Udelsman R. Follicular lesions of the thyroid. Does frozen section evaluation alter operative management? *Ann Surg* 1995;222:101-6.

## Clinical findings and treatment of patients with thyroid cancer treated at over 1500 hospitals in the United States in 1996

Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, Shah JP, Fremgen AM, Stewart AK, Holzer S, for the U.S. and German Thyroid Cancer Study Group. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. *Cancer (Cytopathol)* 2000;89:202-17.

### SUMMARY

**Background** Thyroid cancer is sufficiently rare that few institutions accumulate large numbers of patients, and the findings in patients evaluated and treated at those places may be biased by the fact that many of the patients were referred there. Therefore, information on the characteristics of the patients evaluated and treated at a large number of hospitals may provide a broader insight into how the patients are being treated and what needs to be done to raise the overall standard of care nationally.

**Methods** A prospective cohort study was conducted at over 1500 hospitals in the United States in 1996 under the auspices of the American College of Surgeons Commission on Cancer. The hospitals reported demographic, diagnostic-test, pathological and treatment data on 5583 patients.

**Results** Of the 5583 patients, 79 percent were diagnosed and treated at the same institution. 4522 patients (81 percent) had papillary carcinomas, 583 (10 percent) had follicular carcinomas, 205 (4 percent) had Hurthle-cell carcinomas, 177 (3 percent) had medullary carcinomas (15 percent of which were familial), and 96 (2 percent) had anaplastic carcinomas.

Some characteristics of the patients in the papillary-carcinoma and follicular-carcinoma groups are shown in the table.

The papillary carcinomas tended to be smaller, 16 percent being >3 cm vs. 39 percent of the follicular carcinomas, but were more often multifocal, 29 percent vs. 16 percent.

Characteristic	Papillary Carcinoma	Follicular Carcinoma
Age 30 to 49 years	49%	42%
Women	77%	71%
History of radiation	5%	4%
Family history of thyroid cancer	5%	4%
<b>Symptoms and signs</b>		
Thyroid mass	75%	78%
Hoarseness or dysphagia	18%	24%
Lymphadenopathy	27%	22%
<b>Diagnostic tests</b>		
Needle aspiration of thyroid	53%	53%
Lymph node aspiration	7%	5%
Incisional biopsy	13%	11%
Thyroid ultrasonography	38%	41%
Radionuclide scan	39%	42%
CT or MRI of neck	18%	18%
Laryngoscopy	6%	6%

With respect to treatment, approximately 75 percent of the patients in both groups had near-total or total thyroidectomy, and nearly the same proportions were considered to have no residual tumor after surgery. No lymph nodes were examined at the time of surgery in 54 percent and 77 percent, respectively. Approximately 50 percent of the patients received radioiodine at least once and approximately 50 percent received thyroid hormone. The 30-day postoperative mortality was 0.2 percent.

**Conclusion** The diagnostic tests done in patients with thyroid carcinoma and the treatments varied considerably in the United States in 1996. Areas identified where care needs to be improved include more frequent use of fine-needle aspiration biopsy and preoperative laryngoscopy and more frequent resection of lymph nodes.

### COMMENTARY

The 5583 patients in this study from over 1500 hospitals represent only about one third of the estimated 15,600 new cases of thyroid carcinoma in the United States in 1996 (1) (the estimate for 1999 was 18,100 [2]). Where and how the other 10,000 or so patients were evaluated and treated is not commented upon in the article, and is not obvious.

While the report does not therefore provide a complete picture of thyroid

carcinoma in this country in 1996, it nonetheless contains a wealth of information about all types of thyroid carcinoma. The demographic and clinical findings in the patients with the different types of carcinoma were similar to those in single-center studies. However, some aspects of diagnosis and treatment seem in disagreement with practices believed by many to simplify diagnosis and improve survival. These include the infrequent use of fine-needle aspiration biopsy and the rather frequent use of incisional biopsy and of CT or

MR imaging, and the rather low frequency of postoperative radioiodine and thyroid hormone therapy.

