THOMSON
AMERICAN HEALTH CONSULTANTS

Primary Care Reports

The Practical, Peer-Reviewed Journal for Primary C

NEWSLETTER & ELECTRONIC PUBLISHERS FOUNDATION
EDITORIAL EXCELLENCE AWARD WINNER

Volume 10, Number 9 **September 2004**

Thyroid disease is commonly encountered in primary care practices because it occurs in a significant proportion of the general population. (See Table 1.) *Routine thyroid disease usually is managed by the primary care provider. An understanding of the various diseases, appropriate diagnostic tests, therapeutic options, and complications of therapy is essential for proper management of the many patients with thyroid disorders.*

The diagnosis of thyroid disorders can be difficult for several reasons. While some thyroid diseases do have distinctive clinical features, others have more subtle manifestations and may be relatively difficult to recognize. The presentation of thyroid disorders is especially likely to be blunted in older patients, who often do not display the classic thyroid disease manifestations seen in younger patients. An accurate diagnosis is nonetheless possible based on clinical presentation, history, physical examination, signs and symptoms of thyroid dysfunction, and proper interpretation of the appropriate laboratory and imaging tests.

This article provides an overview of the initial evaluation and management of patients with various thyroid disorders such as thyrotoxicosis, hypothyroidism, thyroid nodules, and thyroid cancer. The critical question of when to obtain the input of an endocrine consultant also is addressed at several points in the management of these thyroid conditions.

—The Editor

Making Sense of Thyroid Disease: A Primary Care Approach

Authors: **Mandana Ahmadian, MD,** Fellow, Section of Endocrinology and Metabolism, Carl T. Hayden Veterans Affairs Medical Center, Phoenix, AZ; and **James V. Felicetta, MD**, Chairman, Department of Medicine, Carl T. Hayden Veterans Affairs Medical Center, Phoenix, AZ; Professor of Clinical Medicine, University of Arizona, Tucson.

Peer Reviewer: **Allan J. Wilke, MD,** Associate Professor, Medical College of Ohio, Toledo.

Thyrotoxicosis

Thyrotoxicosis is a relatively common disease caused by excessive serum concentrations of thyroid hormones. The term thyrotoxicosis refers to the biochemical and physiologic manifestations of excessive quantities of thyroid hormones. These thyroid hormones may not necessarily derive from the thyroid gland; exogenous sources of excess hormone also exist, as in factitious (deliberate self-administration) or iatrogenic (provider error) thyrotoxicosis. The related term hyperthyroidism is reserved for those thyrotoxic disorders that result from direct overproduction of hormone by the thyroid gland itself, of which Graves' disease is the most common. The severity of the symptoms of thyrotoxicosis depends upon the duration of disease, the degree of thyroid hormone excess, the patient's age, the presence or absence of extrathyroidal manifestations, and the specific disorder producing the thyrotoxicosis. Table 2 shows the differential diagnosis of thyrotoxicosis.

There are a number of major clinical manifestations of thyrotoxicosis. The skin often is warm and moist due to cutaneous vasodilation and to excessive sweating. Pruritus and hives occasionally are seen. The nails are soft, and loosening of the nails from the nail bed (oncholysis, or Plummer's nails) is characteristic. Thinning of the hair also frequently occurs. Stare and lid lag, both due to sympathetic overactivity, are common features of thyrotoxicosis. Ophthalmopathy and infiltrative dermopathy (so-called pre-tibial myxedema, seen mainly in young women) are unique features occurring only in patients with Graves' disease.

Thyrotoxicosis frequently causes symptoms related to the cardiac system that can be quite disabling for some patients. The majority of thyrotoxic patients have palpitations and shortness of breath on exertion. Systolic hypertension and widened pulse pressure also are common findings. A recent study of 2000 elderly individuals age 60 years and older with suppressed thyroid-stimulating hormone (TSH) showed that fully 20% had developed atrial fibrillation.[1]

Weight loss of up to 25 or 30 pounds is common in thyrotoxicosis. The weight loss is due to the increased metabolism and the increased gut motility, as well as to the associated malabsorption and hyperdefecation. A mild normochromic normocytic anemia, caused by an increase in plasma volume, also can be observed. Extra-gonadal conversion of testosterone to estradiol is increased; this enhanced estrogen formation can lead to gynecomastia, reduced libido, and erectile dysfunction. Oligomenorrhea can occur in female patients.

***Primary Care Reports*™**, ISSN 1040-2497, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Valerie Loner.
SPECIALTY EDITOR: Shelly Morrow Mark.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
GST Registration Number: R128870672.
POSTMASTER: Send address changes to ***Primary Care Reports*™**, P.O. Box 740059, Atlanta, GA 30374.

Periodicals postage paid at Atlanta, GA.
Back issues: $26. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.

E-Mail Address: customerservice@ahcpub.com
Editorial E-Mail Address: shelly.mark@thomson.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $349
(Student/Resident rate: $170).

Multiple Copies
1-9 additional copies: $314 each; 10 or more copies: $279 each.

Canada
Add GST and $30 shipping

Elsewhere
Add $30 shipping

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 36 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

This program has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. This volume has been approved for up to 40 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

This program is intended for primary care and family practice physicians. It is in effect for 36 months from the date of publication.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Shelly Morrow Mark,** Specialty Editor, at (954) 566-9203 or e-mail: shelly.mark@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

To reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief) serves as a consultant to Aventis and Sanofi and does research for AstraZeneca. Dr. Melvin serves on the speaker's bureau of Eli Lilly and Merck. Dr. Felicetta (author) is a consultant and is on the speaker's bureau for Abbott. Drs. Ahmadian (author) and Wilke (peer reviewer) report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.
This publication receives no commercial support.

Excess thyroid hormone also stimulates bone resorption and can lead to hypercalcemia. Longstanding, untreated thyrotoxicosis, therefore, often will result in accelerated osteoporosis. Proximal muscle weakness and decreased muscle mass are additional features of thyrotoxicosis. Tremor, anxiety, and nervousness also are symptoms encountered frequently.

Advanced age, as well as the co-existence of concomitant non-thyroidal disease, sometimes may blunt many symptoms of thyrotoxicosis in the elderly. The resulting diagnosis of apathetic, or masked, hyperthyroidism, sometimes is made during the work-up of new-onset atrial fibrillation, unexplained weight loss, or myopathy. Indeed, the classic presentation of the nervous, tremulous patient with thyrotoxicosis is far more commonly seen in younger rather than older individuals.

Evaluation

Laboratory evaluation should begin with a sensitive TSH assay, which is the single best screening test for thyrotoxicosis. The confounding effects of varying quantities of the primary binding protein for thyroid hormones, thyronine-binding globulin (TBG), is eliminated by measuring the free hormone level directly, rather than the total (protein-bound plus free) hormone level. The free thyroxine level reflects the true thyroid status more accurately than the TSH measurement in patients who are not yet at equilibrium. Such patients would include those recently treated for hyperthyroidism as well as those who recently have begun thyroid hormone replacement. Elderly patients and noncompliant individuals should be monitored routinely with both TSH and free levothyroxine (T_4) measurements.

The majority of patients with thyrotoxicosis have a suppressed TSH and an increased free T_4. A small number of thyrotoxic patients (fewer than 5% overall) have a normal free T_4 level but an increased free triiodothyronine (T_3) level, reflecting a condition known as T_3 thyrotoxicosis. T_3 thyrotoxicosis is more common in patients with relative iodine deficiency, in whom the preferential synthesis of T_3 reflects a physiologic effort to conserve iodine. In rare cases, a TSH-secreting pituitary adenoma, or hyperplasia of the TSH-secreting cells, may cause hyperthyroidism, in which case the serum TSH will be somewhat elevated. Thyroid antibodies, including anti-peroxidase (previously known as anti-microsomal) and anti-thyroglobulin, also can be obtained; their presence suggests autoimmune thyroid disease such as Graves' disease or Hashimoto's thyroiditis. Graves' disease is an autoimmune disorder predisposing to hyperthyroidism, while Hashimoto's thyroiditis is an autoimmune disease predisposing to hypothyroidism.

