

# CLINICAL THYROIDOLOGY

VOLUME XV • ISSUE 1

MARCH 2003

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# CLINICAL THYROIDOLOGY

VOLUME XV • ISSUE 1

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## Clinical Thyroidology

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## The Literature and *Clinical Thyroidology*

My charge as editor of *Clinical Thyroidology* is to summarize and comment on recently published papers describing original research on thyroidology that I think will be of interest to clinicians. I am looking for diversity, originality, and quality. The search for diversity means that I am reluctant to select an article on a topic covered in the preceding one or two issues of the journal, unless the results of the new study confirm a very important observation or are diametrically opposed. The search for originality means looking for papers on unusual topics, and in unexpected places. The search for quality means making rather subjective judgments, and is the most difficult of the searches.

What are the qualities of high-quality clinical research? They include establishing appropriate inclusion and exclusion criteria for patient enrollment in the study, inclusion of appropriate control subjects, selection of appropriate tests and treatments, selection of appropriate end points, and use of appropriate analytic methods. These qualities are applicable to most types of studies, including retrospective case studies and even studies of single patients.

High-quality writing means that the study is described in sufficient detail that the reader has a clear picture of exactly who was studied, what was done, and what was found. This means that the study and control subjects must be described in detail, as must the design, execution, and outcomes of the study. Important details in all these areas are all too often lacking. (Authors may say that they do not have enough space to do all this, but they would if they shortened their often lengthy introductions and discussions.) One area that has particularly vexed me is reference to a table or figure without any information about what the reader is supposed to see. Another is the poor description of research methods, particularly with respect to questionnaires. All too often there is little information about what the questionnaire is about, how it is scored, and what the scores mean. Then, there are the inconsistencies—even contradictions—between the abstract, methods, results, and even discussion. All these problems are the responsibility of authors. Reviewers must focus on the research, and its suitability for the particular journal, rather than the details of the presentation, although many reviewers do worry about the presentation. Editors, most of whom are part time and have time-limited appointments, are usually too busy to devote much time to the clarity of manuscripts they have accepted. And few journals have manuscript editors to review, much less edit, each accepted manuscript in detail.

Medical journals can do more to encourage both good research and good writing, by stating what they expect of authors. They can call attention to guidelines that have been developed to promote accurate reporting of studies (1-3). They can provide space on their Web pages for authors to provide more details about studies. They can devote more space to postpublication review, by publication of correspondence, certainly including critical correspondence, of papers recently published in their journal. Regarding this type of review, I encourage readers (and authors) to let me know if I have not summarized an article correctly, or if I or another commentator has erred in fact. We speak for ourselves, not the American Thyroid Association or anyone else, and we should set the record straight whenever we have erred.

Robert D. Utiger, M.D.

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*Clinical Thyroidology* is available  
on the ATA web site ([www.thyroid.org](http://www.thyroid.org)).

## Most thyroid disorders are not a risk factor for breast cancer

Simon MS, Tang MT, Bernstein L, Norman SA, Weiss L, Burkman RT, Daling JR, Deapen D, Folger SG, Malone K, Marchbanks PA, McDonald JA, Strom BL, Wilson HG, Spirtas R. Do thyroid disorders increase the risk of breast cancer? *Cancer Epidemiol Biomarkers Prev* 2002;11:1574-8.

### SUMMARY

**Background** Some, but not all, studies have revealed associations between thyroid disorders and breast cancer, but many of the studies have focused on limited types of thyroid disorders, for example thyroid cancer. In this study the relationships between many thyroid disorders and treatments for these disorders and breast cancer were determined in women with breast cancer and control women.

**Methods** The study group consisted of women with breast cancer who were enrolled in the Contraceptive and Reproductive Experiences study of the National Institute of Child Health and Human Development, a population-based case-control study carried out at five locations in the United States (Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle). Women eligible for enrollment were white and black women aged 35 to 64 years with newly diagnosed breast cancer between 1994 and 1998. The control group consisted of women living in the same county selected by random-digit dialing, matched to the study women by age (in five-year groups), race, and county of residence.

During a personal interview the women were asked if they had ever had any thyroid problem or received any thyroid medication or treatment. Women who answered "yes" were then shown a list of thyroid disorders and treatments and asked to indicate all that applied to them. No attempt was made to confirm the responses independently.

**Results** The women in the study and control groups were similar in age distribution, race, education, body-mass index (five years before interview), and reproductive histories, including age at menarche, and pregnancy history, menopausal status, and oral contraceptive or postmenopausal estrogen treatment.

There was no relationship between a history of thyroid disorder and breast cancer, except for thyroid cancer (Table). The increased risk in women with a history of thyroid cancer was limited to parous women (odds ratio, 3.4; 95 percent confidence interval, 1.5 to 8.1). The intervals between the diagnosis of a thyroid disorder and the times of interview were similar in the two groups.

Table. Relationships between a History of Thyroid Disorder and Treatments and Breast Cancer.

	Cases (n=4572)	Controls (n=4677)	OR (95% CI)*
History of thyroid disorder			
Never	3751 (82%)	3876 (83%)	1.0
Ever	820 (18%)	801 (17%)	1.1 (0.9-1.2)
Type of thyroid disorder			
Graves' disease	39 (0.9%)	33 (0.7%)	1.2 (0.8-1.9)
Hashimoto's disease	34 (0.7%)	37 (0.8%)	0.9 (0.6-1.5)
Hyperactive thyroid	125 (3%)	141 (3%)	0.9 (0.7-1.1)
Hypoactive thyroid	465 (10%)	530 (11%)	0.9 (0.8-1.0)
Goiter	120 (3%)	119 (2%)	1.0 (0.8-1.3)
Nodules	71 (2%)	63 (1%)	1.1 (0.8-1.6)
Thyroid cancer	23 (0.5%)	10 (0.2%)	2.7 (1.2-5.9)
Therapy			
Thyroxine	499 (11%)	537 (12%)	0.9 (0.8-1.1)
Thyroid extract	87 (2%)	93 (2%)	0.9 (0.7-1.3)
Radioiodine	102 (2%)	105 (2%)	1.0 (0.8-1.3)

\*OR, odds ratio; CI, confidence interval.

There was no relationship between any type of thyroid hormone or antithyroid treatment, including radioiodine treatment, and breast cancer (Table), and the duration or time of treatment was similar in the two groups.

**Conclusion** Thyroid disorders, both as a group or as individual disorders, except thyroid cancer in parous women, or treatments for thyroid disorders are not associated with an increase in risk for breast cancer.

### COMMENTARY

This was for the most part a negative study, confirming the results of most previous studies of a possible relationship between thyroid disorders and breast cancer. Is there any biologic reason to think that hyperthyroidism or hypothyroidism might increase a woman's risk of breast cancer? Breast tissue has thyroid hormone receptors, and thyroid hormone probably has a small role in breast development. Women with hyperthyroidism have high serum estradiol concentrations, which might stimulate breast growth. Nonetheless, there is little direct evidence for a role

for thyroid hormone excess, or deficiency, in breast cancer. The possibility of a relationship was probably suggested simply because both thyroid disease (and thyroid hormone treatment) and breast cancer are common in women.

The small increase in breast cancer in women who had thyroid cancer confirms the results of an earlier study; in that study the relative risk was 1.4 (95 percent confidence interval, 1.2 to 1.7) (1). Radioiodine therapy has been incriminated as the link between thyroid cancer and breast cancer, because breast tissue contains iodine transporters and therefore might receive excess radiation in women with thyroid cancer who were

treated with radioiodine. Simon et al. found no relationship between this therapy and breast cancer, but most of the women who received radioiodine must have had hyperthyroidism, not thyroid cancer (Table).

Robert D. Utiger, M.D.

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1. Chen AY, Kevy L, Goepfert H, et al. The development of breast cancer in women with thyroid cancer. *Cancer* 2001;92:225-31.

## Increased thyroid autoimmunity but not thyroid dysfunction in infertile women

Poppe K, Glinoeer D, Van Steirteghem A, Tournaye H, Devroey P, Schiettecatte J, Velkeniers B. Thyroid dysfunction and autoimmunity in infertile women. *Thyroid* 2002;12:997-1001.

### SUMMARY

**Background** Women with overt thyroid dysfunction may have menstrual abnormalities and be infertile. However, the extent to which thyroid dysfunction contributes to infertility is not known. In this study thyroid function and autoimmunity were evaluated in the female partner of couples who sought evaluation for infertility.

**Methods** The study subjects were 438 consecutive women (mean age, 32 years; range, 21 to 50), who had been infertile for at least one year despite regular cycles and unprotected intercourse, and their partners. The evaluation of the women included history, physical examination, transvaginal ultrasonography, hysterosalpingography or laparoscopy (if indicated), and measurements of serum gonadotropins, prolactin, thyrotropin (TSH), free thyroxine (T<sub>4</sub>), and antithyroid peroxidase antibodies. Semen analyses were done on the male partners. Based on the results of these studies, the infertility was categorized as being caused by endometriosis, tubal disease, ovulatory dysfunction, male infertility, or idiopathic.

For comparison, serum TSH, free T<sub>4</sub>, and antithyroid peroxidase antibodies were measured in 100 aged-matched women who had at least one spontaneous pregnancy and no history of reproductive dysfunction.

**Results** The cause of infertility was attributed to the woman in 197 couples (45 percent) and the man in 168 couples (38 percent), and was idiopathic in 73 couples (17 percent). Among the 197 infertile women, 116 (59 percent) had ovulatory dysfunction, 60 (30 percent) had tubal disease, and 21 (11 percent) had endometriosis. The median serum TSH concentration and frequency of high serum antithy-

roid peroxidase antibody concentrations were slightly higher in women with some causes of infertility, as compared with the control women (Table). The median serum free T<sub>4</sub> concentrations were 1.1 or 1.2 ng/dl (14 or 15 pmol/L) in all the groups and subgroups.

Table. Serum TSH and Antithyroid Peroxidase (TPO) Antibody Concentrations in Infertile and Control Women.

	Median Serum TSH (mU/L)	Serum TPO (% high)	RR (95% CI)
Female infertility (n=197)	1.3	18	2.2 (1.0-5.1)
Endometriosis (n=21)	1.2	29	3.6 (1.1-11.8)
Tubal disease (n=60)	1.2	18	2.3 (0.9-6.1)
Ovulatory dysfunction (n=116)	1.5	16	2.0 (0.8-4.9)
Male infertility (n=168)	1.3	11	1.3 (0.6-3.2)
Idiopathic (n=73)	1.2	7	0.9 (0.3-2.7)
Control women (n=100)	1.1	8	1.0

RR, relative risk; CI, confidence interval.  
\*P<0.02, as compared with control women.

Among the 438 women, 4 (1 percent) had a high serum TSH concentration, of whom 2 had overt hypothyroidism and 2 had subclinical hypothyroidism. Nine women (2 percent) had a low serum TSH concentration, of whom 2 had overt hyperthyroidism and 7 had subclinical hyperthyroidism. Most of the women with abnormal serum TSH concentrations had high serum antithyroid peroxidase antibody concentrations. They were distributed among all the infertility groups and subgroups. Four women (4 percent) in the control group had thyroid dysfunction (hypothyroidism, 1 woman; hyperthyroidism, 3 women).

**Conclusion** Women with infertility, especially those with endometriosis, have serologic evidence of thyroid autoimmune disease more often than do fertile women, but the frequency of thyroid dysfunction is not increased.

### COMMENTARY

Hypothyroidism seems to be no more common in infertile than normal women. Here, 4 of 438 women (1 percent) had hypothyroidism, a rate not different from that in the control women. In two other surveys of infertile women, hypothyroidism, nearly always subclinical hypothyroidism, was detected in 16 of 704 women (2 percent) and 12 of 299 women (4 percent) (1,2). Seventeen of these 28 women had ovulatory dysfunction, and 11 of the 17 women became pregnant after T<sub>4</sub> therapy was begun. A cause and effect cannot be taken for granted, because some infertile women

become pregnant with no treatment, but given the simplicity and safety of T<sub>4</sub> therapy it seems prudent to look for and treat hypothyroidism in infertile women for a few months before embarking on clomiphene or more complex fertility therapy.

Little is known about the effect of hyperthyroidism, in particular subclinical hyperthyroidism, or antithyroid therapy on fertility. Nonetheless, cautious antithyroid drug therapy should be considered for infertile women with subclinical hyperthyroidism who want to become pregnant soon, because it too is simpler than fertility therapy. Radioactive iodine therapy is best avoided in women who

desire pregnancy very soon.

Robert D. Utiger, M.D.