Robert D. Utiger, M.D.

#### References

1. Parker SL, Long T, Bolden S, Wingo PA. Cancer statistics, 1996. *CA Cancer J Clin* 1996;65:5-27.
2. Landis AH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin* 1999;49:8-31.



## Paclitaxel has some efficacy in patients with anaplastic thyroid carcinoma

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Ain KB, Egorin MJ, DeSimone PA, for the Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. Treatment of anaplastic thyroid cancer with paclitaxel: phase 2 trial using ninety-six-hour infusion. *Thyroid* 2000;10:587-94.

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### SUMMARY

**Background** There is no effective therapy for patients with anaplastic carcinoma of the thyroid. Paclitaxel has activity against anaplastic carcinoma cells cultured *in vitro* and grown in nude mice.

**Methods** Nineteen patients (6 women, 13 men, mean age 62 years, range 47 to 86) with anaplastic carcinoma in whom the tumor persisted or recurred after surgery and radiation therapy were given continuous intravenous infusions of paclitaxel in doses 120 mg/m<sup>2</sup> (7 patients) or 140 mg/m<sup>2</sup> (12 patients) for 96 hours. Up to six infusions were given at 3-week intervals. Eight patients had been treated by total thyroidectomy and 3 by partial thyroidectomy; the remaining 8 patients had only a diagnostic biopsy. Response was assessed by measurements of tumor in the thyroid bed in 14 patients, elsewhere in the neck in 7 patients, in the lungs in 11 patients, and in the mediastinum and abdomen in 5 patients by physical examination and imaging after the second, fourth and sixth treatments.

**Results** Ten of the 19 patients (53 percent) responded transiently to paclitaxel. One patient had complete disappearance of tumor and 9 patients had partial responses (50 percent or more reduction in the sum of the diameters of all measurable tumor deposits); 1 other patient had stabilization of tumor. The median survival after initiation of paclitaxel therapy was 24 weeks (32 weeks in

the patients who responded vs. 10 weeks in those who did not,  $P=0.40$ ). Women responded more often than men, and younger patients more often than older patients. There was no correlation between plasma paclitaxel clearance (measured in 10 patients) and responses to therapy. The adverse effects were nausea, vomiting, diarrhea, fever, alopecia and stomatitis, none of which was severe.

**Conclusion** Paclitaxel has some efficacy in patients with anaplastic carcinoma of the thyroid.

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### COMMENTARY

Paclitaxel is obviously not highly effective in patients with anaplastic carcinoma, but it is a step forward. The proportion of patients having a partial or complete response was as high or higher than in patients treated with other chemotherapy regimens, many of them more complex and toxic (reviewed in 1). In some patients tumor size decreased and then increased within the 3-week treatment interval, a dramatic demonstration of the rapid growth of anaplastic carcinomas.

This study serves as a model of how chemotherapy regimens ought to be devised, from tests in cultured tumor

cells to animals to patients. Perhaps the animal studies can be omitted at some point. The first steps along this path have been taken with regard to gene therapy, in that the gene for the tumor suppressor molecule p53 (which is often mutated in anaplastic carcinomas) has been inserted into cultured anaplastic carcinoma cells, which then died (1).

Robert D. Utiger, M.D.

#### References

1. Ain KB. Anaplastic thyroid carcinoma: behavior, biology, and therapeutic approaches. *Thyroid* 1998;8:715-26.

2. Nagayama Y, Yokoi H, Takeda K, et al. Adenovirus-mediated tumor suppressor p53 gene therapy for anaplastic thyroid carcinoma *in Vitro* and *in Vivo*. *J Clin Endocrinol Metab* 2000; 85:4081-6.

## Thyroid hormone receptors are present in the brain very early in fetal life

Kilby MD, Gittoes N, McCabe C, Verhaeg J, Franklyn JA. Expression of thyroid receptor isoforms in the human fetal nervous system and the effects of intrauterine growth restriction. *Clin Endocrinol* 2000;53:469-77.