Once a biochemical diagnosis of thyrotoxicosis has been established, the next step is to establish the etiology of the disease. A radioactive iodine uptake and scan are required to help in determining a specific etiology prior to definitive therapy. Graves' disease is the most common etiology of thyrotoxicosis, but there are a number of other important entities encountered with some frequency.

The radioactive iodine uptake is diffusely increased in Graves' disease because of the intense thyroidal stimulation

Table 1. Prevalence of Thyroid Dysfunction

CONDITION	PREVALENCE IN ADULT POPULATIONS,%
Hypothyroidism	2
Subclinical hypothyroidism	5-17
Hyperthyroidism	0.2
Subclinical hyperthyroidism	0.1-6.0

Adapted from: Ladenson PW, et al. *Arch Intern Med* 2000;160:1573-1575.

Table 2. Differential Diagnosis of Thyrotoxicosis

- Graves' disease
- Toxic multinodular goiter
- Toxic adenoma (Plummer's disease)
- Iodine-induced (Jod-Basedow)
- Thyroiditis with transient thyrotoxicosis (painless thyroiditis, silent thyroiditis, postpartum thyroiditis)
- TSH-secreting tumor
- Thyrotoxicosis factitia (self-administration of excessive exogenous hormone)
- Subacute thyroiditis
- Trophoblastic tumor
- Ectopic thyroid tissue (struma ovarii, functioning metastatic thyroid cancer)

from thyroid-stimulating immunoglobins (TSI). Hyperthyroidism also can be associated with overactive nodules, as in toxic multinodular goiter, which is common in the elderly, or with a single toxic adenoma (Plummer's disease), seen primarily in middle-aged patients. Patients with hot nodules driving their hyperthyroidism typically demonstrate increased localized uptake in the area of the nodule, but with relative suppression of the remainder of the gland. The uptake typically is quite depressed in subacute (deQuervain) thyroiditis, silent thyroiditis, iodine-induced hyperthyroidism (Jod-Basedow hyperthyroidism), factitious thyrotoxicosis (self-administration of excessive exogenous hormone), and in iatrogenic thyrotoxicosis due to provider or pharmacist error. There is nothing to stimulate the gland to take up iodine, and so the uptake is very low. The TSH level in these conditions is suppressed by the high circulating hormone levels, and, unlike Graves' disease, there are no stimulating antibodies to drive iodine uptake by the gland.

Treatment

The goals of treatment of thyrotoxicosis are both to control symptoms and to restore euthyroidism. Three distinct treatment modalities are available for Graves' disease: radioactive iodine, antithyroidal drugs, and surgical intervention. Beyond these three definitive treatment options, patients with hyperthyroidism typically have symptoms reflecting excessive beta-adrenergic activity, such as palpitations, tachycardia, atrial fibrillation, and anxiety. Thyroid hormone has a major effect to potentiate the adrenergic effects of catecholamines. These symptoms, therefore, can be treated very effectively with beta-blockade. All beta-blockers are useful in relieving such symptoms, although they do not have any direct effect on thyroid hormone action or production. Short-acting propranolol (Inderal), however, has long been the traditional choice in treating hyperthyroid patients. Propranolol also inhibits the conversion of T_4 to T_3 at higher doses, an effect known to be useful in patients with impending thyroid storm. Thyroid storm is a rare but very severe, life-threatening form of thyrotoxicosis characterized by hypotension, temperature instability, mental status changes, and cardiac arrhythmias. All patients with Graves' disease should be seen by an endocrinologist prior to the institution of definitive therapy, although the primary care provider usually will want to initiate treatment with beta-blockers to reduce the patient's adrenergic symptoms as rapidly as possible.

Radioactive Iodine. Radioiodine currently is the treatment of choice in the United States for most patients with Graves' disease. Radioiodine is given orally as iodine 131 either in solution or, more commonly, as a capsule. The radioiodine is incorporated rapidly into the thyroid. The isotope produces radiation thyroiditis via its beta-emissions, typically resulting in fibrosis and euthyroidism within 6-18 weeks. Radioiodine therapy is considered quite safe, with no known increased risk of birth defects, infertility, or malignancy. The overall radiation exposure is similar to that associated with a standard barium enema. However, radioiodine is absolutely contraindicated during pregnancy because of the potential to ablate the fetal thyroid gland. A pregnancy test, therefore, should be obtained in all women of childbearing age prior to administering radioiodine therapy. Also, pregnancy should be postponed for a period of at least six months following radioiodine therapy. The majority of patients treated with radioiodine, unfortunately, do develop hypothyroidism eventually, typically within the first year after treatment. Such patients obviously require lifelong thyroid replacement therapy.[2]

Elderly patients and patients with underlying cardiac disease may require antithyroid drugs before radioiodine treatment to deplete the gland of stored hormone, and to reduce the risk of the accelerated hyperthyroidism that can be associated with post-radiation thyroiditis.

Two prospective studies also have demonstrated worsening of pre-existing Graves' ophthalmopathy following radioiodine treatment. Administration of steroids along with radioiodine therapy has been shown to decrease the likelihood of worsening pre-existing ophthalmopathy.[3-5]

Antithyroid Drugs. There are two commonly used antithyroid drugs, both of the thionamide class. Both methimazole (MMI) (Tapazole) and propylthiouracil (PTU) actively are transported into the thyroid gland where they inhibit important steps of thyroid hormone synthesis. Propylthiouracil also inhibits the conversion of T_4 to T_3 when higher doses are used. Methimazole has a longer half-life than PTU and can be given

once daily; methimazole also has a more favorable side effect profile. The remission rate with antithyroid drugs is higher in those patients with only mild hyperthyroidism and smaller goiters. In general, though, most patients treated with antithyroid drugs experience a fairly rapid recurrence of their thyrotoxicosis when the drugs are discontinued. As noted above, these drugs sometimes are used prior to radioiodine therapy to achieve pre-treatment euthyroidism. Pregnancy is one fairly clear indication for antithyroid drug treatment. Of the antithyroid drugs available, PTU is the preferred drug during pregnancy. The goal of treatment in such cases is to control maternal hyperthyroidism without causing fetal hypothyroidism. The dose can be tapered after euthyroidism has been achieved. Fetal goiter or bradycardia suggest over-treatment. PTU is not concentrated significantly in breast milk, reaching levels of only 10% of those found in serum.[6] If breast-feeding is desired, the medication should be taken just after breast-feeding. Some pediatric endocrinologists also prefer antithyroid drugs to treat childhood Graves' disease.

Antithyroid drugs, however, infrequently can be associated with very serious and even fatal side effects, such as agranulocytosis, hepatitis, and vasculitis. Arthralgias and rash also are seen with some frequency when antithyroidal drug therapy is employed.