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2. Arojoki M, Jokimaa V, Juuti A, et al. Hypothyroidism among infertile women in Finland. *Gynecol Endocrinol* 2000; 14:127-31.



## Ghrelin secretion is decreased in hyperthyroidism

Riis AL, Hansen TK, Moller N, Weeke J, Jorgensen JOL. Hyperthyroidism is associated with suppressed circulating ghrelin levels. *J Clin Endocrinol Metab* 2003;88:853-7.

### SUMMARY

**Background** Ghrelin is an appetite-stimulating (orexigenic) hormone secreted primarily by the stomach. Serum ghrelin concentrations rise with fasting and fall with eating. On a more long-term basis, serum ghrelin concentrations tend to be increased in patients who are dieting and those with cachexia, and decreased in those with obesity. Patients with hyperthyroidism typically lose weight and have an increase in appetite, and might therefore be expected to have an increase in ghrelin secretion. In this study serum ghrelin was measured in patients with hyperthyroidism before and after antithyroid drug treatment.

**Methods** The study subjects were 9 women (age range, 26 to 49 years) with hyperthyroidism caused by Graves' disease and 9 age-matched normal women. The women with hyperthyroidism were studied before and after treatment with methimazole for 2 to 3 months, whereas the normal women were studied once. No information is provided about changes in weight or food intake before treatment in the women with hyperthyroidism.

Serum ghrelin was measured after an overnight fast and after a three-hour period during which insulin was infused in a dose of 0.6 mU/kg/min; euglycemia (90 mg/dl [5 mmol/L]) was maintained by a glucose infusion. Serum insulin, leptin, and other substances were also measured. Body composition was measured by dual x-ray absorptiometry and energy expenditure by indirect calorimetry.

**Results** The women with hyperthyroidism weighed 59.2±2.2 kg (mean±SE) before treatment and 64.4±2.9 kg after treatment, and the normal women weighed 69.9±3.9 kg. The women with hyperthyroidism had less total fat and a lower lean body mass than did the normal women, and

both values increased during antithyroid drug treatment. Their estimated energy expenditure was 52±2 kcal/day/kg lean body mass before treatment and 38±2 kcal/day/kg lean body mass after treatment, as compared with 34±1 kcal/day/kg lean body mass in the normal women. The pre- and post-treatment serum free thyroxine (T<sub>4</sub>) concentrations were 10.8±1.0 ng/dl (139±13 pmol/L) and 2.2±0.2 ng/dl (28±2 pmol/L) in the women with hyperthyroidism, and the concentration was 1.7±0.1 ng/dl (22±1 pmol/L) in the normal women.

The mean fasting serum ghrelin concentration was lower in the women with hyperthyroidism than in the normal women, and it increased after antithyroid drug treatment (Table). The fasting serum insulin and glucose concentrations were similar in the women with hyperthyroidism and the normal women.

Table. Mean (±SE) Serum Concentrations of Ghrelin and Other Hormones and Metabolites in Women with Hyperthyroidism before and after Treatment and Normal Women.

	Women with Hyperthyroidism		Normal Women
	Base Line	After Treatment	
Serum ghrelin (pg/ml)	1080±195*	1480±215	1870±195
Serum leptin (ng/ml)	8.5±1.2	8.2±1.0	10.3±2.1
Serum free fatty acids (μmol/L)	849±81	609±53	578±48
Serum beta-hydroxybutyrate (μmol/L)	362±81	97±25	88±21
Serum glycerol (μmol/L)	101±10*	50±5	63±8

\*P<0.05, as compared with the normal women.

**Conclusion** Ghrelin secretion is decreased in women with hyperthyroidism, indicating that it does not play an important role in the increase in appetite that is characteristic of the disorder.

### COMMENTARY

The simple explanation for the characteristic loss of weight that occurs in patients with hyperthyroidism is that their energy expenditure increases, at least in part due to an increase in thermogenesis. Energy intake increases, although usually not enough to maintain body weight. But what is the signaling system whereby appetite and food intake are increased?

One possibility is leptin deficiency. Weight loss is associated with decreased leptin production, and leptin deficiency stimulates food intake. However, serum

leptin concentrations for the most part have been normal in patients with hyperthyroidism (1), as they were in this study by Riis et al.

Obesity is associated with low serum ghrelin concentrations, and the concentrations rise during diet-induced weight loss in obese people (2). Thus, patients with hyperthyroidism might be expected to have high serum ghrelin concentrations, because they have often lost weight and are likely to be eating fewer calories than they use. But, according to Riis et al., the patients have low concentrations, suggesting that ghrelin secretion is responding normally to increased food

intake rather than causing it.

Robert D. Utiger, M.D.

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2. Cummings DE, Weigle DS, Frayo RS, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 2002;346:1623-30.

## Some women with hyperthyroidism have polycystic ovaries

Skjoldebrand Sparre L, Kollind M, Carlstrom K. Ovarian ultrasound and ovarian and adrenal hormones before and after treatment for hyperthyroidism. *Gynecol Obstet Invest* 2002;54:50-5.

### SUMMARY

**Background** Women with hyperthyroidism may have irregular menstrual cycles, their cycles may be anovulatory, and their fertility may be decreased. The frequency of irregular menstrual cycles has varied in different studies, and little is known about the appearance of the ovaries in these women. In this study menstrual cycle characteristics, ovarian structure, and serum androgens were determined in women with hyperthyroidism.

**Methods** The study subjects were 18 women (mean age, 36 years; range, 27 to 49) with newly diagnosed hyperthyroidism (Graves' disease, 15 women; other causes, 3 women). All the women had a serum free thyroxine (T<sub>4</sub>) concentration >1.7 ng/dl (22 pmol/L) and a serum TSH concentration <0.08 mU/L. The women were studied at the time of diagnosis and after treatment for one and three months. The studies consisted of ovarian ultrasonography and measurements of serum total and free testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA sulfate), sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), cortisol, and corticosteroid-binding globulin. Treatment consisted of methimazole, 30 mg daily; T<sub>4</sub>, 0.1 mg daily, was added after one month. The results of ultrasonography were analyzed according the phase of the woman's menstrual cycle, and were compared with the results at the same phase in women with regular cycles.

**Results** All the women reported having had regular menstrual cycles in the past, but there is no information about pregnancies. Ten women reported having irregular cycles before the onset of symptoms of hyperthyroidism (interval not given). The other 8 women had regular cycles, but 2 of them had noted hypomenorrhea.

Before treatment, 15 of the 18 women (83 percent) had abnormal ovarian ultrasonographic findings. The abnormal-

ities, which varied among the women and according to the phase of the cycle, included the presence of multiple or single large (preovulatory) follicles at inappropriate times, irregular cysts, and two-compartment cysts. Serum FSH and LH concentrations were normal. The mean serum total testosterone, SHBG, and DHEA concentrations were higher and the mean serum cortisol concentration was lower in the women with hyperthyroidism than in age-matched normal women (Table).

Table. Serum Androgen and Cortisol Concentrations in Women with Hyperthyroidism and Age-Matched Normal Women.

Serum	Women with Hyperthyroidism (n=18)	Normal Women (n=18)	P Value
Total testosterone (ng/dl)	43 (14-118)	37 (11-60)	
SHBG (nmol/L)	114 (30-201)	36 (20-63)	<0.001
Free testosterone (ng/dl)	0.5 (0.2-1.2)	0.7 (0.2-1.4)	<0.05
DHEA (ng/dl)	351 (194-580)	466 (160-1486)	<0.05
DHEA sulfate (µg/dl)	144±19	155±16	
Cortisol (µg/dl)	9.4±0.6	13.8±1.8	<0.05

Values are means (range, or SE).  
Conversion factors: testosterone, multiply by 34.7=pmol/L; DHEA, multiply by 0.035=nmol/L; DHEA sulfate, multiply by 0.027=mmol/L; cortisol, multiply by 27.6=nmol/L.

During treatment, serum free T<sub>4</sub> and SHBG concentrations decreased progressively in all women, whereas serum free testosterone concentrations increased slightly (as did serum cortisol and corticosteroid-binding globulin, but not free cortisol, concentrations). Among the 10 women who had irregular cycles before treatment, 7 (70 percent) had regular cycles during treatment. Two women became pregnant during treatment. The results of ovarian ultrasonography were abnormal in 9 of the 11 women (82 percent) studied after treatment for 1 month, but were normal in all 7 women studied after treatment for 3 months.

**Conclusion** Some women with hyperthyroidism have polycystic ovaries, as determined by ultrasonography, and the changes resolve during antithyroid drug therapy.

### COMMENTARY

The ultrasonographic findings in these women are not well described, at least for readers not versed in the ultrasound anatomy of the ovaries, but seem to indicate the presence of polycystic ovaries in many of the women. However, the presence of polycystic ovaries, as detected by ultrasonography, correlates poorly with the polycystic ovarian syndrome. Women with hyperthyroidism may have irregular menstrual cycles, one part of the definition of the polycystic ovarian syndrome, but they do not have either clinical or biochemical evidence of

hyperandrogenism, the other part of the definition. They do have high serum SHBG and total testosterone concentrations (although not in this study), but their serum free testosterone concentrations are often low. Still, one could envision the excess SHBG delivering excess testosterone to the ovaries, possibly compromising follicular development, and of course the excess T<sub>4</sub> and triiodothyronine might have deleterious effects on the ovaries.

The characteristics of the menstrual cycles in the women with hyperthyroidism in this study were not described in any detail. The most extensive data on

this topic are from a study of 214 women with hyperthyroidism (1). Among them 168 (78 percent) had regular cycles, 24 (11 percent) had hypomenorrhea, 15 (7 percent) had polymenorrhea, 5 (2 percent) had oligomenorrhea, and 2 (1 percent) had hypermenorrhea.

Robert D. Utiger, M.D.

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## Thyroxine therapy after antithyroid drug therapy does not alter long-term outcome in patients with hyperthyroidism caused by Graves' disease

Hoerrmann R, Quadbeck B, Roggenbuck U, Szabolcs I, Pfeilschifter J, Meng W, Reschke K, Hackenberg K, Dettmann J, Prehn B, Hirche H, Mann K, and the Basedow Study Group. Relapse of Graves' disease after successful outcome of antithyroid drug therapy: results of a prospective randomized study on the use of levothyroxine. *Thyroid* 2002;12: 1119-28.

### SUMMARY

**Background** Treatment of patients with hyperthyroidism caused by Graves' disease with an antithyroid drug and thyroxine ( $T_4$ ) has not resulted in a lower rate of recurrent hyperthyroidism, as compared with antithyroid-drug therapy alone, in most studies. In this prospective study the efficacy of treatment with  $T_4$  in preventing recurrent hyperthyroidism was assessed in patients who remained euthyroid for one month after stopping antithyroid-drug therapy.

**Methods** The study subjects at the time of group assignment and randomization (see below) were 332 patients (284 women, 48 men; mean age, 42 years [range, 18 to 70]) with hyperthyroidism caused by Graves' disease.

The patients were treated with an antithyroid drug alone (54 percent) or combined with  $T_4$  (46 percent) for 12 to 15 months, and had to be clinically euthyroid and have normal serum  $T_4$  and triiodothyronine ( $T_3$ ) concentrations during the last 6 months of therapy. All therapy then was discontinued. One month later, the patients were reevaluated. The 225 patients (68 percent) who had a normal serum thyrotropin (TSH) concentration at this time were randomly assigned to receive  $T_4$  or no therapy. The dose of  $T_4$  was adjusted so as to maintain subclinical hyperthyroidism. After 12 months, the patients in the  $T_4$ -therapy group were randomly divided into two groups;  $T_4$  was continued in one group and stopped in the other. Among the remaining patients, 39 (12 percent) had overt hyperthyroidism, 61 (18 percent) had subclinical hyperthyroidism, and 7 (2 percent) had subclinical hypothyroidism.

The 225 patients randomly assigned to receive  $T_4$  or no therapy and the other patients, excluding the 39 patients with overt hyperthyroidism, were evaluated periodically for 24 months. The primary study end point was recurrence of

overt hyperthyroidism during follow-up in the patients randomly assigned to the  $T_4$ -therapy and no-therapy groups. In the  $T_4$ -therapy group, overt hyperthyroidism had to be confirmed after cessation of  $T_4$  therapy. A total of 44 patients dropped out of the study.

**Results** The demographic and clinical characteristics of the patients in the two main groups and the other three groups at the one-month evaluation were similar, except that (by definition) the patients in the non-randomized groups had abnormal serum TSH concentrations.