### SUMMARY

**Background** Thyroid hormones stimulate neural development early in gestation, but little is known about the ontogeny of thyroid hormone receptors in fetal neural tissue.

**Methods** RNA was extracted from brain tissue of 13 fetuses aborted at from 10 to 16 weeks gestation. The RNA was reverse transcribed and amplified using primers for the  $\alpha 1$ ,  $\alpha 2$ ,  $\beta 1$  and  $\beta 2$  isoforms of the receptor. In addition, brain tissue obtained from 11 fetuses aborted in the first trimester (gestational age 11 to 13 weeks), 12 fetuses aborted in the second trimester (gestational age 15 to 25 weeks), 21 stillborn fetuses (gestational age 26 to 40 weeks) and 18 stillborn fetuses with intrauterine growth retardation (gestational age 23 to 29 weeks, birthweight <10th percentile) were studied for thyroid receptor isoforms by immunochemistry using antibodies against each isoform.

**Results** mRNA for all four isoforms of the thyroid receptor was detected in brain tissue from all the 10- to 16-week fetuses studied. The immunochemical studies revealed

some  $\alpha 1$  and  $\alpha 2$  receptors but no  $\beta 1$  or  $\beta 2$  receptors in the brain tissue of first-trimester fetuses. There was staining for all the receptors in the brains of approximately 70 percent of the second-trimester fetuses and all the third-trimester fetuses. The staining was largely confined to the pyramidal cells of the cerebral cortex and the Purkinje cells of the cerebellum, and there was little staining of glial cells or cells of the choroid plexus. The proportion of neurons that stained for each isoform increased progressively with increasing gestational age, so that by the third trimester all the neurons in each section of cerebral cortex and cerebellum were stained. The intensity of staining for all isoforms was less in the brains of the fetuses with intrauterine growth retardation, as compared with the fetuses of the same gestational age.

**Conclusion** mRNA and protein for all four isoforms of the thyroid receptor are present in neurons of the cerebral cortex and cerebellum early in gestation, and the proportion of neurons containing receptor protein increases throughout gestation.

### COMMENTARY

The presence of both thyroid receptor mRNA and protein in the brain very early in gestation provides strong evidence that the receptors are produced in brain tissue and that the tissue is responsive to thyroid hormone, and therefore that the hormone plays a role in very early development of the brain. In another recent study in which the mRNAs for the  $\alpha 1$ ,  $\alpha 2$  and  $\beta 1$  isoforms of the thyroid receptor were measured in brain tissue of fetuses (1), the content of the  $\alpha$  isoforms increased progressively from 8 to 14 weeks, whereas that of the  $\beta 1$  isoform was curvilinear, being lower at 10 to 12 weeks than earlier or later.

If thyroid receptors are there, they must have some thyroid hormone, specifically triiodothyronine ( $T_3$ ), to activate them (excluding the  $\alpha 1$  isoform that does not bind  $T_3$ ). Binding of  $T_3$  may either activate the receptors, so that they have transcriptional activity, or reverse the transcriptional activity of

unliganded receptors. Initially, this  $T_3$  has to come from the mother, either directly or via deiodination of maternal thyroxine ( $T_4$ ) in the brain of the fetus.

The finding of lower levels of all receptor isoforms in the brains of the fetuses with intrauterine growth retardation suggests that decreased thyroid hormone action could contribute to the mental retardation that occurs in some of these infants. Quantitatively, the brain contains more of the  $\alpha$  than the  $\beta$  isoforms, and their distribution is not uniform. This is perhaps most evident for the  $\beta 2$  isoform, which is found mostly in the hypothalamus (and pituitary), but it is likely that there are region-specific differences in the distribution of all the isoforms and also that the different isoforms are linked to different neurochemical reactions. The lesser abundance of the  $\beta$  isoforms seems to fit with the clinical observations that patients who have inactivating mutations in the gene for the  $\beta$  isoforms of the receptor have a low incidence of mental retardation (2). These patients, who have high serum thyroid hormone

concentrations, have a high incidence of hyperactivity, which could reflect activation of the more abundant  $\alpha 1$  isoform of the thyroid receptor.