Surgery. Surgery previously was a very widely used modality in the treatment of Graves' disease. Indeed, many famous clinics in the United States, such as the Cleveland Clinic, the Lahey Clinic, and the Ochsner Clinic, built their early reputations on the strength of their thyroid surgery programs. Now, however, thyroid surgery is performed only rarely in the treatment of Graves' disease. Surgery occasionally is performed in pregnant patients who refuse radioiodine therapy, in those intolerant to antithyroid drugs, and in those with co-existent thyroid cancer. The most serious potential complications of thyroid surgery include hypoparathyroidism and vocal cord paralysis due to inadvertent injury to one or both of the recurrent laryngeal nerves. The pool of skilled thyroid surgeons is much smaller than it was in earlier years when surgery was employed far more widely.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is an increasingly recognized entity. This condition is defined by a suppressed TSH below the reference range in the presence of normal levels of free T_4 and T_3. The clinical significance of subclinical hyperthyroidism relates to three potential complications: progression to overt hyperthyroidism, subtle cardiac abnormalities, and accelerated osteoporosis. The risk of atrial fibrillation is increased three- to five-fold in persons older than 60 years with subclinical hyperthyroidism.[1] Subclinical hyperthyroidism also may be a risk factor for accelerated osteoporosis in postmenopausal women. Data on osteoporosis, fracture, and atherosclerotic disease are inconsistent, and most data come from patients who take L-thyroxine or have clinically evident thyroid disease. The complications of subclinical hyperthyroidism and the evidence supporting treatment for this condition recently were reviewed by a panel with representatives from the American Thyroid Association (ATA), the American Association of Clinical Endocrinologists (AACE), and the Endocrine Society. The following were the formal recommendations. A repeat serum TSH always should be obtained early to confirm the presence of suppressed TSH. Also, free T_4 and T_3 levels should be measured to be able to exclude central hypothyroidism or nonthyroidal illness. The time of repeat testing depends upon the presence of signs and symptoms of hyperthyroidism and upon cardiac abnormalities or other serious conditions, and may vary between 2 weeks and 3 months. Individuals with repeat serum TSH levels below 0.45 microunits/mL should undergo further investigation to establish the etiology of the low TSH; a radioactive iodine uptake and scan can serve to distinguish between Graves' disease and subacute thyroiditis. If the patient is receiving levothyroxine treatment for treatment of hypothyroidism and does not have nodular disease, the dose needs to be adjusted to keep the TSH level within the reference range. However, thyroid cancer patients and certain patients with thyroid nodules require actual TSH suppression.

Elderly individuals with serum TSH levels between 0.1 to 0.45 microunits/mL may be considered for antithyroid treatment because of the possible association with increased cardiovascular mortality. If the serum TSH is lower than 0.1 microunits/mL, treatment definitely is needed if the patient has Graves' disease. Destructive autoimmune thyroiditis, however, is self-limiting and usually does not require any therapy other than beta-blockade for symptomatic relief. Patients with nodular thyroid disease experience a higher rate of conversion from subclinical hyperthyroidism to overt hyperthyroidism, thus warranting definitive therapy.[7-9]

Hypothyroidism

Many structural or functional abnormalities can impair the production of thyroid hormones and cause hypothyroidism. Clinically apparent acquired impairment of thyroid function affects about 2% of adult women, and roughly 0.1-0.2% of adult men. The incidence may be as high as 10% in adults 65 and older.[10,11]

The causes of hypothyroidism can be divided into the following categories:

Infancy

1. Maldevelopment of the thyroid gland
2. Inborn deficiency of hormone biosynthesis or action
3. Hashimoto's thyroiditis
4. Hypopituitarism or hypothalamic disease (central hypothyroidism)
5. Severe iodine deficiency (very uncommon in the United States.)

Adults

1. Hashimoto's thyroiditis
2. Lymphocytic thyroiditis
3. Thyroid ablation, either surgical or after radioiodine therapy
4. Hypothalamic or pituitary disease
5. Drug-induced: iodine, amiodarone, lithium, thiocyanate,

perchlorate, antithyroid drugs, and others

6. Familial thyroid hormone resistance (Refetoff's syndrome).

Primary hypothyroidism accounts for approximately 99% of cases, with fewer than 1% stemming from TSH deficiency or hypothalamic disease. Adult primary hypothyroidism is caused most frequently by chronic autoimmune thyroiditis (Hashimoto's thyroiditis).

Clinical Features. The symptoms of hypothyroidism (*see Table 3*) relate to both the duration and severity of the disease, as well as to the rapidity with which it develops. It should be noted that only a minority of patients with chronic thyroiditis actually have hypothyroidism. Also, if hypothyroidism is present, it sometimes may not persist. In a very limited number of cases, patients with thyroiditis actually may undergo a change from a hypothyroid state to a euthyroid or even a hyperthyroid state because of the development of antibodies directed against the TSH receptor.

There are many typical signs and symptoms associated with hypothyroidism. Mental status abnormalities are exceptionally common with hypothyroidism. Patients with hypothyroidism may demonstrate reduced memory, mental slowing, depression, and paresthesias. Deep tendon reflexes typically show a delayed relaxation phase.

The cardiovascular manifestations of hypothyroidism in-clude bradycardia, reduced cardiac output, diastolic hypertension with reduced pulse pressure, and accelerated coronary artery disease. The accelerated atherosclerosis is presumed to be related to the elevated cholesterol and triglyceride levels that are characteristic of hypothyroidism. Patients with severe hypothyroidism also may develop a pericardial effusion, with very quiet heart sounds and decreased voltage on the electrocardiogram.

Constipation is common in hypothyroidism, and ascites with a high protein content also may be seen with myxedema. Myopathy involving the proximal muscles, with elevated CPK levels (MM isoenzyme) is common; arthralgias and joint stiffness are other occasional manifestations. The skin usually is dry and cool, and the hair is thin and dull. Occasionally there may be a loss of the lateral portion of the eyebrows, which is a more useful sign in younger patients. Menorrhagia from anovulatory cycles may occur, and adolescents may experience primary amenorrhea from hypothyroidism. Growth retardation is very common in children with hypothyroidism; they will not resume a normal growth pattern until their thyroid hormone levels are restored to normal.

Evaluation

In the majority of cases, measurement of the serum thyrotropin (thyroid-stimulating hormone, TSH) level is the most discriminating and accurate test in the initial diagnosis of hypothyroidism.[12] Additionally, the following tests can be ordered:

- Free T4
- Thyroid antibodies: anti-thyroid peroxidase (antimicrosomal) and anti-thyroglobulin auto-antibodies. Thyroid autoantibodies are positive in roughly 95% of patients with autoimmune thyroiditis, with anti-thyroid peroxidase (anti-TPO) antibody positive in a higher percentage of patients than anti-thyroglobulin antibody.

Table 3. Common Symptoms of Hypothyroidism

• Fatigue	• Dementia, depression
• Weight gain	• Bradycardia
• Cold intolerance	• Constipation
• Skin and hair dryness	• Menstrual irregularity, infertility
• Myalgia	• Edema

The potential co-existence of other autoimmune endocrinopathies such as Addison's disease, pernicious anemia, autoimmune hypophysias, hypoparathyroidism, and hypogonadism should be considered in patients with Hashimoto's thyroiditis. Individuals with Hashimoto's thyroiditis are at significantly greater risk of developing other autoimmune endocrinopathies.

An elevated TSH, together with a subnormal free T_4 level, confirms the diagnosis of primary hypothyroidism. Finding a low T_4 and low or normal TSH should prompt a pituitary evaluation to investigate possible secondary or tertiary (hypothalamic) hypothyroidism. The diagnosis of hypothyroidism in severely ill patients can be quite complicated because thyroid function tests typically give misleading results during acute illness. If there is no clinical suspicion of thyroid disease, thyroid function tests normally should not be ordered during periods of severe acute illness. However, if there is clinical suspicion of thyroid disease, an endocrinologist should be consulted for assistance in interpreting the results of thyroid function testing. Severe non-thyroidal illness frequently is associated with marked depressions in both T_4 and T_3 levels, as well as suppression of TSH. The recovery phase from severe non-thyroidal illness can produce even more confusing results, with occasional marked elevations of the TSH level as the suppressive effects of illness-associated cytokines on TSH secretion dissipate.