The frequency of recurrent overt hyperthyroidism was similar in the  $T_4$ -therapy and no-therapy groups, but was significantly higher (intention-to-treat analysis,  $P < 0.01$ ) in the group with subclinical hyperthyroidism 1 month after antithyroid ( $\pm T_4$ ) therapy was stopped (Table). In the  $T_4$ -therapy group, the recurrence rates during year 2 were similar in those who did and did not continue  $T_4$ .

Table. Recurrent Overt Hyperthyroidism during Follow-up after Antithyroid Drug ( $\pm T_4$ ) Therapy for 12 to 15 Months.

	No.	Recurrent Overt Hyperthyroidism
$T_4$ -therapy group	114	
12 months		20 (18%)
24 months		27 (24%)
No-therapy group	111	
12 months		22 (20%)
24 months		36 (32%)
Subclinical hyperthyroidism	61	
12 months		20 (33%)
24 months		30 (49%)

**Conclusion** Among patients with Graves' hyperthyroidism, treatment with  $T_4$  after antithyroid drug therapy does not reduce the frequency of recurrent hyperthyroidism.

### COMMENTARY

This was a complex but carefully conducted study, and the main result is clear—the frequency of recurrent hyperthyroidism in patients who were euthyroid one month after stopping antithyroid drug ( $\pm T_4$ ) therapy was not altered by  $T_4$ -induced subclinical hyperthyroidism. So low TSH secretion—and presumed thyroid atrophy—does not somehow protect against Graves' disease, or there is a protective effect that is coun-

terbalanced by the slightly higher serum  $T_4$  and  $T_3$  concentrations needed to keep serum TSH concentrations low.

Among all 332 patients evaluated at one month, a total of 132 (40 percent) had recurrent overt hyperthyroidism then or later. The authors do not give the number of patients treated initially with the goal of later enrollment in this study, but it must have been more than 332. So the likelihood of recurrent (or persistent) hyperthyroidism is almost certainly higher than 40 percent.

One practical observation was that 23 of the 61 patients (38 percent) with subclinical hyperthyroidism at the one-month evaluation had normal serum TSH concentrations at one year, whereas 20 patients (33 percent) in this group had overt hyperthyroidism by then (Table). The importance of this observation is that a low serum TH concentration does not herald the imminent return of clinically important hyperthyroidism.

Robert D. Utiger, M.D.

## Hypothyroidism and other endocrine problems are common in children with brain tumors after treatment

Gurney JG, Kadan-Lottick NS, Packer RJ, Neglia JP, Sklar CA, Punyko JA, Stovall M, Yasui Y, Nicholson HS, Wolden S, McNeil DE, Mertens AC, Robison LL. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors. Childhood Cancer Survivor Study. *Cancer* 2003;97:663-73.

### SUMMARY

**Background** Children with brain tumors who survive for a prolonged period may have late endocrine and other adverse effects of treatment. In this study conducted by the Childhood Cancer Survivors Study group, the endocrine and cardiovascular effects of treatment were determined in long-term survivors of brain tumors.

**Methods** The study subjects were 1818 children, adolescents, and young adults (<21 years old) who were treated for a brain tumor between 1970 and 1986 at 25 centers and who survived for at least 5 years after diagnosis. This study focused on the 1607 patients (734 females, 873 males) who responded to a questionnaire or telephone interview that included questions about thyroid dysfunction and therapy, growth hormone deficiency and therapy, pubertal development and treatment of pubertal delay, and cardiovascular problems. Their ages at diagnosis were: ≤4 years, 547 patients (34 percent); 5 to 9 years, 480 patients (30 percent); and ≥10 years, 580 patients (36 percent). The tumor was an astrocytoma/glioma in 1066 patients (66 percent), medulloblastoma in 343 patients (21 percent), and ependymoma or other tumor in 198 patients (12 percent). Treatment consisted of surgery in 414 patients (26 percent); surgery and external-beam radiation in 682 patients (42 percent); surgery, radiation, and chemotherapy in 446 patients (28 percent); and other treatment in 65 patients (4 percent). The calculated radiation doses ranged from <4000 to >5500 cGy to the brain and <150 to >2000 cGy to the thyroid. At follow-up, 621 (39 percent) were aged <20 years, and 986 (61 percent) were aged 20 years or older. At that time, 174 patients (11 percent) were dead; the questionnaire was completed by a family member. The control group consisted of 3418 siblings of patients in the entire survivor cohort, who completed the same questionnaire.

**Results** Hypothyroidism and growth hormone deficiency were common in the patients (Table). In addition, 259 patients (16 percent) received growth hormone therapy and 103 patients (6 percent) received some treatment to induce puberty. There were 17 cases of hyperthyroidism, 29 cases of thyroid enlargement or thyroid nodules, 34 cases of primary amenorrhea (20 times the rate in the control group), and 20 cases of low sperm counts. Overall, 691 patients (43 percent) reported some endocrine problem or treatment. For all conditions and treatments the frequency was highest in the patients treated with surgery, radiation, and chemotherapy; intermediate in those treated with surgery and radiation, and lowest in those treated with surgery alone. However, the patients in the chemotherapy group also received higher doses of radiation.

Table. Post-Treatment Incidence of Hypothyroidism, Growth Hormone Deficiency, and Osteoporosis in 1607 Children with Brain Tumors.

	No. of Cases (%)	Rate (per 1000 person-years)	Relative Risk (95% CI)*
Hypothyroidism	25 (16%)		
Diagnosis to end of therapy	57	19.6	34 (24-50)
End of therapy to 5 years	92	14.1	23 (16-32)
5 years to interview	106	7.8	14 (10-21)
Growth hormone deficiency	342 (21%)		
Diagnosis to end of therapy	76	26.3	316 (128-786)
End of therapy to 5 years	140	21.8	264 (108-648)
5 years to interview	126	9.6	278 (111-695)

\*The reference group is the sibling group. CI denotes confidence interval.

Overall, 289 patients (18 percent) had one or more adverse cardiovascular outcome (stroke, arrhythmia, blood clots, chest pain), of which stroke was the most common (79 patients [5 percent]; relative risk, approximately 50).

**Conclusion** Among surviving children with brain tumors, hypothyroidism and other endocrine problems are common, and the onset is often years after treatment.

### COMMENTARY

Though not confirmed, the diagnoses and hormonal treatments described by the patients, the siblings, or their parents are likely to be accurate. Many of the patients were probably still being followed regularly, and they were likely to be medically knowledgeable. With respect to hypothyroidism, the questionnaire asked if the person has thyroid deficiency, and also if the person is taking thyroid hormone. (The questionnaire can be seen at [www.cancer.umn.edu/ccss](http://www.cancer.umn.edu/ccss)).

What the questionnaire does not do is ask about the basis for the diagnosis of hypothyroidism. It is likely that many patients had primary hypothyroidism, because the radiation dose to the thyroid was in the range known to reduce thyroid function, but the dose to the brain was sufficient to cause central hypothyroidism as well. In another posttreatment study of children with brain tumors (median follow-up, 12 years), primary hypothyroidism was more common than central hypothyroidism (24 vs. 6 percent) (1). It is likely that in some patients radiation damage to the hypothalamus or pituitary limits the compensatory response to

thyroid radiation damage, and in other patients radiation damage to the thyroid exaggerates the effect of TSH deficiency; either sequence would serve to increase the severity of hypothyroidism.

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## Hyperprolactinemia is uncommon and has little clinical impact in patients with hypothyroidism

Raber W, Gessl A, Nowotny P, Vierhapper H. Hyperprolactinaemia in hypothyroidism: clinical significance and impact of TSH normalization. *Clin Endocrinol* 2003;58:185-91.

### SUMMARY

**Background** Some patients with hypothyroidism have hyperprolactinemia, and it may contribute to reproductive dysfunction in hypothyroidism. This study was undertaken to determine the frequency of hyperprolactinemia in a large cohort of patients with hypothyroidism, the impact of hyperprolactinemia on the patients' reproductive function, and the effect of thyroxine (T<sub>4</sub>) therapy on hyperprolactinemia.

**Methods** The study subjects were 1003 consecutive patients (938 women, 65 men) with primary hypothyroidism seen in a thyroid clinic between 1997 and 2000. There were 93 patients with high serum thyrotropin (TSH) and low serum T<sub>4</sub> concentrations (overt hypothyroidism) and 910 patients with high serum TSH and normal serum T<sub>4</sub> concentrations (subclinical hypothyroidism). Approximately 50 percent were asymptomatic and had been referred to the clinic for thyroid evaluation or for a second opinion after they were found to have hypothyroidism elsewhere. Serum prolactin was measured once in all patients. Hyperprolactinemia was defined as a serum prolactin value >20 ng/ml in women and >18 ng/ml in men.

The patients were questioned about medications that might cause hyperprolactinemia and reproductive function. Among the women, 66 were taking an oral contraceptive and 50 estrogen. Six patients were taking neuroleptic drugs, and 12 patients were taking neuroleptic and antidepressant drugs. All the patients with hyperprolactinemia had repeat measurements of serum prolactin after T<sub>4</sub> therapy for at least three months. Those patients with persistently high values were offered magnetic resonance imaging (MRI) of the brain.

**Results** Hyperprolactinemia was present in 79 women (8 percent), including 11 pregnant or lactating women, and 5 men (8 percent). Among the 817 women not taking any estrogen or neuroleptic or antidepressant drugs 39 (5 percent) had hyperprolactinemia. The frequency of hyperprolactinemia was similar in the patients with overt hypothyroidism (10 percent) and those with subclinical hypothyroidism (8 percent). The mean ( $\pm$ SD) serum prolactin concentration was 49 $\pm$ 40 ng/ml in the women with hyperprolactinemia and 33 $\pm$ 13 ng/ml in the men with hyperprolactinemia. There was no correlation between serum prolactin and TSH concentrations. Based on inspection of Figure 1 in the paper, 28 of the 84 patients (33 percent) with hyperprolactinemia had serum prolactin concentrations >42 ng/ml; 27 of these 28 patients had serum TSH concentrations <15 mU/L.

Seventeen of the 47 premenopausal women (36 percent) with hyperprolactinemia had oligo- or amenorrhea, as compared with 68 of the 423 premenopausal women (16 percent) with normal serum prolactin concentrations. No woman who was not pregnant or lactating had galactorrhea.

Premenopausal women were more likely to be taking estrogen than postmenopausal women, but there was no correlation with hyperprolactinemia or normoprolactinemia.

Serum prolactin concentrations fell to normal during T<sub>4</sub> therapy in 37 patients (51 percent of those treated), including some of those taking estrogen or drugs. Among the 36 patients in whom the concentration remained high, 8 of the 18 who then had a brain MRI had a pituitary abnormality.

**Conclusion** Hyperprolactinemia is uncommon in patients with hypothyroidism, and when present in premenopausal women is not correlated with menstrual dysfunction.

### COMMENTARY

In population surveys, about 1 to 2 percent of people have hyperprolactinemia (1), and it is usually mild. The frequency is increased in patients with hypothyroidism, but the hyperprolactinemia is nearly always mild in them as well (so mild that it might well have been absent if measured several more times). And there are often confounding factors, as in these patients, that should make one hesitant to ascribe hyperprolactinemia to hypothyroidism. Given that the hyperprolactinemia is usually mild, the absence of menstrual cycle disturbances

is not surprising. In some patients the high values may be due to the presence of macroprolactin, a complex of prolactin and antiprolactin antibodies, which when tested for is found in about 20 percent of serum samples with high prolactin concentrations.

The lack of correlation between serum TSH and prolactin values suggests that severity of thyroid deficiency is not the sole determinant of hyperprolactinemia, but what the other determinants might be is not known. One possibility is the duration of hypothyroidism.

As a practical matter, there is no reason to measure serum prolactin

routinely in patients with hypothyroidism, even those with abnormal menstrual cycles. On the other hand, serum TSH should be measured in all in patients with hyperprolactinemia.

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## Despite adequate thyroxine therapy, patients with hypothyroidism feel less well than other patients

Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study. *Clin Endocrinol* 2002;57:577-85.

### SUMMARY

**Background** Some patients with hypothyroidism have persistent symptoms despite treatment with thyroxine ( $T_4$ ) in doses sufficient to restore serum  $T_4$  and thyrotropin (TSH) concentrations to normal. This study was undertaken to assess systematically the well-being of a large number of patients being treated for hypothyroidism.