Robert D. Utiger, M.D.

#### References

1. Iskaros J, Pickard M, Evans I, et al. Thyroid hormone receptor gene expression in first trimester human fetal brain. *J Clin Endocrinol Metab* 2000;85:2620-23.
2. Refetoff S. Resistance to thyroid hormone. In Braverman LE, Utiger RD, eds. *The thyroid. A fundamental and clinical text*. 8th ed. Philadelphia: Lippincott Williams and Wilkins, 2000, 1028-43.

## A thyroid hormone analogue with differential cardiac and hepatic actions

Trost SU, Swanson E, Gloss B, Wang-Inverson DB, Zhang H, Volodarsky T, Grover GJ, Baxter JD, Chiellini G, Scanlan TS, Dillman WH. The thyroid hormone receptor- $\alpha$ -selective agonist GC-1 differentially affects plasma lipids and cardiac activity. *Endocrinology* 2000;141:3057-64.

### SUMMARY

**Background** Thyroid hormones have multiple actions. These actions are mediated by three different thyroid hormone nuclear receptors (TR- $\alpha$ 1, TR- $\beta$ 1 and TR- $\beta$ 2) that are distributed differently among different tissues (there is a TR- $\alpha$ 2 isoform that does not bind thyroid hormone). For example, cardiac tissue contains relatively more TR- $\alpha$  whereas the liver contains more TR- $\beta$ . The structure of the triiodothyronine ( $T_3$ )-binding region of TR- $\beta$ 1 and - $\beta$ 2 is the same, but that of TR- $\alpha$ 1 is slightly different, making it possible to design ligands that preferentially activate TR- $\alpha$  or the two isoforms of TR- $\beta$ .

**Methods** GC-1 is  $T_3$  analogue in which the iodine atoms of the inner ring are replaced by methyl groups and the iodine atom on the outer ring is replaced by an isopropyl group. The ether link between the rings is replaced by a methylene link and the amino side chain by an oxyacetic acid group. The affinity of GC-1 for the  $\beta$  isoforms of the receptor is 10 times greater than for the  $\alpha$ 1 isoform. The cardiac and hepatic actions of GC-1 were compared with those of  $T_3$  in hypothyroid mice and in normal rats with diet-induced hypercholesterolemia, and tissue and plasma concentrations of  $T_3$  and GC-1 were measured in the rats.

**Results** In hypothyroid mice given  $T_3$  or GC-1 for 4 weeks,  $T_3$  increased heart rate and cardiac contractility more than did equimolar amounts of GC-1. It was also more potent

in raising the myocardial content of the mRNAs for myosin heavy chain- $\alpha$  and - $\beta$ , sarcoplasmic reticulum adenosine triphosphatase, and HCN2, a cardiac pacemaker channel. In these latter actions,  $T_3$  was approximately 9 times more potent than an equimolar amount of GC-1. In contrast, in these mice,  $T_3$  and GC-1 were equipotent in lowering serum cholesterol concentrations, and GC-1 was more potent in lowering serum triglyceride concentrations.

In hypercholesterolemic rats given  $T_3$  or GC-1 for 7 days, the dose of GC-1 needed to lower serum cholesterol concentrations was approximately 10 times higher than that of  $T_3$  and the dose needed to lower serum TSH concentrations by 30 percent was approximately 20 times higher. In contrast, the dose of GC-1 needed to increase the heart rate by 15 percent was greater than 120 times higher. As compared with  $T_3$ , the tissue to plasma ratio of GC-1 was slightly lower in the liver and much lower in the heart.