Subclinical Hypothyroidism

Another important entity to recognize is subclinical hypothyroidism, defined by a mildly increased TSH in the presence of normal free T_4 and T_3 levels. It is a very common disorder, with a prevalence from 1% to 10% of the adult population. It is encountered most frequently in women and in the elderly. Subclinical hypothyroidism usually is an asymptomatic state, most commonly caused by autoimmune thyroiditis. The rate of progression to overt hypothyroidism varies between 3-20% per year; this rate appears to be greater in those patients with positive thyroid antibodies and/or goiter. There is not enough evidence to support or refute the association of subclinical hypothyroidism and systemic hypothyroid symptoms, cardiac dysfunction, or neuropsychiatric symptoms. The available data do not support early treatment for patients with subclinical hypothyroidism with a TSH level between 4.5-10 microunits/mL, but thyroid function tests should be repeated at 6- to 12-month intervals to monitor the course of the disease. Pregnant women and women

of childbearing age with subclinical hypothyroidism planning to become pregnant should be treated because of increased risk of fetal wastage or subsequent neuropsychiatric complications in the offspring due to thyroid insufficiency.[9]

Patients with TSH levels greater than 10 microunits/mL should be treated, and such treatment potentially may prevent the manifestations of hypothyroidism.[9]

Patients with TSH between 5 and 10 microunits/mL in conjunction with goiter or with positive anti-thyroid peroxidase antibodies also should be treated.[13]

Treatment

Thyroid hormone replacement with levothyroxine is the treatment of choice for routine primary hypothyroidism. It generally can be initiated at the full replacement dose of 1.6 mcg/kg/day in young healthy adults. Older patients, as well as patients with known cardiac disease, usually require a lower initial dosage of 12.5-25 mcg/day, along with very close monitoring. Dosage should be titrated carefully in increments of 12.5-25 mcg/day every 6-8 weeks until the TSH level normalizes. TSH is the test of choice for monitoring long-term replacement.

Patients ideally should receive the same brand of levothyroxine throughout treatment to avoid hormonal fluctuations caused by differences in the binders in the various preparations. Certain drugs such as cholestyramine, ferrous sulfate, sucralfate, calcium, and some antacids containing aluminum hydroxide can affect the absorption of thyroid hormones. The patient should be advised not to take the thyroid hormone at the same time as any of the above-mentioned drugs. Other drugs sometimes may interfere with thyroid hormone binding, such as anticonvulsants, or affect the metabolism of thyroid hormone. As examples of the latter phenomenon, either sertraline or rifampin may accelerate thyroid hormone clearance, thus necessitating a higher replacement dose. Thyroid hormone replacement doses normally increase during pregnancy because of the greater hormone binding capacity of TBG, caused by the increased estrogen and progestin levels associated with pregnancy. The serum TSH level is the test of choice to monitor thyroid status during pregnancy. TSH should be rechecked at 6- to 8-week intervals after each adjustment of the replacement thyroxine dose. Patients should be advised not to take levothyroxine with iron supplements or multivitamins since the latter may inhibit the absorption of the thyroid hormone.[6]

In recent years a number of small studies have evaluated the potential advantages of treating hypothyroidism with the combination of both T_4 and T_3 hormones. However, the possible long-term risks of the resulting elevations and fluctuations in serum T_3 levels have not been evaluated systematically. The overall evidence to date is insufficient to justify an approach that combines T_4 and T_3 as a form of replacement therapy.

It also is critical to identify those patients with polyglandular syndromes prior to initiation of thyroid hormone replacement therapy. These individuals may well have concurrent autoimmune adrenal insufficiency associated with their autoimmune hypothyroidism. These patients must receive their glucocorticoid replacement therapy prior to their thyroid hormone administration to avoid potential precipitation of acute adrenal insufficiency by the rising thyroid hormone levels.[14-18]

Although most providers can successfully diagnose and treat hypothyroidism, the American Academy of Clinical Endocrinologists (AACE) recommends consultation with an endocrinologist in the following specific situations:

- Patients age 18 years or younger;
- Patients unresponsive to therapy;
- Pregnant patients;
- Cardiac patients;
- Presence of goiter, nodule, or other structural changes in the thyroid gland; and
- Presence of other endocrine disease.

Thyroid Nodules

Thyroid nodules are among the most common of endocrine abnormalities, particularly in countries with low dietary iodine intake. The Framingham study has shown an estimated lifetime risk of developing a thyroid nodule of 5-10%, with a prevalence of 6.4% in women and 1.5 % in men. If one includes nonpalpable nodules, which frequently are detected during ultrasound, the prevalence becomes much higher. Two studies of patients undergoing neck ultrasound for evaluation of possible hyperpararthyroidism demonstrated thyroid nodules in 40-46% of patients.[19,20]

The great majority of thyroid nodules are benign. The likelihood that any given single thyroid nodule harbors a malignancy is less than 10%, and possibly closer to 5%. Nevertheless, because of the ever-present possibility of cancer, appropriate systematic evaluation and treatment is required of all thyroid nodules.[21]

Clinical Evaluation

The majority of thyroid nodules are asymptomatic, and most patients with thyroid nodules are euthyroid. A comprehensive history and physical examination should elicit any signs or symptoms of hyper- or hypothyroidism.

The purpose of the clinical evaluation is to gather information that can help to stratify a given patient's risk for malignancy. Factors that increase this risk include a family history of medullary or papillary thyroid cancer, or of familial polyposis (Gardner's syndrome), a history of recent thyroid growth, a history of neck or head irradiation, extremes of age, male gender, local pressure symptoms, difficulty with swallowing, and hoarseness. The physical examination should focus on the consistency of the nodule. A smooth, mobile, or tender nodule is likely to be benign, whereas a firm to hard, irregular, and nontender nodule is more suggestive of malignancy. Lymphadenopathy in the cervical or supraclavicular regions suggests papillary cancer. A multinodular gland in which all nodules have the same consistency is less likely to harbor a malignancy; however, a nodule with recent growth, firm consistency, or

other irregularities is suspicious for malignancy even in a multinodular gland. Coexisting thyroid disease is also important to note. Patients with thyroid lymphoma frequently have underlying Hashimoto's thyroiditis. There also is an increased risk of differentiated thyroid carcinoma in patients with Graves' disease.

Table 4 summarizes features that are associated with a higher risk of malignancy.

The following elements of the history and physical examination favor benign disease, although they do not exclude the presence of thyroid cancer:

- Family history of Hashimoto's thyroiditis or other autoimmune thyroid disorders;
- Family history of thyroid nodule or goiter;
- Symptoms of hyperthyroidism or hypothyroidism;
- Pain or tenderness;
- Soft, smooth, and mobile nodule; and
- Multinodular goiter without a dominant nodule.

Table 4. Risk Factors Associated with Malignancy of a Thyroid Nodule

HISTORY

- External irradiation during childhood
- Age < 20 or > 60 years
- Male gender
- Family history of thyroid cancer
- Hoarseness, dysphagia
- Rapid growth

PHYSICAL EXAMINATION

- Firm or hard
- Fixed to soft tissue
- Local symptoms
- Lymphadenopathy

Adapted from: Singer PA. Evaluation and management of the solitary thyroid nodule. *Otolaryngol Clin North Am* 1996;29: 577-592.