**Methods** A total of 961 patients aged 18 to 75 years who had been taking  $T_4$  for at least four months were identified in five general practices in the United Kingdom. These patients and 961 age-, sex-, and practice-matched patients not taking  $T_4$  were sent a three-part questionnaire. In part one they were asked to indicate which of 12 common medical conditions they had and to list the medications they were taking at that time. In parts two and three, respectively, they were asked 12 questions about their psychological well-being (the General Health Questionnaire, designed to determine psychological distress) and questions about 12 symptoms of thyroid dysfunction (the Thyroid Symptom Questionnaire). Possible responses to the questions on the general questionnaire ranged from better than usual to much less than usual, and were scored on a scale of 0 to 3 (possible total score, 0 to 36) and a scale of 0 to 1 (possible total score, 0 to 12). Responses to the thyroid questionnaire ranged from symptom absent to present, and were scored in the same two ways. Thus, higher scores indicated less well-being, or more thyroid symptoms. The patients' most recent serum TSH values were obtained from their records.

**Results** Questionnaires were returned by 597 patients (62 percent) in the  $T_4$ -therapy group and 551 patients (57 percent) in the control group. The mean ages of the respondents in the  $T_4$ -therapy and control groups were 60 and 59 years, respectively, and 85 and 87 percent, respectively, were

women. The main reasons for  $T_4$  therapy were spontaneously-occurring hypothyroidism (64 percent), hypothyroidism after radioiodine therapy (18 percent), and hypothyroidism after thyroid surgery (11 percent). The frequency of diabetes, cardiovascular disease, hypertension, and depression was higher in the  $T_4$ -therapy group than in the control group, as was chronic drug therapy for diabetes, cardiovascular disease, and gastrointestinal dysfunction.

As scored by the 36-point method, the mean total score on the general questionnaire was 12.1 in the  $T_4$ -therapy group, 12.1 in the 397 patients in the  $T_4$ -therapy group who had a normal serum TSH concentration within the preceding year, and 11.4 in the control group ( $P=0.03$  and  $P=0.02$ , respectively, versus the control group), indicating less well-being in the  $T_4$ -therapy groups. The mean total scores on the thyroid questionnaire were 12.6 in the  $T_4$ -therapy group, 12.8 in the patients in the  $T_4$ -therapy group with normal serum TSH values, and 11.5 in the control group ( $P<0.001$ , for both  $T_4$  groups versus the control group).

As scored by the 12-point method, the total score was  $\geq 4$  in 25 percent of the  $T_4$ -therapy group, 26 percent of the patients in the  $T_4$ -therapy group who had normal serum TSH values, and 19 percent of the control group ( $P=0.04$  and  $P=0.02$ , respectively, versus the control group). Similarly, the thyroid symptom score was  $\geq 4$  in 37 percent of the patients in the  $T_4$ -therapy group, 39 percent of the patients in the  $T_4$ -therapy group who had normal serum TSH values, and 25 percent in the control group ( $P<0.001$ , for both  $T_4$  groups versus the control group).

**Conclusion** Patients with hypothyroidism who are adequately treated with  $T_4$  score slightly less well on tests of psychological well-being and have more thyroid symptoms than do other age- and sex-matched patients.

### COMMENTARY

There are several possible explanations for the lesser psychological well-being and the presence of more symptoms of hypothyroidism in patients with hypothyroidism being treated with  $T_4$  than other patients. One is that some of the patients in the  $T_4$ -therapy group did not have hypothyroidism, and in them the  $T_4$  therapy itself caused some of the symptoms. Although the investigators did not confirm the diagnosis by review of the patients' records, the patients provided explicit information about the cause

of their hypothyroidism. Another is the higher self-reported frequency of other medical problems in the  $T_4$ -therapy group than the control group, but the authors adjusted for differences in comorbidity in their analysis. Another is patient self-selection, but the overall response rates were reasonably high and similar in both groups, and there is no reason to suspect that among those patients with symptoms more in the  $T_4$ -therapy group than the control group responded to the questionnaire. Still another is that the therapy was not appropriate, either because the dose of

$T_4$  was not optimal or triiodothyronine (or some other product of the thyroid) was not given along with the  $T_4$ .

It is easy, but not very helpful, to tell patients with hypothyroidism who have symptoms despite adequate  $T_4$  therapy that their symptoms have some other explanation. What the results of Saravanan et al. suggest is that we need to focus less on serum TSH values and think more about how to treat patients with hypothyroidism in new ways.

Robert D. Utiger, M.D.

## Mortality after coronary artery bypass grafting is higher in women with hypothyroidism treated with thyroxine than other women

Zindrou D, Taylor KM, Bagger JP. Excess coronary artery bypass graft mortality among women with hypothyroidism. *Ann Thorac Surg* 2002;74:2121-5.

### SUMMARY

**Background** Patients with hypothyroidism who have coronary artery disease are treated in the same way as are other patients with this disease, including coronary artery bypass grafting. Most previous studies, all small, suggested that the outcome of bypass grafting was similar in thyroxine (T<sub>4</sub>)-treated hypothyroid patients and patients not taking T<sub>4</sub>. In this study the short-term outcome of coronary artery bypass grafting was compared in 58 patients with hypothyroidism receiving long-term T<sub>4</sub> therapy and other patients.

**Methods** Between 1993 and 2000, 3631 patients (606 women, 3025 men) underwent coronary artery bypass grafting at the Hammersmith Hospital in London, England. Among them, there were 58 patients (30 women, 28 men) with a history of hypothyroidism who were being treated with T<sub>4</sub>. The clinical characteristics and the operative details in these women and men were compared, and their 30-day mortality rates were compared with the rates in the other women and men. Thyroid function was not assessed at the time of surgery in the other women and men.

**Results** The clinical characteristics of the T<sub>4</sub>-treated women and men with hypothyroidism were similar, except that the women had a slightly higher mean free T<sub>4</sub> concentration and more were taking a diuretic (Table). The bypass and aortic cross-clamp times were longer in the women.

There were 6 deaths (5 women, 1 man) within 30 days after surgery among the 58 T<sub>4</sub>-treated hypothyroid patients. The

mortality rate in the 30 women (17 percent) was higher than in the other 576 women (6 percent, P=0.02). The mortality rate in the T<sub>4</sub>-treated hypothyroid men (4 percent), was similar to that in the other 2997 men (3 percent, P=0.80). Four of the women and the 1 man died of progressive heart failure, and the other woman died of ventricular arrhythmia. Among the T<sub>4</sub>-treated hypothyroid women independent variables associated with death were lower T<sub>4</sub> dose, lower serum free T<sub>4</sub> concentration, diuretic therapy, and no aspirin therapy.

Table. Clinical Characteristics of Women and Men with Hypothyroidism Undergoing Coronary Artery Bypass Surgery.

	Women (n=30)	Men (n=28)
Age (yr)	64±9	63±9
Diabetes mellitus	10 (33%)	6 (21%)
Hypertension	19 (63%)	12 (43%)
Previous myocardial infarction	13 (43%)	14 (50%)
Duration of thyroid disease (yr)	13±11	13±13
Dose of T <sub>4</sub> (µg/day)	104±42	109±49
Serum free T <sub>4</sub> concentration (ng/dl)	1.6±0.5	1.2±0.3*
Serum thyrotropin concentration (mU/L)	5.1±5.4	7.2±9.2
Diuretic therapy	11 (37%)	3 (11%)*
Aspirin therapy	26 (87%)	23 (82%)*
Left ventricular ejection fraction <35%	2 (7%)	2 (7%)
Bypass time (minutes)	68±21	80±20*
Cross-clamp time (minutes)	33±12	43±14*

Values are means (±SD).

\*P<0.01-0.03, for the comparison between women and men.

To convert serum free T<sub>4</sub> values to pmol/L, multiply by 12.9.

**Conclusion** Short-term mortality after coronary-artery bypass grafting is higher in women with hypothyroidism receiving long-term T<sub>4</sub> therapy than in other women.

### COMMENTARY

Coronary artery disease and hypothyroidism are common in older people; therefore, clinicians may face the challenge of their coincidence in the same patient. Because the positive chronotropic and inotropic effects of T<sub>4</sub> increase myocardial oxygen demand, T<sub>4</sub> therapy is usually instituted cautiously in patients with hypothyroidism known or suspected to have coronary artery disease. So when hypothyroidism is diagnosed on the eve of coronary artery surgery, clinicians face a conundrum. Will T<sub>4</sub> therapy worsen myocardial ischemia, with all of its consequences? Or will patients with hypothyroidism who are untreated or treated inadequately face other, greater perioperative risks?

In small case-control studies, the mortality rates of cardiac surgery were no higher in patients with hypothy-

roidism than in euthyroid patients. However, some problems, including intraoperative hypotension, perioperative heart failure, and postoperative neuropsychiatric and gastrointestinal complications, were more common in the hypothyroid patients (1). The finding of Zindrou et al. of a higher 30-day mortality rate after coronary-bypass surgery in women taking T<sub>4</sub> may have little to do with hypothyroidism, because all the women were taking T<sub>4</sub>. Nothing is said about the problems identified in ref. 1 that might contribute to mortality. So, while this study confirms that the mortality rate after coronary artery bypass surgery is higher in women than in men, it does little to answer the question of whether patients with hypothyroidism have a higher mortality rate than those who are euthyroid.

Universal preoperative thyroid function testing and collection of information about duration of T<sub>4</sub> therapy, if any, pre-

operative complications, and outcome in patients undergoing coronary-artery bypass surgery would answer the questions posed initially. In the meantime, in caring for patients with hypothyroidism and coronary artery disease who need surgery, clinicians must use their judgment in balancing the risks of delay of surgery, for a few days or more of T<sub>4</sub> therapy, and the risks of surgery in untreated patients.

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## In Pendred's syndrome, some *PDS* gene mutations result in abnormal localization of pendrin in thyroid cells

Rotman-Pikielny P, Hirschberg K, Maruvada P, Suzuki K, Royaux IE, Green ED, Kohn LD, Lippincott-Schwartz J, Yen PM. Retention of pendrin in the endoplasmic reticulum is a major mechanism for Pendred syndrome. *Hum Mol Genet* 2002;11:2625-33.

### SUMMARY

**Background** Pendrin is a glycoprotein that in the thyroid gland is located in the apical membrane of thyroid follicular cells. It transports iodide from the cytoplasm of the cells to the lumen of thyroid follicles, where it is oxidized and incorporated into tyrosine residues of thyroglobulin, some of which are coupled to form thyroxine and triiodothyronine. Pendred's syndrome is a congenital disorder characterized by mutations in the *PDS* gene that result in decreased iodine oxidation and organification, and therefore in goiter and occasionally hypothyroidism, and also in deafness. It is inherited as an autosomal recessive trait. This study was done to determine the mechanism by which several mutations in pendrin reduce thyroid hormone biosynthesis.

**Methods** The cellular location of wild-type and mutant pendrin was studied in monkey kidney (COS) cells and FRTL5 rat thyroid cells that were transfected with *PDS* cDNA that had been linked to DNA encoding green fluorescent protein (GFP) to form GFP-*PDS* chimeras. FRTL5 cells, but not COS cells, naturally contain pendrin. The *PDS* genes were wild-type *PDS* and three of the most common mutants, L236P (leucine replaced by proline), T416P (threonine replaced by proline), and G384E (glycine replaced by glutamic acid). Transcription of the transfected GFP-*PDS* chimeras results in synthesis of GFP-pendrin. The transfected cells were cultured for varying intervals and examined by fluorescence scanning microscopy. Pendrin and proteins of the Golgi apparatus and endoplasmic reticulum were identified in the cells by immunofluorescence using specific antibodies.

**Results** GFP-wild-type pendrin was localized primarily in the plasma membrane of the COS cells, with a small amount in the endoplasmic reticulum. In FRTL5 cells, GFP-wild-type pendrin also was localized in the plasma membrane. In these cells the distribution of GFP-wild-type pendrin and endogenous pendrin, as detected by immunofluorescence using antipendrin antibodies, was similar.

The GFP-L236P-pendrin was localized almost completely in the endoplasmic reticulum, as detected both by fluorescence microscopy and staining with antipendrin antibodies in COS cells and FRTL5 cells and fluorescence microscopy in COS cells. GFP-T416P-pendrin and GFP-G384E-pendrin were also localized primarily in the endoplasmic reticulum in COS cells.

The GFP-L236P-pendrin did not aggregate in a small area of the endoplasmic reticulum, but was evenly distributed throughout it, and it was very slowly transferred to the plasma membrane. Co-transfection of COS cells with GFP-L236P-pendrin and a membrane protein of viral origin did not prevent transfer of the viral protein to the plasma membrane. Similarly, co-transfection of cells with Y(yellow)FP-L236P-pendrin and GFP-wild-type pendrin did not block the transfer of wild-type pendrin to the plasma membrane, whereas the L236P-pendrin remained in the endoplasmic reticulum.