**Conclusion** The  $T_3$  analogue GC-1 lowers serum lipid concentrations more effectively than it stimulates cardiac function, indicating that its ability to activate TR isoforms differs from that of  $T_3$ .

### COMMENTARY

The recognition that there are multiple TRs and that their tissue distribution differs has provided impetus to the long-sought goal of finding thyroid hormone analogues with different potency in different tissues. In older studies, one analogue, D-thyroxine ( $T_4$ ), proved to be as active in stimulating cardiac function as in lowering serum cholesterol concentrations. Another, triiodothyroacetic acid, did seem to have more potent hepatic and skeletal actions than cardiac actions (1).

GC-1 has yet to be tested in humans, but it seems to have some desirable properties. As more is learned about the three-dimensional structure of

the receptors, it should be possible to design other analogues with even more differential activity. Furthermore, there are other ways that analogues with different potency in different tissues might be devised. For example, analogues might be devised such that TR co-activator and co-repressor molecules bind differently to analogue-TR complexes than  $T_3$ -TR complexes. Another way to alter  $T_3$  action differentially might be to alter extrathyroidal  $T_3$  production by devising compounds that selectively inhibit one of the two deiodinases that catalyze conversion of  $T_4$  to  $T_3$ .

Robert D. Utiger, M.D.

### References

1. Sherman SI, Ringel MD, Smith MJ, et al. Augmented hepatic and skeletal thyromimetic effects of tiratricol in comparison with levothyroxine. *J Clin Endocrinol Metab* 1997;82:2153-8.

## Low frequency of anti-sodium-iodide transporter antibodies in autoimmune thyroid disease

Seissler J, Wagner S, Schott M, Lettman M, Feldkamp J, Scherbaum WA, Morgenthaler NG. Low frequency of autoantibodies to the human Na<sup>+</sup>/I<sup>-</sup> symporter in patients with autoimmune thyroid disease. *J Clin Endocrinol Metab* 2000;85:4630-4.

### SUMMARY

**Background** Some patients with autoimmune thyroid disease have serum antibodies that react with the sodium-iodine transporter in thyroid cells, but the frequency of detection of the antibodies in patients with Graves' disease or Hashimoto's disease is uncertain.

**Methods** Serum samples from 177 patients with hyperthyroidism caused by Graves' disease, 72 patients with Hashimoto's disease and 165 normal subjects were tested for anti-sodium/iodine transporter antibodies. The ratio of women to men in the three groups was 4 to 1, 3 to 1 and 1 to 4, respectively). The serum samples were analyzed in a radioligand assay using recombinant radiolabeled sodium/iodine transporter as antigen. Because antibodies were readily detected in a few normal subjects, the test was considered positive if the serum sample bound more radiolabeled antigen than the samples from 95 percent of the normal subjects (threshold value defined as 20 arbitrary units). Serum antithyroid peroxidase and thyrotropin (TSH)

receptor-binding inhibitory antibodies were also measured.

**Results** Nineteen of the 177 patients with Graves' disease (11 percent), 15 of the 72 patients with Hashimoto's disease (21 percent) and 8 of the 165 normal subjects (5 percent) had a positive test for sodium/iodine transporter antibodies. The proportion of patients with positive tests decreased substantially if the threshold value for a positive test was raised. Antithyroid peroxidase antibodies were detected in 100 percent of the patients with Hashimoto's disease, and 90 percent of the patients with Graves' hyperthyroidism had TSH receptor-binding inhibitory antibodies.

**Conclusion** Most patients with Graves' hyperthyroidism or Hashimoto's thyroiditis do not have high serum concentrations of anti-sodium/iodine transporter antibodies.

### COMMENTARY

Since identification of the sodium/iodine transporter, several groups of investigators have looked for antibodies to the transporter or peptide components of it in the serum of patients with autoimmune thyroid disease using immunoassays and also bioassays in which the serum is tested for its ability to inhibit iodide transport in cells transfected with the transporter gene (1-4). Given that many patients with autoimmune thyroid disease have serum antibodies to multiple components of thyroid tissue, it is not surprising that they have antibodies to the transporter or peptide components of it. The frequency of positive tests varied considerably in different studies, perhaps not surprisingly because a different assay was used in each.