Evaluation

Patients with thyroid nodules should have an ultrasensitive TSH assay performed to assess the possible presence of either hyperthyroidism or hypothyroidism. If the patient has a family history of medullary thyroid cancer or Multiple Endocrine Neoplasia type II (MEN II syndrome), a calcitonin level also should be obtained to try to identify a possible medullary carcinoma. Although a few authorities disagree, it generally is neither necessary nor cost-effective to obtain calcitonin measurements routinely in the assessment of patients with thyroid nodules.[22]

Of all currently available methods of evaluating nodular thyroid disease, fine-needle aspiration biopsy has been found to have the greatest diagnostic accuracy, approaching 95%. Analysis of recent data suggests a false-negative rate of 1-11%, a false-positive rate of 1-8%, a sensitivity of 65% to 98%, and a specificity of 72-100%.[23,24]

The limitations of fine-needle aspiration relate to the skill of the operator, the expertise of the cytologist reading the specimen, and the inherent difficulty in distinguishing some benign cellular adenomas from their malignant counterparts. However, the introduction of fine-needle aspiration has overall had a very substantial impact on the management of patients with thyroid nodules.[25] The percentage of patients undergoing thyroidectomy has decreased by 25%, and the yield of carcinoma in patients who undergo surgery has increased concomitantly from 15% to at least 30%. Fine-needle aspiration also has decreased the cost of care by roughly 25%.

One study reviewed 14,380 fine-needle thyroid biopsies performed at the Mayo Clinic.[25] The authors found that 4% of all lesions were malignant, 64% benign, 11% suspicious, and 21% non-diagnostic. False-negative cytologic results mainly were due to sampling errors or to diagnosis. Sampling errors tended to occur with very small (< 1 cm) or very large (> 4 cm) nodules, hemorrhagic nodules, and with multinodular glands. Error in these settings can be minimized by obtaining multiple specimens or by performing ultrasonographically guided needle biopsy.

An inadequate sample must be considered nondiagnostic, and a repeat aspiration should usually be done. Between 5-20% of solitary thyroid nodules are classified by fine needle aspiration as indeterminate or suspicious. Some of these lesions harbor follicular or Hurthle-cell neoplasms. The diagnosis of such lesions can be made only histologically, with demonstration of either capsular or vascular invasion.[26]

Imaging

A radionuclide scan is indicated when the serum TSH is suppressed, or when the results of a fine-needle aspiration are indeterminate. Other imaging modalities, such as computed tomography (CT) or magnetic resonance imaging (MRI), have no role in the initial evaluation of thyroid nodules. Theoretically, malignant thyroid tissue neither traps nor incorporates iodine, and, therefore, will appear cold on radioiodine scan. Normally functioning nodules are warm, and hyperfunctioning nodules are hot on the scan. Approximately 80-85% of all thyroid nodules are hypofunctioning, but only 10-15% of hypofunctional nodules are malignant; therefore, scanning has only low specificity for the diagnosis of thyroid carcinoma. A thyroid scan, however, is a very useful diagnostic test in evaluating asymmetric nodular goiters, hypertrophied lobes simulating a mass, and substernal masses. Another indication for thyroid scanning is to exclude an autonomous adenoma prior to starting a patient with thyroid nodule on thyroid hormone suppression therapy[22]; however, this strategy currently is not employed frequently.

Management

Benign Lesions. Surgery can be done for those infrequent lesions that produce local compressive symptoms, or for cosmetic reasons in those with very large and unsightly goiters. The role of L-thyroxine suppression therapy is controversial.

A recent meta-analysis of all randomized controlled trials examined the effectiveness of thyroid hormone suppressive therapy in patients with benign, solitary thyroid nodules.[27] The analysis showed that treatment for longer than 6 months was associated with a trend toward a reduction of more than 50% in volume of benign thyroid nodules, but statistical significance was not achieved. Certain features of thyroid nodules may predict a better response to L-thyroxine, such as small volume (< 10 ml), or the presence of large amounts of colloid on fine needle aspiration.

The potential side effects of L-thyroxine therapy include deleterious effects on bone and on the heart. There clearly is an increase in postmenopausal bone loss in women taking enough L-thyroxine to suppress serum TSH less than 0.1 microunits/mL. There also are harmful cardiac effects, including an increase in heart rate, in left ventricular wall thickness, and in the frequency of arrhythmias, especially in individuals older than 60 years of age.

Cystic nodules and autonomously functioning nodules do not shrink with levothyroxine, and thus it should not be used in such cases.

Management of Incidentally Detected Nodules. The overall prevalence of incidentally detected nodules is increasing rapidly. Most of these incidental nodules (incidentalomas) are picked up by ultrasound. A recent study introduced a new approach to the nonpalpable thyroid nodule.[28] These authors found that a combination of sonographic features was useful in predicting malignancy. They reported that 87% of the cancers were hypoechoic and solid. The cancers also typically showed irregular margins, an intranodular vascular pattern, or microcalcifications (psammoma bodies). Larger nodule size was not a risk factor for malignancy in the series. In general, nodules smaller than 1 cm can be assessed initially with a baseline TSH and then followed with annual exams to detect any increase in size.

Management of Multinodular Goiter. The clinical and laboratory evaluations outlined above also apply to patients with multinodular goiter (MNG). If the baseline TSH is suppressed, a thyroid scan should be obtained to search for an autonomous nodule. Patients with autonomous nodules should undergo radioactive iodine ablation; they typically require 2-3 times as large a dose of radioiodine as Graves' patients. Surgery is the preferred treatment in patients with compressive symptoms. A dominant nodule within an MNG should be biopsied, as well as any rapidly growing nodules. Even a diffuse goiter without a dominant nodule that is rapidly growing should be biopsied to rule out primary thyroid cancer, as well as lymphoma. In general, patients with asymptomatic euthyroid multinodular goiters can be followed with annual examinations and TSH measurements.

Radioactive iodine has been used in some patients with euthyroid MNG. A reduction in thyroid volume of up to 60% has been reported with this modality. A study comparing radioactive iodine and levothyroxine therapy in patients with benign MNG found that radioactive iodine treatment was superior at decreasing thyroid volume. The volume reduction was 38% at one year and 44% at two years with radioiodine, as opposed to only 1% at one year and 7% at two years with levothyroxine. It is important to note that, for levothyroxine to be effective, serum TSH needs to be suppressed, with potential adverse effects on the cardiovascular system and on bone metabolism.[15,29,30]

Thyroid Nodules in Pregnancy

The management of thyroid nodules during pregnancy is similar to the approach taken in the nonpregnant state. The TSH may be suppressed during the 8-14th weeks of pregnancy. It also is important to recognize that beta HCG produced by the placenta activates the TSH receptors; however, the TSH level rarely falls below 0.1 microunits/mL during pregnancy. Radioisotopes are absolutely contraindicated during pregnancy, and so radionuclide scans cannot be performed. If a nodule appears suspicious for malignancy, or if the cytology is positive for malignancy, surgery can be performed safely during the second trimester. An alternative approach is to defer the fine-needle aspiration biopsy until the postpartum period.

Thyroid Cancer

Thyroid carcinoma accounts for only 1% or fewer of all human cancers, but it is the most common endocrine malignancy. The incidence of thyroid carcinoma ranges from 0.5 to 10 cases per 100,000 persons per year.[16]

The majority of thyroid carcinomas originate from the follicular cells, but medullary carcinoma arises from the parafollicular cells. The subtypes of follicular cell-derived cancers are:

1. papillary;
2. follicular;
3. oxyphilic or Hurthle cell; and
4. anaplastic.

