

Seminar

Hypothyroidism

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Hypothyroidism is common, potentially serious, often clinically overlooked, readily diagnosed by laboratory testing, and eminently treatable. The condition is particularly prevalent in older women, in whom autoimmune thyroiditis is common. Other important causes include congenital thyroid disorders, previous thyroid surgery and irradiation, drugs such as lithium carbonate and amiodarone, and pituitary and hypothalamic disorders. Worldwide, dietary iodine deficiency remains an important cause. Hypothyroidism can present with nonspecific constitutional and neuropsychiatric complaints, or with hypercholesterolaemia, hyponatraemia, hyperprolactinaemia, or hyperhomocysteinaemia. Severe untreated hypothyroidism can lead to heart failure, psychosis, and coma. Although these manifestations are neither specific nor sensitive, the diagnosis is confirmed or excluded by measurements of serum thyrotropin and free thyroxine. Thyroxine replacement therapy is highly effective and safe, but suboptimal dosing is common in clinical practice. Patient noncompliance, drug interactions, and pregnancy can lead to inadequate treatment. Iatrogenic thyrotoxicosis can cause symptoms, and, even when mild, provoke atrial fibrillation and osteoporosis. We summarise present understanding of the history, epidemiology, pathophysiology, and clinical diagnosis and management of hypothyroidism.

Hypothyroidism is the most common pathological hormone deficiency. The variety of end-organ effects and wide range of disease severity—from entirely asymptomatic individuals to patients in coma with multisystem failure—can make hypothyroidism an elusive clinical entity. Once suspected, the diagnosis can usually be quickly confirmed or excluded, treatment is straightforward, and the patient's prognosis is excellent. This review summarises current understanding of the history, epidemiology, pathophysiology, and clinical diagnosis and management of hypothyroidism.

History

In 1874, Gull described several previously healthy women who acquired clinical features similar to those in cretinism. 4 years later, Ord coined the term myxoedema to describe a syndrome in five women with coarse features, mental dullness, dry skin, hypothermia, and oedema. At much the same time, two Swiss thyroid surgeons, Kocher and Reverdin, independently described cachexia strumipriva, a cretin-like state developing after thyroidectomy. In 1883, the Clinical Society of London formed a committee to investigate the connection between myxoedema, cretinism, and cachexia strumipriva; and 5 years later, the committee issued its landmark report linking the three conditions. In 1912, Hashimoto described autoimmune thyroiditis in four women with goitres that seemed to have turned into lymphoid tissue (struma lymphomatosa); and in 1956, Roitt and colleagues reported the presence of circulating thyroid autoantibodies in this disorder. Treatment for hypothyroidism with sheep thyroid extract was first

reported by Murray in 1891. Thyroid hormone was crystallised in 1914 by Kendall. Reports of thyroxine's synthesis by Harington and Barger, and of its initial physiological testing both appeared in 1927. Triiodothyronine was discovered by Pitt-Rivers and Gross in 1952; and its endogenous generation from thyroxine was described by Ingbar, Sterling, and Braverman in 1970. In 1963, Condliffe purified thyrotropin (thyroid stimulating hormone), and soon thereafter Odell and Utiger both reported the first immunoassays for human thyrotropin. In 1971, Mayberry and Hershman simultaneously described use of thyrotropin immunoassays for diagnosis of hypothyroidism.

Definitions

Hypothyroidism can be classified on the basis of its time of onset (congenital or acquired), the level of endocrine dysfunction responsible (primary or secondary, also termed central, hypothyroidism), and its severity (overt [clinical] or mild [subclinical]). In patients with primary hypothyroidism, in whom serum thyrotropin is elevated, the distinction between overt and mild hypothyroidism can be defined biochemically by whether the serum free thyroxine concentration is below or within the reference range, respectively. The term myxoedema is now usually

Search strategy

PubMed and Cochrane Library databases were searched for the terms hypothyroid, hypothyroidism, myxoedema, central hypothyroidism, subclinical hypothyroidism, mild hypothyroidism, and congenital hypothyroidism. These searches were cross-referenced with keywords relevant to the subsections. Additional references were identified from textbooks, reviews, and original research articles. We also relied on our own knowledge of current issues in the speciality and recent relevant work—referencing articles that, in our opinion, represent important contributions. We gave priority, wherever possible, to randomised controlled trials, and to high-quality cross-sectional and case-control studies.