More important is whether sodium/iodine transporter antibodies have any biological importance. Antibodies that inhibit iodide transport might contribute to thyroid hypofunction in

patients with Hashimoto's thyroiditis. There is reason, however, to be skeptical that any transporter antibodies inhibit iodide transport, because in a recent study serum samples that inhibited iodide transport lost activity when dialyzed and retained it after the immunoglobulins were extracted (4). These results do not deny the existence of transporter antibodies as detected by immunoassay, just their biological activity.

Robert D. Utiger, M.D.

#### References

1. Endo T, Kogai T, Nakazato M, et al. Autoantibody against Na<sup>+</sup>/I<sup>-</sup> symporter in the sera of patients with autoimmune thyroid disease. *Biochem Biophys Res Comm* 1996;224:92-5.
2. Morris JC, Bergert ER, Bryant WP. Binding of immunoglobulin G from patients with autoimmune thyroid disease to rat sodium-iodide symporter

peptides: evidence for the iodide transporter as an autoantigen. *Thyroid* 1997;7:527-34.

3. Allan RA, Findlay C, Metcalfe RA, et al. The modulation of the human sodium iodide symporter activity by Graves' disease sera. *J Clin Endocrinol Metab* 1992;83:1217-21.
4. Chin HS, Chin DKH, Morgenthaler NG, et al. Rarity of anti-Na<sup>+</sup>/I<sup>-</sup> (NIS) antibody with iodide uptake inhibiting activity in autoimmune thyroid disease (AITD). *J Clin Endocrinol Metab* 2000;85:3937-40.



## Hypothyroidism can be transferred by bone marrow transplantation

Marazuela M, Steegman JL. Transfer of autoimmune hypothyroidism following bone marrow transplantation from a donor with Graves' disease. *Bone Marrow Transplantation* 2000;26:1217-20.

### SUMMARY

**Background** Both Graves' disease and chronic autoimmune thyroiditis may be caused by autoantibodies that bind to the thyrotropin (TSH) receptor, and both disorders may occur sequentially in the same patient. Here, a man who received a bone marrow transplant from his sister, who had Graves' hyperthyroidism and was in remission, developed autoimmune hypothyroidism 10 months after transplantation. After donating the marrow the sister developed subclinical hypothyroidism and then hyperthyroidism.

### Case Reports

**The Recipient.** A 23-year-old man with acute lymphoblastic leukemia in relapse was treated with cyclophosphamide and 12 Gy total body radiation and then received a bone marrow transplant ( $3.8 \times 10^8$  mononuclear cells/kg body weight) from his ABO- and HLA-identical sister. His serum TSH and thyroxine ( $T_4$ ) concentrations were normal and antithyroid microsomal antibodies were not detected in serum. Despite prophylaxis, he had an episode of graft-versus-host disease and then a cytomegalovirus infection, both of which responded to appropriate therapy. At 5 months after transplantation, his serum TSH concentration was normal, and no antithyroid or other autoantibodies were detected. At 8 months, immunologic reconstitution was normal; serum antithyroid microsomal antibodies were detected in a titer of 1:400. At 10 months, he complained of weakness and somnolence. His thyroid gland was not enlarged. His serum TSH concentration was 60 mU/L, his serum free  $T_4$  concentration was low-normal (0.9 ng/dL [11.6 pmol/L]), and tests for antithyroid peroxidase, antithyroglobulin and TSH receptor-binding inhibitory anti-

bodies were positive. There was complete chimerism of peripheral blood mononuclear and polymorphonuclear cells. He was treated with  $T_4$ . At 16 months,  $T_4$  therapy was stopped; 2 months later he had subclinical hypothyroidism (serum TSH concentration 9.6 mU/L, serum free  $T_4$  concentration 1.0 ng/dL [12.9 pmol/L]), and another test for TSH receptor-binding inhibitory antibodies was positive.  $T_4$  therapy was resumed. At 24 months he was asymptomatic, with no evidence of leukemia.