The majority of thyroid carcinomas are well-differentiated papillary or follicular variants, and they carry a generally favorable prognosis. Anaplastic carcinoma accounts for fewer than 10% of cases, while medullary thyroid carcinoma accounts for another 5-10%. Much less frequently occurring thyroid malignancies are lymphoma, sarcoma, and metastases from extrathyroidal malignancies. Differentiated thyroid cancers are two to four times more frequent in women than in men. The female predominance decreases, however, both in the prepubertal and the postmenopausal periods.[31]

Thyroid cancer is one of the most curable cancers, and long-term survival is quite common. However, patients are at continuing risk of tumor recurrence for decades after the initial diagnosis. Long-term, sometimes life-long, surveillance is necessary. Determining the appropriate intensity of such surveillance requires a thorough understanding of the patient's tumor and of its typical prognosis. Optimal care of patients with thyroid cancer requires a multidisciplinary team, including endocrinologists, surgeons, pathologists, and nuclear medicine specialists.

Patients with thyroid cancer have either a palpable neck mass or an incidental thyroid nodule that is identified by other diag-

nostic modalities. The diagnosis of thyroid cancer requires cytologic or histologic confirmation. As previously mentioned, fine-needle aspiration is the most cost-effective method to distinguish between benign and malignant lesions. For follicular carcinoma, capsular and vascular invasion are the key features of distinguishing between benign and malignant. The diagnosis of follicular carcinoma requires a surgical specimen.

Papillary Thyroid Carcinoma

Papillary thyroid carcinoma (PTC), including mixed papillary-follicular cancer, accounts for approximately 75% of all differentiated thyroid cancer. Minimal PTC is defined as cancer smaller than 1 cm, which does not extend beyond the thyroid capsule, and which is neither metastatic nor angio-invasive. This type of PTC carries an excellent prognosis, with a mortality rate of about 0.1% and a recurrence rate of 5%.[32]

Follicular Cancer

Follicular cancers are divided into minimally and extensively invasive categories. Patients with the minimally invasive forms have an excellent prognosis. Larger follicular or Hurthle cell neoplasms are more likely to have an unfavorable course, especially in men and in patients older than 50 years. Distant metastases to lung or to bones are sometimes already present at the time of initial diagnosis.

Management of Patients with Papillary or Follicular Thyroid Cancer

Surgery is the primary treatment for patients with papillary and follicular thyroid cancer. Surgery should be performed by a surgeon with considerable expertise in thyroid surgery. Unilateral total lobectomy sometimes may be adequate therapy for patients with minimal, localized PTC. A total or near-total thyroidectomy is required for high-risk patients with papillary or invasive follicular cancer, usually followed by radioactive iodine ablation of any remnant thyroid tissue. Radioiodine therapy with iodine 131 also is indicated in patients with distant metastases, in those with locally invasive neck disease, and in those with cervical nodal metastases. Ablation of remnant thyroid tissue in patients with low-risk cancer, however, has not been shown to improve survival.[33]

Differentiated thyroid carcinoma is very TSH-dependent. Levothyroxine should be withheld for 4-6 weeks prior to scanning and therapy to maximize TSH stimulation of the remaining thyroid tissue. An alternative approach has been developed to avoid severe hypothyroid symptoms, which frequently are tolerated rather poorly by patients. The alternative approach takes advantage of the short half-life of liothyronine, which is given for the first 3-4 weeks after levothyroxine is stopped. A TSH measurement then is obtained 10 days after discontinuing the T_3 therapy. A TSH value greater than 30 microunits/mL is considered adequate for scanning and therapy, leaving only a 10-day period for potentially debilitating hypothyroid effects. Yet another alternative approach is to use human recombinant TSH (Thyrogen), in which case there is no need to withdraw thyroid hormone at all. Recombinant TSH is quite expensive, however, and the sensitivity in detecting very small lesions may be slightly less than with the traditional hormone withdrawal approach.

Most endocrinologists agree that life-long thyrotropin suppression therapy is indicated in patients with differentiated thyroid cancer. However, long-term levothyroxine suppressive therapy may have definite adverse effects on bones and on the heart. The AACE recommends aiming for a TSH target range of 0.1-0.4 in patients with low-risk thyroid cancer, and for a lower target range of less than 0.01 to less than 0.1 in high-risk patients. It must be noted, however, that no prospective data have yet been published to address the issue of the optimal degree of TSH suppression.

The follow-up of patients with differentiated thyroid cancer needs to be individualized, depending upon the extent and the stage of the malignancy. Serum thyroglobulin (Tg) is a very useful and specific tumor marker for differentiated thyroid cancer. The serum Tg level should be undetectable (< 2 ng/ml) after successful near or total thyroidectomy, followed by subsequent radioiodine ablation. An undetectable serum Tg in the presence of an elevated TSH excludes residual or metastatic tumor in more than 99% of cases. All Tg samples, however, must be screened routinely for anti-Tg Ab, since the presence of antibiodies either may falsely elevate or lower the Tg readings. Serum Tg and TSH should be followed in all patients with differentiated thyroid cancer every six months for the first three years after initial therapy, and then yearly thereafter. Also, extremely de-differentiated tumors, which carry a very poor prognosis, often stop producing thyroglobulin altogether, such that low levels of Tg do not invariably predict good outcomes.

Some investigators withdraw thyroid hormone therapy annually, either to measure Tg or to obtain a scan. The frequency of such testing should be individualized, based primarily upon the tumor staging. Obviously, if a patient has a rising Tg level, further diagnostic studies urgently are required. Since most recurrences are in the neck, initial imaging should be focused on this area. Real-time high-frequency ultrasonography, CT, MRI, and PET scanning all are useful modalities in this setting.

Cancer recurrence usually is treated either surgically or with radioactive iodine. External beam radiation is used only rarely as adjuvant therapy, and chemotherapy is of very limited efficacy.[31]

Medullary Thyroid Carcinoma

Approximately 6-8% of thyroid cancers are medullary thyroid carcinomas (MTC); roughly 75% of these are sporadic, and the other 25% are hereditary. Despite its relative rarity, MTC is nonetheless responsible for up to 13.4% of all deaths that are attributable to thyroid cancer.

Medullary carcinoma sometimes is associated with other endocrine syndromes. It frequently occurs as a component of familial multiple endocrine neoplasia syndromes (MEN) types 2A and 2B, or as part of a kindred with familial MTC. MEN II A and B are autosomal dominant inherited syndromes. Patients with MEN 2A or 2B syndromes primarily are characterized by the occurrence of both multifocal MTC and of pheochromocy-

toma, which is bilateral in 40-50% of cases. In addition, patients with MEN 2A may develop parathyroid hyperplasia and hyperparathyroidism, and less commonly, Hirschsprung's disease. Conversely, patients with MEN 2B syndrome usually are affected at a younger age with more aggressive tumors. In addition, these patients usually have a Marfanoid body habitus and demonstrate mucosal gangliomas in the gastrointestinal tract, conjunctivae, tongue, and lips. Hyperparathyroidism, on the other hand, is not a feature of the MEN 2B syndrome. The RET proto-oncogene has been identified as the culprit in the pathogenesis of MEN 2 syndromes, and it is now a widely used diagnostic marker.

Medullary carcinoma results from a malignant transformation of parafollicular C cells, which are of neuroendocrine origin. The tumor marker produced by these cells is the hormone calcitonin. An elevated pre-operative calcitonin level confirms the diagnosis of MTC and also provides a baseline for post-operative monitoring. The pre-operative level also may hint at the total amount of tumor burden. Levels less than 1000 pg/mL are seen when the tumor is confined to the thyroid, while higher levels are seen with microscopic distant disease (1000-10,000 pg/mL) or with gross metastatic disease (above 10,000 pg/mL). A normal baseline level of calcitonin, however, does not definitively exclude the diagnosis of MTC,[34] and an intravenous pentagastrin challenge to stimulate calcitonin release still may be needed.