**Conclusion** Several mutations in the *PDS* gene result in synthesis of pendrin molecules that are retained in the endoplasmic reticulum and therefore do not reach the plasma membrane of cells, the location and site of action of wild-type pendrin.

### COMMENTARY

Pendred's syndrome is characterized by congenital sensorineural deafness, goiter, and hypothyroidism. Affected patients have a cochlear malformation, known as the Mondini defect, in which the cochlear canals have fewer turns than normal. The onset of deafness precedes development of speech. With respect to the thyroid, most patients have a goiter and an abnormal perchlorate discharge test, but only about half have hypothyroidism.

Pendrin is expressed in the thyroid gland, the inner ear, and renal tubules and collecting ducts. In the thyroid, it is located in the apical membrane, and it functions to transport iodide from the

cytoplasm of thyroid follicular cells to the follicular lumen, where the iodide is oxidized and organified. In the cochlea, it probably serves as a chloride transporter, but how defects in chloride transport cause structural defects in the inner ear and deafness is not known. In the kidney, it serves as a chloride-base exchange system, but defects in pendrin do not seem to alter renal function in any important way.

Several dozen *PDS* gene mutations have been identified. In the thyroid, most of the mutations result in synthesis of pendrin molecules that are retained in the endoplasmic reticulum rather than inserted in the plasma membrane of the cells, as demonstrated by this and other studies (1). The mutations must somehow

prevent the maturation or folding of pendrin, or alter some signal needed for its transfer to the plasma membrane (processes collectively referred to as membrane trafficking). This is a relatively new concept in genetic disease, but one being recognized with increasing frequency.

Robert D. Utiger, M.D.

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## Laser thermocoagulation reduces nodule volume in patients with benign solitary thyroid nodules

Dossing H, Bennedbaek FN, Karstrup S, Hegedus L. Benign solitary solid cold thyroid nodules: US-guided interstitial laser photocoagulation—initial experience. *Radiology* 2002;225:53-7.

### SUMMARY

**Background** Patients with benign solitary solid thyroid nodules may be followed without treatment, or they may be treated with thyroxine or by surgery or injection of ethanol into the nodule. This study evaluated the efficacy of laser thermocoagulation as a treatment for patients with these nodules.

**Methods** The laser-treatment group consisted of 16 patients (13 women, 3 men; median age, 47 years [range, 24 to 67]) with a single palpable thyroid nodule. All the patients had pressure symptoms, and 10 (63 percent) thought their nodule was unsightly. The control group consisted of 15 patients (all women; median age, 40 years [range, 19 to 69]) with smaller nodules. They had no pressure symptoms and had declined laser treatment or surgery. All the patients had a solid benign hypofunctioning nodule, as determined by ultrasonography, fine-needle aspiration biopsy, and radio-nuclide imaging, respectively. All also had normal thyroid function and normal serum calcitonin concentrations.

The treatment consisted of insertion of an 18-gauge needle into the center of the nodule under local anesthesia and with ultrasound guidance. An infrared diode laser fiber was inserted through the needle into the nodule and the needle partially withdrawn. Power was delivered for a median time of 490 seconds (range, 287 to 1200); the median energy delivered was 761 joules (range, 555 to 2388). As monitored by ultrasonography, the treatment resulted in the appearance of an irregular echogenic area surrounding the laser fiber that enlarged with time; treatment was stopped when the enlargement ceased.

The patients in the laser-treatment group were evaluated by measurements of nodule volume and serum thyrotropin at base line and 1, 3, and 6 months after treatment. At base line and 6 months, pressure symptoms and cosmetic complaints were assessed using a visual analogue scale (0, no problems; 10, severe problems), and vocal-cord mobility was assessed by indirect laryngoscopy. The patients in the control group were evaluated only by repeated measurements of nodule volume (median follow-up, 12 months; range, 7 to 18).

**Results** The mean ( $\pm$ SD) base-line nodule volume in the laser-treatment group was  $10.0 \pm 7.9$  ml (range, 1.5 to 25.9), and it decreased by 46 percent to  $5.4 \pm 5.1$  ml (range, 1.2 to 20.9) at six months ( $P < 0.001$ ). The values at 1 and 3 months were approximately 7 and 6 ml, respectively. The patients' visual-analogue scale rating for pressure symptoms decreased from a median ( $\pm$ SD) value of  $5.0 \pm 2.4$  to approximately  $2.5 \pm 2.0$  at 6 months, and the rating for cosmetic symptoms decreased from  $1.0 \pm 1.6$  to  $0.8 \pm 1.5$  ( $P = 0.10$ ). The patients reported only slight transient discomfort after the procedure. No patient had a hemorrhage or local infection, and no patient had any changes in vocal-cord mobility or serum thyrotropin concentrations.

The median base-line nodule volume in the control group was  $2.8 \pm 3.6$  ml (range, 0.8 to 13.4), considerably less than in the laser-treatment group ( $P = 0.005$ ). During follow-up, the median volume in the control group increased by  $20 \pm 26$  percent (range, -15 to 60;  $P = 0.20$ ).

**Conclusion** These preliminary results suggest that ultrasound-guided laser photocoagulation may result in a substantial reduction in nodule volume in patients with a benign solitary solid thyroid nodule.

### COMMENTARY

The procedure described in this paper seems simple and safe, and the decreases in nodule volume and pressure symptoms were substantial. The follow-up period was short, but since the mean decrease in nodule volume was almost as great at 3 months as it was at 6 months a further decrease seems unlikely, and later reenlargement is possible. The nodules in the patients in the control group were so much smaller than the nodules in the patients in the laser-treatment group that the designation of control group seems inappropriate.

The mean 46 percent decrease in nodule volume in the laser-treatment

group is certainly greater than that which has occurred in any group of patients with benign solid nodules treated with thyroxine (1). It is similar to the decrease in nodule volume 6 and 12 months after a single injection of ethanol in 21 similar patients (2), but laser therapy results in less neck pain and tenderness.

Refinements in laser therapy may allow more complete destruction of nodules. The next step then would be to devise a method for rapid cytologic diagnosis, so that patients with benign thyroid nodules could be treated within minutes after biopsy.

Robert D. Utiger, M.D.

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1. Richter B, Neises G, Clar C. Pharmacotherapy for thyroid nodules: a systematic review and meta-analysis. *Endocrinol Metab Clin North Am* 2002;31:699-722.
2. Bennedbaek FN, Nielsen LK, Hegedus L. Effect of percutaneous ethanol injection therapy versus suppressive doses of L-thyroxine on benign solitary solid cold thyroid nodules: a randomized trial. *J Clin Endocrinol Metab* 1998;83:830-5.

## Many thyroid nodules grow slowly with time (I)

Quadbeck B, Pruellage J, Roggenbuck U, Hirche H, Janssen OE, Mann K, Hoermann R. Long-term follow-up of thyroid nodule growth. *Exp Clin Endocrinol Diabetes* 2002;110:348-54.

### SUMMARY

**Background** Thyroid nodular disease is very common, but little is known about its natural history, whether the patients are treated or not. In this retrospective study, consecutive patients with several types of thyroid nodular disease, some of whom were treated, were followed for up to 12 years.

**Methods** The study patients were 95 women (mean [±SD] age, 43±13 years) and 14 men (mean age, 49±12 years), with a total of 139 thyroid nodules that were >1 cm in diameter. The patients lived in Germany in a region of moderate iodine deficiency (urinary iodine excretion, 70 to 75 µg/g creatinine). Among the 109 patients, 81 patients had one nodule, and 28 patients had two or more nodules. As measured by ultrasonography, the volume of 110 nodules (79 percent) was ≤10 ml, and it was >10 ml in 29 (21 percent) (whether any nodules had a cystic component is not stated). Per technetate imaging revealed 86 (62 percent) of the nodules to be functioning and 53 (38 percent) to be nonfunctioning. There were 43 patients with 51 functioning nodules considered to be autonomous, of whom 31 had a serum thyrotropin (TSH) concentration ≤1.0 mU/L; these 43 patients were not treated. Most of the other patients were treated with thyroxine (T<sub>4</sub>, 2 µg/kg/day), iodide (200 µg/day), or both. Patients with nonfunctioning nodules underwent biopsy, and those in whom the biopsy was suspicious for carcinoma were excluded, as were patients with overt hyperthyroidism.

The patients were seen yearly for at least 3 years (mean, 5 years; range, 3 to 12) for assessment of thyroid function and ultrasonography for measurement of thyroid and nodule volume. At the end of the study all ultrasound studies were

evaluated by a single investigator. An increase in nodule volume of ≥30 percent was considered enlargement. During the study, 5 patients had overt hyperthyroidism and were treated with radioiodine, and 8 patients underwent surgery because of rapid nodule growth or appearance of new nodules. Fifteen patients discontinued treatment but continued to be followed.

**Results** The proportion of patients who had an increase in thyroid volume and the proportion of nodules that enlarged ≥30 percent increased progressively during follow-up (Table). The increases in thyroid and nodule volume were independent of thyroid volume, nodule volume, and nodule function at base-line; treatment; and also age, sex, and base-line serum TSH concentration. Whether thyroid gland or nodule volume decreased in any patients is not stated.

Table. Increases (≥30%) in Thyroid Gland and Nodule Volume during Follow-up.

	Baseline	3 Years	5 Years
	(No.)	≥30% Increase in Volume (No. [%])	≥30% Increase in Volume (No. [%])
Thyroid glands	109	25 (23%)	56 (51%)
Nodules	139	66 (48%)	85 (61%)
Nodule volume			
≤10 ml	110	52 (47%)	78 (71%)
>10 ml	29	16 (55%)	*
Functioning nodule	86	44 (51%)	64 (74%)
Nonfunctioning nodule	53	23 (43%)	31 (58%)
Treatment	73	34 (47%)	43 (59%)
No treatment	66	33 (50%)	*

\*Few patients in these groups were studied at 5 years.

**Conclusion** Thyroid nodules are likely to grow with time, independent of nodule volume and function at base line.

### COMMENTARY

These two studies provide a closer look at what happens to patients with benign thyroid nodules with time than has heretofore been available. The results of the studies were similar—many thyroid nodules grow slowly. This was so despite some rather marked differences in the studies. The patients' iodine intake was probably different. They were not evaluated in the same way, most notably with respect to radionuclide imaging. The proportions of patients who had autonomously functioning nodules must

have varied. The nodules were not proven to be benign in all patients in study I. The proportions of nodules that were cystic and their cystic content may have varied. The treatment varied, as did the completeness and duration of follow-up. Finally, the definition of an increase in nodule volume varied.

While a substantial percentage of patients in each study had increases in nodule volume, the magnitude of the increases was probably close to the threshold for enlargement, as defined in each study. (Neither paper contains information about the mean volume, or the

mean increase in volume, of the nodules meeting the respective criteria for enlargement). No patient or physician is likely to notice a 30 percent increase, much less a 15 percent increase, in volume of a nodule, although they might be able to detect a >50 percent increase in nodule diameter, a change noted in only 4 percent of the patients in study II. Nor are these small increases likely to be clinically important.

T<sub>4</sub> treatment was even less effective in preventing growth than it was in placebo-controlled trials (summarized in ref. 1). Decreases in nodule volume are

*continued on page 13*

## Many thyroid nodules grow slowly with time (II)

Alexander EK, Hurwitz S, Heering JP, Benson CB, Frates MC, Doubilet PM, Cibas ES, Larsen PR, Marqusee E. Natural history of benign solid and cystic thyroid nodules. *Ann Intern Med* 2003;138:315-8.

### SUMMARY

**Background** There have been few follow-up studies of patients with benign thyroid nodules, particularly studies in which changes in nodule volume were evaluated as a function of the cystic content of the nodule. In this retrospective United States study patients with benign thyroid nodules were reevaluated months to years after initial evaluation and biopsy, and changes in nodule volume were determined.

**Methods** Between 1995 and 2000, 1358 1-cm or larger nodules were biopsied with ultrasound guidance in 1009 patients. Among these biopsies, 854 (in 700 patients) revealed only benign thyroid follicular cells. These patients were advised to return in 9 to 12 months for repeat ultrasonography, but they were not contacted again after the initial biopsy.