**The Donor.** The donor was the recipient's 19-year-old sister. She had developed Graves' hyperthyroidism, with positive tests for antithyroid microsomal and TSH receptor-binding inhibitory antibodies, two years before donating the bone marrow. She was treated with an antithyroid drug for 18 months. At the time of marrow donation her serum TSH concentration was 3.5 mU/L and her antithyroid microsomal antibody titer was 1:6400. At 12 months after marrow donation her serum TSH concentration was normal, but at 15 months she had subclinical hypothyroidism (serum TSH 11.7 mU/L, serum free  $T_4$  0.8 ng/dL [10.3 pmol/L]), a very high titer of serum antithyroid microsomal antibodies (1:409,600), and a positive test for TSH receptor-binding inhibitory antibodies. At 18 months her serum TSH was 4.7 mU/L. At 21 months she was clinically and biochemically hyperthyroid (serum TSH 0.01 mU/L, serum free  $T_4$  3.5 ng/dL [35.1 pmol/L]).

**Conclusion** The occurrence of hypothyroidism caused by chronic autoimmune thyroiditis in a recipient of marrow from a sibling with Graves' disease suggests that TSH receptor antibodies can act as an agonist in one person (the marrow donor) and an antagonist in another (the marrow recipient).

### COMMENTARY

The authors suggest that the same antibodies caused the different disturbances in thyroid function in the sister and her brother, but that seems unlikely. The TSH receptor antibodies that have TSH agonist actions and cause hyperthyroidism and those that have TSH antagonist actions and cause hypothyroidism are probably structurally similar, but not identical.

The donor had two episodes of Graves' hyperthyroidism, between which she had an episode of subclinical autoimmune hypothyroidism. Therefore, she had T and B lymphocytes sensitized to epitopes of the TSH receptor related to both receptor activation and blockade,

but predominantly activation. What the sister gave to her brother, however, were T lymphocytes primarily from clones capable of inducing the production of TSH receptor-blocking or cytotoxic antibodies or T lymphocytes capable of direct cytotoxic actions. When these clones expanded, he developed hypothyroidism. The fact that he had subclinical rather than overt hyperthyroidism 2 months after cessation of  $T_4$  therapy suggests he did not have severe thyroid injury, and that his hypothyroidism was caused more by TSH receptor-blocking antibodies than thyroid cytotoxicity.

This was a rather unique series of events in this man and his sister, but Graves' hyperthyroidism has been reported in both donors and recipients of bone

marrow transplants. They include a donor-recipient (sister-brother) pair in which the donor and recipient first developed hyperthyroidism 96 months and 112 months, respectively, after transplantation (1).

Robert D. Utiger, M.D.

### References

1. Holland FJ, McConnon JK, Volpe R, Saunders EF. Concordant Graves' disease after bone marrow transplantation: implications for pathogenesis. *J Clin Endocrinol Metab* 1991;72:837-40.

## Successful treatment of Cushing's disease evokes thyroid autoimmunity

Colao A, Pivonello R, Faggiano A, Filippella M, Ferone D, Di Somma C, Cerbone G, Marzullo P, Fenzi G, Lombardi G. Increased prevalence of thyroid autoimmunity in patients successfully treated for Cushing's disease. *Clin Endocrinol* 2000;53:13-9.

### SUMMARY

**Background** Glucocorticoid excess ameliorates thyroid autoimmune disease. Conversely, in occasional patients restoration of normal adrenal function has evoked thyroid autoimmune disease. There has not, however, been a survey of the effect of treatment of patients with glucocorticoid excess on thyroid autoimmunity.