MTC often presents as a thyroid nodule, and associated cervical lymphadenopathy often is detected. Patients rarely may have secretory diarrhea. Distant metastases are slow-growing but quite common; liver, lungs, and bones are the sites most commonly affected. Fine needle aspiration cytology is the standard diagnostic tool for confirming the presence of MTC.

Patients need to be screened for a possible associated pheochromocytoma once the diagnosis of MTC has been established. Genetic screening of the patient and of all first-degree relatives should follow. MEN patients with both medullary carcinoma and pheochromocytoma should have initial treatment directed at the pheochromocytoma to avoid the potentially disastrous effects of a large release of catecholamines during thyroid surgery.

The treatment of choice for medullary carcinoma of the thyroid is total thyroidectomy, along with dissection of the central node compartment. Serum calcitonin should be measured 6-8 weeks post-operatively to assess the potential presence of any residual tumor. CEA levels also can be measured and monitored. Radionuclide scanning is unnecessary, since these tumors do not take up iodine. Local recurrence is treated surgically. The roles of external beam radiation and chemotherapy are negligible, since these modalities have not been shown to improve survival.

The follow-up of such patients should include baseline measurement of calcitonin and of pentagastrin-stimulated calcitonin levels. Patients with elevated calcitonin should be selected carefully for re-operation, after localizing the source of the elevated calcitonin level to the neck with ultrasonography, CT, or MRI.[35]

The overall survival for patients with medullary carcinoma is 72% at 5 years, and 56% at 10 years. Patients with MEN 2A, MEN 2B, and familial MTC syndromes generally have better prognoses than those with sporadic tumors. Other factors associated with a better prognosis include female gender, younger age, a tumor size less than 10 cm, absence of lymph node involvement, early stage disease, complete surgical resection, and normal pre-operative CEA levels.[28,36]

Anaplastic Thyroid Cancer

The worst form of thyroid cancer is anaplastic or undifferentiated thyroid carcinoma. This fortunately is a rare tumor, seen mostly in the fifth and sixth decades of life. It is extremely aggressive, both in terms of local invasiveness and in its ready ability to metastasize. Tumors may represent the transition from a well-differentiated lesion to an undifferentiated one. Anaplastic carcinoma often invades the soft tissue of the neck, trachea, and esophagus, frequently making radical surgery impossible. Metastases to the lung also are common. FNA is the diagnostic procedure of choice.

Treatment of anaplastic thyroid cancer is controversial. As mentioned above, surgery may not be feasible because of the widespread extent of the disease by the time of diagnosis. Anaplastic carcinoma neither concentrates iodine nor expresses Tg, and so neither radioiodine therapy nor scanning is useful. External beam radiation and chemotherapy can be tried, but the prognosis for this malignancy generally is extremely poor.[33]

Conclusion

Thus, it is apparent that thyroid disease is very common and will be encountered frequently by the primary care provider. A working knowledge of the basic diseases that affect the thyroid is essential.

References

1. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994;331:1249-1252.
2. Ginsberg J. Diagnosis and management of Graves' disease. *Canad Med Assoc J* 2003;168:575-585.
3. Bartalena L, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 1998;338:73.
4. Bartalena L, Marcocci C, Bogazzi F, et al. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. *N Engl J Med* 1989;321:1349-1352.
5. Tallstedt L, Lundell G, Torring O, et al. Occurrence of ophthalmopathy after treatment for Graves' hyperthyroidism. The Thyroid Study Group. *N Engl J Med* 1992;326: 1733-1738.
6. Nader S. Thyroid disease and other endocrine disorders in pregnancy. *Obstetric and Gynecology Clinic* June 2004;31: 257-285.

7. AACE Medical guidelines for clinical practice. The evaluation and treatment of hyperthyroidism and hypothyroidism; 2002 update:1-9.
8. Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults. *Ann Intern Med* 2004;140:128-141.
9. Surks MI, et al. Subclinical thyroid disease. *JAMA* 2004;291: 228-238.
10. Danese MD, Powe NR, Sawin CT, et al. Screening for mild thyroid failure at the periodic health examination: A decision and cost-effectiveness analysis. *JAMA* 1996;276:285-292.
11. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham Survey. *Clin Endocrinol* (Oxf) 1995;43:55-68.
12. AACE thyroid guidelines. *Endocrine Practice* 2000;8: 457-469.
13. Cooper DS. Clinical practice: Subclinical hypothyroidism. *N Engl J Med* 2001;345:260-265.
14. AACE Clinical practice guidelines for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocrine Practice* 1995;1:54-62.
15. Kaplan MM, Sarne DH, Schneider AB. Editorial: In search of an impossible dream? Thyroid hormone replacement therapy that treats all symptoms in all hypothyroid patients. *J Clin Endo Metab* 2003;88:4540-4542.
16. Landis SH, et al. Cancer statistics, *CA Cancer J Clin* 1998; 48:6-29.
17. Roti E, et al. The use and misuse of thyroid hormone. *Endocrin Rev* 1993;14:401-423.
18. Singer PA, Cooper DS, Levy EG. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. *JAMA* 1995;273:808-812.
19. Horlocker TT, et al. Prevalence of incidental nodular thyroid disease detected during high-resolution parathyroid ultrasonography. In: Medeiros-Neto G, Gaitan E, eds. *Frontiers in Thyroidology*, vol. 2. New York: Plenum Medical;1985: 1309-1312.
20. Stark DD, Clark OH, Gooding GA, et al. High resolution ultrasonography and computed tomography of thyroid lesions in patients with hyperparathyroidism. *Surgery* 1983; 94:863-868.
21. Singer P. Evaluation and management of the euthyroid nodular and diffuse goiter. In: Braverman LE, ed. *Contemporary Endocrinology; Disease of the Thyroid*. Totowa, NJ: Humana Press Inc;1997:241-263.
22. Mazzaferri EL. Management of a solitary thyroid nodule. *N Engl J Med* 1993;328:553-559.
23. AACE clinical practice guidelines for the diagnosis and management of thyroid nodules. *Endocrine Practice* 1996;2:78-84.
24. Castro MR, Gharib H. Thyroid fine-needle aspiration biopsy: Progress, practice, and pitfalls. *Endocrine Practice* 2003;9: 128-136.
25. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: An appraisal. *Ann Intern Med* 1993;118:282-289.
26. Bennedbaek FN, Hegedus L. Management of the solitary thyroid nodule: Results of a North American survey. *J Clin Endo Metab* 2000;85:2493.
27. Castro MR, Caraballo PJ, Morris JC. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: A meta-analysis. *J Clin Endo Metab* 2002;87: 4154-4160.
28. Modigliani E, et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: Results in 899 patients. The GETC Study Group. Groupe d'etude des tumeurs a calcitonine. *Clin Endocrinol* (Oxf) 1998;48: 265-273.
29. Samuels MH, et al. Evaluation and treatment of sporadic nontoxic goiter-some answers and more questions. *J Clin Endo Metab* 2001;86:994-997.
30. Wesche MF, Tiel-v Buul MM, Lips P, et al. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. *J Clin Endo Metab* 2001;86:998-1005.
31. AACE guidelines. *Endocrine Practice* 2001;7:203-218.
32. Hay ID. Papillar thyroid carcinoma. *Endocrinol Metab Clin North Am* 1990:19:545-576.
33. Singer PA, Cooper DS, Daniels GH, et al. Treatment guidelines for patients with thyroid nodules at well-differentiated thyroid cancer. American Thyroid Association. *Arch Intern Med* 1996;156:2165-2172.
34. Redding AH, Levine SN, Fowler MR. Normal preoperative calcitonin levels do not always exclude medullary thyroid carcinoma in patients with large palpable thyroid masses. *Thyroid* 2000; 10:919-922.
36. Bergholm U, Bergstrom R, Ekbom A. Long-term follow-up of patients with medullary carcinoma of the thyroid. *Cancer* 1997;79:132-138.
35. Clayman GL. Medullary thyroid cancer. *Otolaryngol Clin North Am* 2003;36:91-105.