Among these 700 patients, 268 (38 percent), who had 330 nodules (39 percent), returned 1 to 65 months later (mean, 20). At base line, their mean ( $\pm$ SD) maximum nodule diameter was  $2.4 \pm 1.0$  cm and nodule volume was  $5.5 \pm 9.1$  ml. The characteristics of these patients and their nodules were similar to those of the 432 patients who did not return. A second biopsy was sometimes done, usually on the basis of nodule growth, but not the detailed measurements described below. The repeat ultrasound images were compared directly with the initial images. Nodules were considered to have enlarged if the maximal diameter increased by  $>50$  percent or by  $\geq 3$  mm, or if the volume increased by  $\geq 15$  percent; the latter was the primary end point. Changes in nodule volume were evaluated in relation to patient characteristics, interval between ultrasound studies, cystic content of the nodule, serum thyrotropin (TSH) concentration (at base line), and thyroxine ( $T_4$ ) therapy.

**Results** The size of 129 nodules (39 percent) increased, as measured by a  $\geq 15$  percent increase in nodule volume. In contrast, 14 nodules (4 percent) increased in size, based on a  $>50$  percent increase in maximal diameter, and 86 nodules (26 percent) increased in size, based on a  $\geq 3$  mm increase in diameter.

Nodule volume increased as a function of time and cystic content at base line (Table), but not age, sex, or serum TSH concentration. The estimated median time to a  $\geq 15$  percent increase in nodule volume was 35 months. Based on life-table analysis, the estimated proportion with an increase in volume was 53 percent at 3 years and 89 percent at 5 years.

Table. Factors Related to Growth of Thyroid Nodules.

	Odds Ratio (95% Confidence Interval)
Time between studies	
6 months	1.2 (1.1-1.4)
12 months	1.5 (1.2-1.8)
Nodule $>50\%$ cystic	0.4 (0.2-0.7)
$T_4$ therapy	0.8 (0.5-1.4)

Seventy-four nodules (22 percent), in 61 of the 268 patients (23 percent), were biopsied a second time. The mean volume of these nodules had increased by 69 percent, as compared with an increase of 14 percent in nodules that were not rebiopsied. One biopsy was read as follicular tumor, which proved to be a papillary carcinoma; the volume of this nodule had increased by 79 percent in 3 years.

**Conclusion** Many benign thyroid nodules, especially those that are mostly solid, grow slowly.

*continued from page 12*

not mentioned in either paper, although in study II patients whose nodules had obviously decreased in size would probably not have returned for the second ultrasound study.

Finally, the notion that thyroid nodules that grow are malignant and those that do not grow are benign must be discarded.

Robert D. Utiger, M.D.

### Reference

1. Richter B, Neises G, Clar C. Pharmacotherapy for thyroid nodules: a systematic review and meta-analysis. *Endocrinol Metab Clin North Am* 2002;31:699-722.

## Radioiodine-induced thyroid lobectomy is an alternative to completion thyroidectomy in patients with thyroid carcinoma

Randolph GW, Daniels GH. Radioactive iodine lobe ablation as an alternative to completion thyroidectomy for follicular carcinoma of the thyroid. *Thyroid* 2002;12:989-96.

### SUMMARY

**Background** Some patients with thyroid nodules, especially follicular tumors, who are treated by thyroid lobectomy prove to have thyroid carcinoma. They are then advised to undergo contralateral thyroid lobectomy (completion thyroidectomy), because that lobe may contain carcinoma and also because removing it facilitates detection of persistent or recurrent thyroid carcinoma by radioiodine (I-123 or I-131) imaging or measurements of serum thyroglobulin. This retrospective study was done to determine the efficacy of I-131 to destroy the contralateral lobe of the thyroid in patients who had undergone thyroid lobectomy.

**Methods** The study subjects were 50 patients (30 women and 20 men; mean age, 49 years [range, 18 to 82]) who had undergone thyroid lobectomy. The final diagnosis was papillary carcinoma in 30 patients (60 percent), follicular carcinoma in 14 patients (28 percent), and Hurthle-cell carcinoma in 6 patients (12 percent). The remnant consisted of most or all of one lobe in 34 patients (68 percent), one lobe and the isthmus in 15 patients (30 percent), and one lobe and most of the other lobe in 1 patient (2 percent). The reasons for unilateral surgery included the surgeon's belief that the nodule was benign, the apparent absence of carcinoma in the contralateral lobe at the time of surgery, and complications during surgery that led to a decision to limit the extent of the operation. After a mean interval of 14 months (range, 0.25 to 286), 24-hour thyroid uptake of I-123 was measured, and 29.9 mCi (1106 MBq) of I-131 was given. The patients were treated with thyroxine for 6 months (range, 2 to 43). It was then stopped; six weeks later serum thyrotropin (TSH) was measured. Two to 5 mCi (74 to 185 MBq) of I-131 was given, and thyroid uptake of I-131 was measured 48 to 72 hours later.

The results in these patients were compared with the results in a control group of 50 patients who had undergone total or near-total thyroidectomy for thyroid carcinoma and been treated with thyroxine. The thyroxine was then discontinued, and six weeks later serum TSH and I-131 uptake were measured as in the study group. The mean interval between surgery and I-131 testing in these patients was 4 months (range, 1 to 30)

**Results** The mean serum TSH concentration in the 50 patients in the study group 6 months after treatment with I-131 was 77 mU/L (range, 12 to 284), and it was 71 mU/L (range, 7 to 184) in the 50 patients in the control group. Serum TSH concentrations were  $\geq 25$  mU/L, the value considered sufficient for radioiodine imaging, in 47 patients (94 percent) in each group.

Before I-131 treatment, the mean 24-hour thyroid I-123 uptake in the study group was 19 percent (range, 5 to 36). The 48- to 72-hour I-131 uptake six months after I-131 treatment was 0.8 percent (range, 0 to 12); it was  $\leq 1$  percent in 40 patients (80 percent) and  $< 0.1$  percent in 6 patients (12 percent). In contrast, the mean 48- to 72-hour I-131 uptake in the control group was 2.4 percent (range, 0 to 10), and it was  $< 1$  percent in only 15 patients (30 percent).

After I-131 treatment, 9 patients (18 percent) in the study group had mild to moderate thyroiditis, and 1 (2 percent) had diffuse arthralgia. No patient had transient hyperthyroidism or sialadenitis.

**Conclusion** A single moderate dose of I-131 is sufficient to destroy the remaining thyroid tissue in patients who previously have undergone thyroid lobectomy.

### COMMENTARY

In this study a single dose of I-131 effectively destroyed the remaining thyroid lobe in patients who had undergone unilateral thyroid lobectomy. Note that the patients were given only 29.9 mCi (1106 MBq) of I-131, which was all that could be given without hospitalization when this study was done. Now, a higher dose, which would be expected to destroy the remaining lobe even more often, can be given without hospitalization. And the efficacy of this treatment might be increased even more by administration of TSH before administration of I-131.

Does I-131-induced thyroid lobectomy accomplish the goals of completion thyroidectomy as well as the operation? There are two justifications for the operation, or in fact for contralateral lobectomy done at the time of an initial operation. One is to remove microscopic foci of carcinoma. This is a problem in patients with papillary carcinoma (or follicular variant of papillary carcinoma), but not those with follicular carcinoma. It seems highly likely that these microscopic foci would be destroyed by I-131, even if the I-131 were taken up only by the surrounding normal thyroid tissue (because the beta emissions of I-131 extend well beyond a single thyroid cell).

Only time will tell if microscopic foci of carcinoma survive and become clinically important, but that seems unlikely.

The second justification for completion thyroidectomy is to make it easier to detect and treat persistent or recurrent carcinoma. From this study it appears that as little thyroid tissue remains after lobectomy and treatment with I-131 as remains after near-total thyroidectomy. Therefore, thyroid lobectomy by I-131 treatment should be given serious consideration as an alternative to completion thyroidectomy.

Robert D. Utiger, M.D.



## Serum thyrotropin concentrations rise soon after cessation of thyroxine therapy in patients with thyroid carcinoma

Liel Y. Preparation for radioactive iodine administration in differentiated thyroid cancer patients. *Clin Endocrinol* 2002;57:523-7.

### SUMMARY

**Background** Many patients with thyroid carcinoma are treated with surgery and then iodine-131 (I-131) to destroy any remaining normal thyroid tissue or persistent or recurrent carcinoma. The I-131 is usually administered only when the patients' serum thyrotropin (TSH) concentrations are >25 or 30 mU/L. This study was undertaken to determine the time interval between the cessation of thyroxine (T<sub>4</sub>) therapy and the attainment of serum TSH concentrations ≥30 mU/L in patients with thyroid carcinoma.

**Methods** The study subjects were 13 consecutive patients (11 women, 2 men; age range, 32 to 72 years) with differentiated thyroid carcinoma who had undergone near-total thyroidectomy and were receiving long-term T<sub>4</sub> therapy (duration not stated). Their initial serum TSH concentrations ranged from 0.01 to 0.4 mU/L. Serum TSH, free T<sub>4</sub>, and free triiodothyronine (T<sub>3</sub>) were measured immediately before cessation of T<sub>4</sub> therapy and every 3 to 4 days thereafter until the serum TSH concentration was at least 30 mU/L, at which time I-131 was given. Two patients were studied twice. Five patients were treated with cholestyramine, 4 g twice daily, to accelerate the clearance of T<sub>4</sub>. The results of measurements of serum TSH in these patients were similar to the results in the other patients, and therefore the results in all patients were combined.

**Results** The mean interval from cessation of T<sub>4</sub> therapy to when a patient's serum TSH concentration was at least 30 mU/L was 17 days (95 percent confidence interval, 15 to 19; range, 11 to 28). There was no correlation between the initial serum TSH concentration and this interval. The interval from cessation of T<sub>4</sub> therapy to when the serum TSH concentration was above the upper limit of normal (4.5 mU/L) was 12 days (range, 9 to 21), and was positively correlated with the number of days needed to reach a value of at least 30 mU/L. The interval from the day when the serum TSH concentration reached the upper limit of normal to when it was at least 30 mU/L was 6 days (range, 3 to 13). Once normal, serum TSH concentrations doubled every 2 to 3 days, and were ≥60 mU/L in seven patients by 27 days after cessation of T<sub>4</sub> therapy (data extrapolated from Figure 1 of the paper).

The mean half-life of disappearance of serum free T<sub>4</sub> was 11 days (range, 8 to 13) and that for serum free T<sub>3</sub> was 16 days (range, 10 to 21) (values for patients given cholestyramine excluded). Both serum free T<sub>4</sub> and free T<sub>3</sub> concentrations were inversely correlated with serum TSH concentrations (P<0.001).

**Conclusion** Among patients with thyroid carcinoma who are being treated with T<sub>4</sub> most have serum TSH concentrations at or above the threshold value allowing treatment with I-131 less than 3 weeks after cessation of T<sub>4</sub> therapy.

### COMMENTARY

In these patients with thyroid carcinoma serum TSH concentrations increased rapidly after cessation of T<sub>4</sub> therapy. As a result, the interval between cessation of T<sub>4</sub> therapy and when the concentrations reached the threshold value (30 mU/L) generally considered to be necessary for effective thyroid radioiodine (I-123 or I-131) imaging and I-131 therapy was less than the 4-week interval that is often recommended. Patients who have such a rapid rise in serum TSH concentrations would be expected to have fewer symptoms of hypothyroidism before their studies or treatment are completed and T<sub>4</sub> therapy is resumed. Probable explanations for the rapid rise in serum TSH concentrations in the patients studied by Liel include a more complete thyroidectomy and treatment with lower doses of T<sub>4</sub> than in the past. However, symptoms were not assessed, nor were the T<sub>4</sub> doses stated.

There are four ways to induce high serum TSH concentrations in thyroid-

carcinoma patients who are taking T<sub>4</sub> in order to do thyroid radioiodine imaging or administer a therapeutic dose of I-131. One is simply to stop T<sub>4</sub>. A second is to switch from T<sub>4</sub> to T<sub>3</sub> for several weeks, and then stop it. This procedure probably shortens the interval between cessation of T<sub>4</sub> therapy and attainment of a high serum TSH concentration, and it may result in fewer or a shorter duration of symptoms of hypothyroidism (although these benefits do not seem to have been documented objectively). A third is to reduce the patient's usual dose of T<sub>4</sub> by half, and wait until the serum TSH concentration rises to the threshold value (1). In the study describing this scheme, the 15 patients studied had a mean serum TSH concentration of 63 mU/L after therapy with half-doses of T<sub>4</sub> for 5 to 10 weeks, and at that time the patients had considerably fewer symptoms of hypothyroidism as compared with when the same patients were studied 3 weeks after cessation of 50 µg of T<sub>3</sub> daily. The last is to administer recombinant TSH without

stopping T<sub>4</sub>. There is therefore no hypothyroidism, but the injections are costly and imaging and I-131 therapy may be less effective.