**Methods** Serum free thyroxine (T<sub>4</sub>), free triiodothyronine (T<sub>3</sub>), thyrotropin (TSH) and antithyroglobulin and antithyroid peroxidase antibodies were measured and thyroid ultrasonography was done in 20 patients (16 women, 4 men, age range 18 to 38 years) with Cushing's disease and 40 normal subjects (32 women, 8 men, age range 18 to 38 years). The patients were studied before treatment and after they had normal adrenal function for 6 months. All the patients had a corticotroph adenoma of the pituitary and underwent transsphenoidal adenomectomy; 6 were not cured, of whom 5 were successfully treated by radiation and 1 by total adrenalectomy.

**Results** The mean serum free T<sub>4</sub> and free T<sub>3</sub> concentrations were similar in the patients both before and after treatment and in the normal subjects. Their serum TSH and thyroid antibody concentrations are shown in the table.

Before treatment, 12 patients (60 percent) had low serum TSH concentrations. After treatment 7 (35 percent) had high concentrations. Ultrasonography revealed a nodular goiter in 6 of the normal subjects (15 percent) and 9 of the patients (45 percent) before treatment.

Table. Mean (±SD) Serum TSH and Thyroid Antibody Concentrations before and after Treatment in Patients with Cushing's Disease and Normal Subjects.

	Serum TSH (mU/L)	Serum Antithyroglobulin Antibodies (U/mL)	Serum Antithyroid Peroxidase Antibodies (U/mL)
<b>Patients</b>			
Pretreatment	0.4±0.05	66±16	82±19
Post-treatment	4.7±1.1	387±100	421±131
<b>Normal subjects</b>	2.3±0.4	82±15	99±12

After treatment, these 9 patients still had a nodular goiter, and 6 of them and 1 other patient also had a diffuse hypoechoic pattern suggestive of thyroiditis. These 7 patients with thyroiditis were the ones with high serum TSH concentrations. They also had the highest serum concentrations of both antibodies both before and after treatment, and all had biopsies that revealed chronic lymphocytic thyroiditis.

**Conclusion** Restoration of normal adrenal function in patients with Cushing's disease is associated with marked increases in serum antithyroid antibody concentrations and a high incidence of hypothyroidism.

### COMMENTARY

Glucocorticoids have both direct and indirect effects on pituitary-thyroid function. The direct effects include inhibition of thyrotropin-releasing hormone and TSH secretion, particularly nocturnal TSH secretion, inhibition of the production of thyroid hormone transport proteins, and inhibition of extrathyroidal conversion of T<sub>4</sub> to T<sub>3</sub>. Thus, many patients with Cushing's syndrome have not only slightly low serum TSH concentrations, but also low-normal serum free T<sub>4</sub> and free T<sub>3</sub> concentrations (1).

The indirect effects include inhibition of thyroid autoimmune disease, as

amply documented in this study in which many patients had rises in serum antithyroid antibody concentrations and 7 patients developed subclinical or overt hypothyroidism after successful treatment of Cushing's disease. This is an unusually high frequency, and suggests that glucocorticoid excess somehow evokes but at the same time inhibits thyroid autoimmunity, which then becomes clinically evident after the excess is treated. This pattern is in some ways similar to that of postpartum thyroiditis.

Robert D. Utiger, M.D.

### References

1. Benker G, Raida M, Olbricht T, et al. TSH secretion in Cushing's syndrome: relation to glucocorticoid excess, diabetes, goitre, and the sick' euthyroid syndrome. *Clin Endocrinol* 1990; 33:777-86.

## Thyroid Review Articles

Glinoe D, Delange F. The potential repercussions of maternal, fetal, and neonatal hypothyroxinemia on the progeny. *Thyroid* 2000;10:871-87.

Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001;344:501-9.

Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? *J Clin Endocrinol Metab* 2000;85:3975-87.

Palazzo FF, Hammond LJ, Goode AW, Mirakian R. Death of the auto-immune thyrocyte: is it pushed or does it jump? *Thyroid* 2000;10:561-72.