Physician CME Questions

15. Which of the following thyroid malignancies has the worst prognosis?
    a. Papillary carcinoma
    b. Medullary carcinoma
    c. Anaplastic carcinoma
    d. Follicular carcinoma

16. Which of the following is *not* commonly a cause of thyrotoxicosis?

In Future Issues:

Preoperative Evaluation

a. Graves' disease
b. Factitious self-administration of thyroid hormone
c. Multinodular goiter
d. Hashimoto's thyroiditis

17. Which of the following is *not* a typical symptom of thyrotoxicosis?
a. Anxiety and nervousness
b. Increased sweating
c. Constipation
d. Weight loss

18. Which of the following is *not* typically seen with hypothyroidism?
a. Mental dulling
b. Increased sleepiness
c. Pre-tibial myxedema
d. Bradycardia

19. Which of the following factors is associated with increased risk of thyroid nodule malignancy?
a. Male gender
b. Age younger than 20 years or older than 60 years
c. Firm to hard nodule
d. All of the above

20. Which of the following is *not* typical of hypothyroidism?
a. Low T_3
b. Low T_4
c. Low TSH
d. Low free T_4

CME Answer Key

15. c; 16. d; 17. c; 18. c; 19. d; 20. c

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

New Clinical Guidelines on Cholesterol Management

The National Cholesterol Education Program (NCEP), a product of a collaboration of the National Heart, Lung, and Blood Institutes, the American College of Cardiology, and the American Heart Association, has updated its clinical practice guideline on cholesterol management. Based on several recent studies, that suggest that aggressive lowering of LDL cholesterol benefits high-risk patients, the new guidelines recommend aggressive treatment for patients who are at risk for coronary artery disease. Specifically, patients who are defined as "very high-risk" should be considered for aggressive treatment. Very high-risk patients are defined as those who have cardiovascular disease together with multiple risk factors (especially diabetes), severe and poorly controlled risk factors (such as continued smoking), or metabolic syndrome. The guideline had previously recommended drug therapy in these patients only if the LDL cholesterol was greater than 130 mg/dL, with a goal of 100 mg/dL. The new guideline recommends a treatment threshold of 100 mg/dL, with a goal of 70 mg/dL. "High-risk patients" are defined as those who have coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or 2 or more risk factors (such as smoking or hypertension) that give a greater than 20% chance of having heart attack within 10 years. The LDL goal for these patients remains 100 mg/dL or less, and the new guideline now recommends drug treatment for those high-risk patients with an LDL > 100 mg/dL. Moderately high-risk patients are defined as those with 2 or more risk factors for coronary heart disease and a 10-20% risk of heart attack within 10 years. For these patients, drug therapy is recommended to lower LDL cholesterol under 130 mg/dL, and the option is given to treat to levels under 100 kg/dL. For lower-risk patients, the guideline was not changed. Drug therapies recommended by the NCEP include statins, bile acid resins, nicotinic acid, and ezetimibe. As in previous NCEP guidelines, the role of lifestyle modification is stressed. The full guideline can be viewed in the July 13th issue of *Circulation*, and highlights can be reviewed on-line at www.nhlbi.nih.gov.

Hypothyroidism and Pregnancy

A new study clarifies thyroid replacement therapy during pregnancy. Researchers at Harvard followed 19 women with hypothyroidism through 20 pregnancies, of which 17 resulted in full-term births. Thyroid function, HCG levels, and estradiol were measured before conception, every 2 weeks for the first trimester, and monthly thereafter. Oral doses of levothyroxine were increased during pregnancy to maintain preconception levels. The mean levothyroxine requirements increased 47% during the first half of pregnancy, plateaued by week 16, and remained

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

stable until delivery. The authors recommend that hypothyroid women, who become pregnant, should increase their levothyroxine dose by 30% as soon as pregnancy is confirmed, and should be monitored carefully throughout the duration of their pregnancy (*N Engl J Med*. 2004;351:241-249). Although simple in its design, this is an important study because it is estimated that 1 to 2% of all pregnant women are hypothyroid and need replacement therapy. Hypothyroidism during pregnancy is associated with poor fetal outcomes including impaired cognitive development and increased mortality. Clinicians now have a clear guide to levothyroxine dosing changes during pregnancy.

Anti-Depressants and the Risk of Suicide

The risk of suicidal behavior is relatively high after starting anti-depressants, however, there is no statistical difference between anti-depressants used, according to a new study. Researchers reviewed data from the UK General Practice Research Database from 1993 to 1999, and compared nearly 160,000 users of 4 anti-depressant drugs, 2 SSRIs and 2 tricyclics; fluoxetine, paroxetine, amitriptyline, and dothiepin (a trycyclic anti-depressant not marketed this country). The outcome was first-time non-fatal suicidal behavior, or suicide in treated patients vs comparable patients who did not exhibit suicidal behavior. The relative risks for non-fatal suicidal behavior were 0.83 for amitriptyline (95% CI, 0.61-1.13), 1.16 for fluoxetine (95% CI, 0.90-1.50), and 1.29 for paroxetine (95% CI, 0.97-1.70), compared to those using dothiepin. Perhaps the most startling finding in this study was the 4.07 relative risk for suicidal behavior within 9 days of starting any anti-depressant (95% CI, 2.89-5.74), compared to patients prescribed an anti-depressant 90 days or more before their suicidal behavior. Even more concerning, was a relative risk for fatal suicide among new users of anti-depressants of 38.0 (95% CI, 6.2-231). The authors found no significant associations between use of the various anti-depressants and the risk of suicide (*JAMA.* 2004;292:338-343, ed 379-380). The accompanying editorial points out the timeliness of the study, with regard to current congressional hearings in the use of anti-depressants in young adults. The authors point out that the data on patients aged 10 through 19 is limited however, and further study may be needed in this group.

FDA Actions

The FDA has approved acamprosate (Campral-Merck) for the maintenance of abstinence in patients in alcohol recovery programs. The drug, which has been available in Europe for several years, may not work if patients are still drinking or abusing other drugs when initiating therapy. Acamprosate's mechanism of action is unknown, but it appears to act in the central nervous system. Common side effects include diarrhea, nausea, vomiting, and abdominal pain.

The FDA has approved Merck and Schering-Plough's Vytorin for the treatment of hypercholesterolemia. The drug combines Merck's simvastatin (Zocor) with the jointly developed ezetimibe (Zetia), and is touted to be as potent as the so-called "super statins" atorvastatin (Lipitor) and rosuvastatin (Crestor). The new drug, which is expected to garner a hefty market share, will be priced at $2.30 a pill and should be available this fall.

Imiquimod (Aldera-3M) has received the expanded indication for treatment of superficial basal cell carcinoma. The drug, which is a topical immune modulator, was recently approved for treatment of actinic keratosis, and was initially approved for the treatment of venereal warts.

Brief Notes

The over-the-counter cough medications, dextromethorphan and diphenhydramine, are no better than placebo in suppressing cough in children (*Pediatrics.* 2004;114:e85-e90).

Many women are turning to phytoestrogens in lieu of hormone replacement therapy. The most commonly used of these, isoflavone soy protein, does not improve cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women (*JAMA.* 2004;292:65-74).

Ginseng reduces the effectiveness of warfarin in healthy volunteers. Patients on warfarin should be questioned as to their herbal supplement use (*Ann Intern Med.* 2004;141:23-27).