The comparative efficacy of these schemes in preparing patients with thyroid carcinoma for imaging and I-131 therapy is not known. Among them, stopping T<sub>4</sub> therapy is simpler. This study suggests that the interval between cessation of T<sub>4</sub> therapy and imaging or therapy can be shortened, so that the patients have fewer symptoms of hypothyroidism and the duration of any symptoms is reasonably short.

Robert D. Utiger, M.D.

### Reference

1. Guimaraes V, De Groot LJ. Moderate hypothyroidism in preparation for whole body 131I scintiscans and thyroglobulin testing. *Thyroid* 1996;6:69-73.

## Ultrasonography is the best test for detection of recurrent thyroid carcinoma in the neck

Frasoldati A, Pesenti M, Gallo M, Caroggio A, Salvo D, Valcavi R. Diagnosis of neck recurrences in patients with differentiated thyroid carcinoma. *Cancer* 2003;97:90-6.

### SUMMARY

**Background** The most common site of tumor recurrence in patients with papillary and follicular (differentiated) carcinoma of the thyroid gland is in the neck, either in the bed of the thyroid or in cervical lymph nodes, and in some patients recurrent carcinoma in the neck is the cause of death. In this study the efficacy of iodine-131 (I-131) imaging, ultrasonography, and measurement of serum thyroglobulin for the detection of recurrent tumor in the neck was compared in a large group of patients with differentiated thyroid carcinoma.

**Methods** The study subjects were 494 patients (374 women, 120 men; mean [ $\pm$ SD] age,  $49\pm 18$  years) with differentiated thyroid carcinoma, of whom 423 (86 percent) had papillary carcinoma and 71 (14 percent) had follicular carcinoma. The tumors were considered low risk (Stage I or II according to the TNM system) in 305 patients (62 percent) and high risk (Stage III or IV) in 189 patients (38 percent). Patients with residual tumor in the neck after initial treatment and those with serum antithyroglobulin antibody concentrations  $\geq 20$  U/L were excluded.

All the patients were treated by total thyroidectomy, and some lymph-node dissection was done in 243 patients (49 percent). All patients were then given 50 to 100 mCi (1850 to 3700 MBq) I-131 for remnant destruction. All patients without distant metastases had an undetectable ( $<0.25$  ng/ml) serum thyroglobulin concentration at least once after these treatments. All patients were treated with thyroxine in doses sufficient to lower their serum thyrotropin (TSH) concentrations to  $<0.05$  mU/L.

The patients were evaluated at 6- to 12-month intervals by ultrasonography of the neck, measurements of serum thyroglobulin, and whole-body I-131 scans after administration of 5 mCi (185 MBq) I-131; the latter two tests were done 28 days after cessation of thyroxine therapy, when the patients' mean serum TSH concentration was  $63\pm 12$  mU/L. Tumor

recurrence in the neck was defined as a tumor mass in the neck proven to be carcinoma by ultrasound-guided fine-needle aspiration biopsy or surgical excision of the tissue.

**Results** Recurrent thyroid carcinoma was detected in the neck  $45\pm 21$  months after diagnosis in 51 of the 494 patients (10 percent); the mean follow-up period was  $55\pm 38$  months. Forty-two patients had papillary carcinoma (recurrence rate, 10 percent), and 9 patients had follicular carcinoma (recurrence rate, 13 percent). The frequency of neck recurrence was slightly lower in the low-risk group (27 of 305 patients, 9 percent) than in the high-risk group (24 of 189 patients, 13 percent).

The neck recurrence was detected by ultrasonography in 48 of the 51 patients (94 percent). The recurrence was in the lateral neck region in 19 patients (40 percent) and the central neck region in 29 patients (60 percent). The mean tumor diameter was  $16\pm 9$  mm; the recurrence was palpable in 9 patients (18 percent). Biopsy, done in 46 patients, revealed tumor in 39 (85 percent). Serum thyroglobulin concentrations were  $\geq 2$  ng/ml in 29 patients (57 percent). I-131 uptake was seen in the neck in 23 patients (45 percent). All 38 patients who underwent surgery were found to have recurrent carcinoma (lymph nodes, 30 patients; thyroid bed, 6 patients; soft tissue metastasis, 2 patients). Distant metastases were detected by I-131 scans or other tests at the same time in 15 of the 51 patients (29 percent).

The results of ultrasonography were suspicious for neck recurrence in 45 patients (9 percent), but biopsies were negative, and none had evidence of recurrence by the other tests and during follow-up.

**Conclusion** Ultrasonography of the neck is more sensitive than I-131 scanning or serum thyroglobulin measurements for detecting recurrence of differentiated thyroid carcinoma in the neck.

### COMMENTARY

These results document the high sensitivity of ultrasonography for the detection of recurrent differentiated thyroid carcinoma in the neck, and indeed the procedure has become part of routine follow-up for many patients with these tumors. However, the results of ultrasonography were false positive as often as they were true positive. True positive and false positive results can only be resolved by biopsy, so there will

be many unnecessary biopsies. Doing a biopsy only if the patient has a detectable serum thyroglobulin concentration or I-131 uptake in the neck is not an attractive option; these tests are more specific, but are not sensitive. Perhaps ultrasound criteria can be developed that will distinguish neck masses that are a recurrent carcinoma from those that are not, but that seems unlikely. It seems equally unlikely that other imaging procedures will distinguish between the two types of mass. The only other option is

to wait, and repeat the ultrasound study in three or six months, but given the slow growth rate of thyroid carcinomas that is not likely to be helpful either. And most patients, and their physicians, will be very nervous about waiting, notwithstanding the slow growth rate and good outcome of patients with neck recurrences as detected by physical examination or I-131 scanning. So for now it will have to be biopsy.

Robert D. Utiger, M.D.

## Calcium and calcitriol therapy prevents hypocalcemia after thyroidectomy

Bellantone R, Lombardi CP, Raffaelli M, Boscherini M, Alesina PF, De Crea C, Traini E, Princi P. Is routine supplementation therapy (calcium and vitamin D) useful after total thyroidectomy? *Surgery* 2002;132:1109-13.

### SUMMARY

**Background** Hypocalcemia is a well-recognized complication of thyroid surgery. It usually occurs on the first or second postoperative day, by which time many patients have been discharged from the hospital. This has led to routine temporary calcium and vitamin D treatment so as to minimize the risk of hypocalcemia occurring at home. This study was done to evaluate the efficacy of routine calcium and vitamin D treatment for the prevention of symptomatic hypocalcemia after total thyroidectomy.

**Methods** Seventy-nine patients who were to undergo total thyroidectomy were recruited and gave consent for the study before the operation. At the end of the operation they were randomly assigned to receive calcium, calcium and calcitriol, or neither. Fifty-three patients had a multinodular goiter, 18 had suspicious nodules or thyroid carcinoma, and 8 had a toxic goiter. Patients who had previous neck surgery or were to have a neck dissection were excluded.

Treatment was started on postoperative day 1; in the calcium group it consisted of 1000 mg of elemental calcium three times daily, and in the calcium-calcitriol group it consisted of the same dose of calcium and 0.5 µg of calcitriol twice daily. The patients were evaluated for symptoms and signs of hypocalcemia on postoperative days 1, 2, and 3 (the day of discharge) and on day 7. Serum calcium was measured on days 1, 2, 3, and 7, and serum parathyroid hormone (PTH) was measured on days 1, 2, and 7. Hypocalcemia was defined as a serum calcium value <8.0 mg/dl (2.0 mmol/L) (normal range not given), even if present on only one occasion. Treatment was tapered starting on day 3 on the basis of serum calcium values.

**Results** The study groups were well-matched with respect to age, numbers of women and men, type of thyroid

disease, and numbers of parathyroid glands seen during surgery. Eleven patients in the no-therapy group had symptoms of hypocalcemia, and were treated with calcium and calcitriol, whereas only five patients in the other groups had hypocalcemia (Table). Two patients in the control group had carpedal spasm, 9 had perioral numbness and a positive Chvostek's sign, and 2 were given intravenous calcium. The patients in the other two groups had only mild perioral tingling and a positive Chvostek's sign; none was given intravenous calcium, but 2 patients in the calcium group were given calcitriol.

Table. Symptoms of Hypocalcemia and Serum Calcium Concentrations after Total Thyroidectomy in the No-Therapy, Calcium and Calcium-Calcitriol Groups.

	No-Therapy (n=27)	Calcium (n=26)	Calcium-Calcitriol (n=26)	P Value
Symptoms of hypocalcemia	11 (41%)	2 (8%)	3 (12%)	<0.01
Serum calcium (mg/dl)*				
Day 1	8.4	8.5	8.5	
Day 2	8.2	8.3	8.6	<0.05
Day 3	8.5	8.2	8.8	<0.01
Day 7	9.3	9.1	9.3	
Low serum PTH value on day 7	3 (11%)	1 (4%)	2 (8%)	

\*To convert to mmol/L, multiply by 0.25.

The mean serum calcium concentrations were slightly different in the three groups on days 2 and 3 (Table), but the mean serum PTH concentrations were similar at all times. Treatment with calcium and calcitriol was stopped by day 7 in all but 8 patients. It was stopped within the next 21 days in 6, but 2 were still being treated six months after surgery.

**Conclusion** Administration of calcium alone or calcium and calcitriol for 7 days after total thyroidectomy prevents hypocalcemia.

### COMMENTARY

Symptomatic hypocalcemia is common after total thyroidectomy, as in this study (41 percent of patients in the no-therapy group), and it is clear that it can be prevented by routine administration of calcium or calcium and calcitriol (1). The two treatment regimens used in this study were equally effective in preventing hypocalcemia. On the other hand, they did not raise serum calcium concentrations above normal, or even enough to inhibit PTH secretion. On postoperative days 3 and 7 the mean serum calcium concentrations were little higher and the mean serum PTH concentrations were

not lower in either treatment group as compared with the no-therapy group (some patients in the latter group were taking calcium and calcitriol then).

Postthyroidectomy hypocalcemia can to some extent be predicted by measurement of serum PTH at the end of the operation (2), but it seems simpler and safer to treat all the patients for a week or so. With respect to the two regimens, the calcium and calcitriol regimen seems preferable, especially in older patients in whom vitamin D deficiency, and therefore decreased calcium absorption, are common.

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Robert D. Utiger, M.D.

## Many patients with pulmonary hypertension have thyroid autoimmune disease

Chu JW, Kao PN, Faul JL, Doyle RL. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. *Chest* 2002;122:1668-73.

### SUMMARY

**Background** Primary pulmonary hypertension is a rare disorder that is characterized by progressive pulmonary hypertension in the absence of identifiable cardiac or pulmonary disease or exposures, for example anorexigenic drug therapy, that may result in pulmonary hypertension. In some case studies, patients with the disorder were found to have an unexpectedly high frequency of thyroid dysfunction or thyroid autoimmunity. This prospective study was designed to determine the frequency of both thyroid dysfunction and thyroid autoimmunity in patients with primary pulmonary hypertension.

**Methods** Sixty-three consecutive adult patients given a diagnosis of primary pulmonary hypertension were enrolled in the study. The diagnosis was based on a resting mean pulmonary artery blood pressure >25 mm Hg, as determined during right heart catheterization, and the absence of left-sided heart disease and interstitial or other lung disease. The patients were evaluated for thyroid disease by history, physical examination, and measurements of serum thyrotropin (TSH), free thyroxine (T<sub>4</sub>), and antithyroid peroxidase and antithyroglobulin antibodies at base line and periodically thereafter (mean, 1 year; range, 0.1 to 2.3). Patients with hyperthyroidism and a diffuse goiter were considered to have Graves' disease. Patients with two of the following findings—a diffuse goiter, a high serum antithyroid antibody concentration, and repeatedly high serum TSH concentrations—were considered to have Hashimoto's disease. Patients with any one of these three findings were considered to have autoimmune thyroid disease.

**Results** The mean age of the 63 patients was 47 years (range, 19 to 79); 53 were women and 10 were men. The pul-

monary hypertension was considered to be idiopathic in 24 patients, and it was associated with a connective tissue disorder in 13 patients, liver disease in 6 patients, anorexigenic drugs or drug abuse (cocaine, amphetamine) in 17 patients, and HIV infection in 3 patients.

Thirty-one patients (49 percent) had one of the three thyroid disorders, of whom 13 had been given the thyroid diagnosis in the past and 18 were newly identified. Among these 31 patients, 14 (45 percent) had Hashimoto's disease, 8 (26 percent) had Graves' disease, 8 (26 percent) had autoimmune thyroid disease, and 1 (3 percent) had lymphocytic hypophysitis; 21 of the 31 patients (68 percent) were treated for hyperthyroidism or hypothyroidism. Twenty-one patients (68 percent) had a high serum antithyroid peroxidase antibody concentration, and 18 (58 percent) had a high serum antithyroglobulin antibody concentration. Some patients with each subtype of pulmonary hypertension had a thyroid disorder, but the frequency was highest in those with the idiopathic subtype (16 of 24 patients [67 percent]).

Thirty-five of the patients had been given the diagnosis of primary pulmonary hypertension in the three months before they were evaluated for thyroid disease. Among them, 17 (48 percent) had one of the three thyroid disorders. The thyroid disorder was previously diagnosed in 4 patients, newly diagnosed in 12 patients (Hashimoto's disease, 4 patients; Graves' disease, 4 patients; autoimmune thyroid disease, 4 patients), and diagnosed during follow-up in 1 patient (Graves' disease).

**Conclusion** Among patients with primary pulmonary hypertension, approximately half have some type of thyroid autoimmune disease.

### COMMENTARY

There is no study in which approximately 50 percent of otherwise normal subjects had thyroid autoimmune disease, and therefore the association described by Chu et al. may be real. Nonetheless, it is always prudent to be skeptical about observations of associations between different disorders, especially when the possibly associated disorder—thyroid autoimmune disease—is common, and the established disorder—in this instance primary pulmonary hypertension—is rare. Furthermore, neither is a single, discrete entity. Thyroid function varies wide-

ly in patients with thyroid autoimmune disease, and even the genetic factors conferring susceptibility to the different types of thyroid autoimmune disease vary. In the case of primary pulmonary hypertension, it has several causes, or at least is associated with several other disorders and several different drugs, but the pathology and pathophysiology seem to be similar whether it is categorized as idiopathic or as one of the other subtypes. Primary pulmonary hypertension may be the result of an autoimmune process that can be initiated by multiple, seemingly unrelated factors in a genetically susceptible host.

How thyroid autoimmunity and pulmonary vascular autoimmunity might be related is not known, but it would seem not to be via thyroid dysfunction. On the other hand, thyroid dysfunction could exacerbate the clinical manifestations of primary pulmonary hypertension, for example, by increasing pulmonary artery pressure, increasing peripheral oxygen demand, or decreasing respiratory muscle strength. Thus, whatever the relationship between the two disorders, it is prudent to assess thyroid function in patients with primary pulmonary hypertension.

Robert D. Utiger, M.D.



## Monoclonal antithyrotropin receptor antibodies can be produced that mimic the actions of antithyrotropin receptor antibodies of Graves' disease

Sanders J, Jeffreys J, Depraetere H, Richards T, Evans M, Kiddie A, Brereton K, Groenen M, Oda Y, Furmaniak J, Rees Smith B. Thyroid-stimulating monoclonal antibodies. *Thyroid* 2002;12:1043-50.

### SUMMARY

**Background** The production of antibodies to the thyrotropin (TSH) receptor that mimic the actions of TSH on the thyroid is central to the pathogenesis of hyperthyroidism in patients with Graves' disease. For years, the only source of these antibodies was the serum of patients with the disease. However, lately polyclonal and monoclonal antibodies that react with the TSH receptor have been produced by immunization of animals with TSH receptors or portions of the receptor or TSH receptor cDNA, but for the most part the antibodies blocked, rather than mimicked, the action of TSH. This study was undertaken to produce monoclonal antibodies to the TSH receptor that activated the receptor.

**Methods** Twenty mice were immunized with TSH-receptor cDNA. A 1:50 dilution of serum from 7 of the mice inhibited the binding of I-125-TSH to immobilized TSH receptors. Spleen cells from the mouse with the highest level of inhibitory activity were cultured *in vitro*. Four cultures produced anti-TSH receptor antibodies. Cells from these cultures were cloned, and ultimately three monoclonal antibodies with different light- or heavy-chain variable regions were isolated. These antibodies (hereafter referred to as thyroid-stimulating monoclonal antibodies [TSmA]-1, -2, and -3) were purified and tested for their ability to inhibit I-125-TSH binding to TSH receptors and to stimulate cyclic adenosine monophosphate (cAMP) production by porcine thyroid cells and by Chinese hamster ovary (CHO) cells transfected with TSH receptor cDNA. The ability of serum from patients with Graves' hyperthyroidism and normal subjects to inhibit the binding of I-125-TSmA

to TSH receptors was studied. All the patients with Graves' hyperthyroidism had serum antibodies that blocked I-125-TSH binding to TSH receptors.

**Results** The three TSmAs inhibited I-125-TSH binding to TSH receptors. The inhibition was dose-dependent, and as little as 20 ng of antibody protein/ml could be detected. The TSmAs also stimulated cAMP production by porcine thyroid cells and CHO cells expressing TSH receptors.

Serum from 4 patients with Graves' hyperthyroidism caused dose-dependent inhibition of the binding of I-125-TsmA-2 to TSH receptors. The serum of 2 of these patients stimulated cAMP production in porcine thyroid cells, and that of the other 2 blocked the stimulatory action of TSH in these cells. Serum from 18 patients with Graves' hyperthyroidism inhibited binding of I-125-TsmA-2 and I-125-TSmA-1 to TSH receptors and binding of I-125-TSH to TSH receptors with approximately equal potency. Serum from 10 normal subjects and 2 patients with adrenal insufficiency who had high serum anti-21-hydroxylase concentrations did not inhibit the binding of either I-125-TSmA or I-125-TSH to TSH receptors. Serum from patients with Graves' hyperthyroidism, but not normal subjects, inhibited the binding of TSH receptors to immobilized TSmA.

**Conclusion** Monoclonal anti-TSH receptor antibodies induced by immunization of mice of TSH receptor cDNA have many of the properties of TSH receptor antibodies present in the serum of patients with Graves' hyperthyroidism.

### COMMENTARY

There is no naturally occurring animal counterpart to Graves' disease, but it—or something like it—can now be induced in mice and hamsters by immunization with TSH receptors or cDNA for the receptor. Some of the TSH receptor antibodies that are produced stimulate thyroid growth and function, and in a few instances the increases were sustained and the animals had something that looked like Graves' ophthalmopathy. Often, however, immunization resulted in production of antibodies that blocked the action of TSH. All the monoclonal antibodies in this study were

stimulatory, but they blocked both stimulatory and inhibitory antibodies present in the serum of patients with Graves' hyperthyroidism.

Assuming monoclonal mouse TSmA can be produced in large amounts, it should now be possible to examine the effects of prolonged administration of these antibodies in mice. Will they stimulate thyroid function *in vivo*, and will the stimulatory action be sustained? Is their administration accompanied by thyroid enlargement or by infiltration of lymphocytes into the thyroid, both of which occur in Graves' disease? Do some or all TSmA cause ophthalmopathy? Even if these questions are answered in the

affirmative, the key question will remain. What initiates the production of TSH receptor-stimulating antibodies?

Robert D. Utiger, M.D.

## Thyrotropin does not stimulate all aspects of fetal thyroid development and function

Postiglione MP, Parlato R, Rodriguez-Mallon A, Rosica A, Mithbaokar P, Maresca M, Marians RC, Davies TF, Zannini MS, De Felice M, Di Lauro R. Role of the thyroid-stimulating hormone receptor signaling in development and differentiation of the thyroid gland. *Proc Soc Natl Acad Sci USA* 2002;99:15462-7.

### SUMMARY

**Background** The thyroid gland begins to develop as a thickening of the floor of the pharynx that then migrates caudally and divides into the two lobes that lie alongside the trachea. In mice, the tissue acquires thyroid-specific functions only after migration is complete on about embryonic day 13. In this study the role of thyrotropin (TSH) and TSH receptors in the development of the thyroid gland and thyroid biosynthetic processes were studied in mice with genetic defects in the TSH signaling pathway.

**Methods** Thyroid morphology, expression of thyroid transcription factors (thyroid transcription factor 1 [TTF-1], thyroid transcription factor 2 [TTF-2], and Pax8), and expression of the sodium-iodide transporter, thyroglobulin, and thyroid peroxidase were studied at various stages of development in five groups of mice. The abnormal groups were: mice with homozygous complete TSH deficiency (*tsb*<sup>0/0</sup>), which also are deficient in growth hormone and prolactin; mice with a mutation in the gene for the TSH receptor that decreases the affinity of the receptor for TSH (*tsb-receptor*<sup>-/-</sup>); mice in which the gene for the TSH receptor is deleted (*tsb-receptor*<sup>0/0</sup>), and mice in which the gene for the TSH receptor is mutated so that it is constitutively activated (*tsb-receptor*<sup>+/+</sup>). The thyroid content of transcription factors and other substances was determined by immunochemical or in situ hybridization methods. In wild-type mice, sodium-iodide transporters can be detected at embryonic day 16, thyroglobulin at day 14.5, and thyroid peroxidase at day 16.

**Results** At embryonic day 17, the size and histology of the thyroid gland was similar the *tsb*<sup>0/0</sup>, *tsb-receptor*<sup>-/-</sup>, and wild-

type mice (both sexes). In contrast, at postnatal age 2 months, the thyroid gland was smaller in *tsb*<sup>0/0</sup> and *tsb-receptor*<sup>-/-</sup> mice than in wild-type mice.

The thyroid-cell content of TTF-1, TTF-2, and Pax8 at embryonic day 17 and age 2 months was similar in the *tsb*<sup>0/0</sup>, *tsb-receptor*<sup>-/-</sup>, *tsb-receptor*<sup>0/0</sup>, and wild-type mice. At embryonic day 17, the thyroglobulin content was only slightly lower in the *tsb*<sup>0/0</sup> and *tsb-receptor*<sup>-/-</sup> mice and similar in the *tsb-receptor*<sup>0/0</sup> mice, as compared with wild-type mice. In contrast, the content of sodium-iodide transporters and thyroid peroxidase was markedly lower or undetectable in the three groups of mutant mice. The sodium-iodide transporter was equally detectable in salivary tissue from all four groups of mice.

In the *tsb-receptor*<sup>+/+</sup> mice, a sequence that encodes a TSH receptor that is constitutively activated was added to the gene for TTF-1, so that the TSH receptor is activated (independently of TSH) when TTF-1 expression begins at about embryonic day 8. These mice were mated with the other mutant mice. The thyroid content of sodium-iodide transporters at age 2 months was similar in *tsb*<sup>0/0</sup>-*tsb-receptor*<sup>+/+</sup> mice, *tsb-receptor*<sup>-/-</sup>-*tsb-receptor*<sup>+/+</sup> mice, and wild-type mice, indicating restoration of TSH signaling in the mice carrying both mutations. At embryonic days 12.5 and 13.5, however, sodium-iodide transporters and thyroid peroxidase were not detected in *tsb-receptor*<sup>+/+</sup> mice, indicating that TSH signaling does not accelerate the appearance of these proteins.

**Conclusion** During fetal life in mice, TSH signaling is not important for thyroid growth and thyroglobulin production, but is important for the development of thyroid iodide transport and thyroid peroxidase.

### COMMENTARY

TSH, acting through the TSH receptor, is the major stimulator of the growth and function of the thyroid gland after birth. Several questions concerning the role of this signaling cascade in thyroid ontogeny were, however, awaiting definite answers. Does TSH contribute to the migration or proliferation of thyroid follicular cells? Is it essential for the expression of the key gene products necessary for thyroid hormone synthesis?

The thyroid gland is properly located in mice and patients with TSH deficiency or inactivating mutations of the TSH-receptor gene, indicating that thyroid development and migration are

independent of TSH stimulation. However, in these instances, the thyroid is hypoplastic, suggesting some role for TSH during development. The characterization of thyroid development during embryogenesis in mutant mice lacking TSH or its receptor by Postiglione et al. now provides answers to these questions. After completion of organogenesis, thyroid tissue was not only normally located, but also similar in size in the mutant and wild-type mice. Thus, morphologic differentiation is independent of TSH signaling, and its role in the proliferation of thyroid cells and maintenance of follicular architecture is limited to the postnatal period. The results also document that the effects of TSH signaling on thyro-

globulin expression are minimal, but that this pathway is essential for sodium-iodide transporter and thyroid peroxidase expression. Remarkably, sodium-iodide transporter expression is maintained in the salivary glands, indicating that expression of the transporter is regulated in a tissue-specific manner.

This elegant study exemplifies how careful phenotyping of animals with both naturally occurring and man-made mutations provides fundamental insights into the molecular mechanisms controlling organogenesis, differentiation and function.

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