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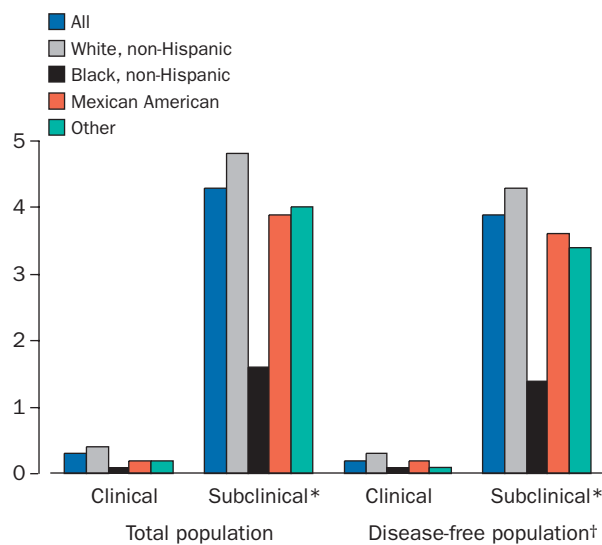
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reserved for cases of overt hypothyroidism that are severe or complicated, or both. Cretinism refers to the syndrome of mental retardation, deafness, short stature, and characteristic facial deformities occurring with untreated congenital hypothyroidism.

Epidemiology

Hypothyroidism is a common disorder, arising more often in women than men and increasing in incidence with age, especially after the onset of middle life. Because primary hypothyroidism is much more frequent than secondary hypothyroidism (about 1000 to 1) in both sexes at all ages, serum thyrotropin measurement can be used to estimate the prevalence of hypothyroidism in populations. In a community survey in the UK, the Whickham¹ study recorded an abnormally high serum thyrotropin concentration in 7.5% of women and 2.8% of men. In the recent NHANES III survey² of 17 353 Americans representing US demographics, 4.6% had raised thyrotropin: 0.3% with overt hypothyroidism and 4.3% with mild hypothyroidism (figure). In individuals aged 65 years and older, 1.7% had overt hypothyroidism and 13.7% had mild hypothyroidism. Similarly, in women older than 60 years of age in a Birmingham general medical practice, overt and mild hypothyroidism was present in 2.0% and 9.6%, respectively.³ In women and men aged older than 74 years screened at a Colorado health fair, the prevalence of hypothyroidism (defined as a serum thyrotropin greater than 10 mU/L) was even higher: 21% and 16%, respectively.⁴ In the NHANES III survey, the prevalence of hypothyroidism was higher in whites than in Hispanics and African-Americans (5.1%, 4.1%, and 1.7%, respectively).

Special populations with higher risk of developing hypothyroidism include postpartum women;⁵ individuals with a family history of autoimmune thyroid disorders;^{6,7} and patients with previous head and neck or thyroid irradiation or surgery, other autoimmune endocrine conditions (eg, type 1 diabetes mellitus, adrenal insufficiency, and ovarian failure), some other non-endocrine autoimmune disorders (eg, coeliac disease, vitiligo, pernicious anaemia, and Sjögren's syndrome,



Prevalence of hypothyroidism in USA by ethnic background and known thyroid status

*Subclinical hypothyroidism is defined by elevated serum thyrotropin concentration with normal serum free thyroxine. †Disease-free population is defined by the reported absence of known thyroid disease, goitre, or thyroid medication use.

multiple sclerosis), primary pulmonary hypertension, and Down's and Turner's syndromes (panel 1).

Aetiology

Congenital hypothyroidism

Worldwide, the most common cause of congenital hypothyroidism remains endemic iodine deficiency.⁸ In regions with sufficient dietary iodine, congenital hypothyroidism occurs in 1 of 4000 livebirths in regions of sufficient dietary iodine; the condition is twice as common in female infants and is a sporadic disorder in 85% of cases.⁹ In these children, congenital hypothyroidism is due to thyroid gland agenesis or dysgenesis¹⁰ and defective thyroid hormone biosynthesis.¹¹ Thyroid dysgenesis has been associated with mutations in the genes for *PAX8* and the thyroid transcription factors 1 (*TTF1*) and 2 (*FOXE1*). Defects in thyroid hormone biosynthesis have been related to mutant genes encoding thyroid peroxidase, sodium-iodide symporter, pendrin, thyroid oxidase 2, and thyroglobulin. Numerous inherited defects causing absent or ineffective thyrotropin stimulation have also been described, including mutant genes for transcription factors needed for pituitary thyrotrope differentiation (*POU1F1*, *PRO1*, *LHX3*, *HESX1*), the thyroid releasing hormone receptor, thyrotropin β -chain, and thyrotropin-receptor. In pseudohypoparathyroidism, hypothyroidism can result from a mutation in the gene for Gsx which transduces thyrotropin receptor binding to adenylate cyclase activation. Transplacental transmission of anti-thyrotropin receptor inhibitory antibodies from a mother with autoimmune thyroid disease to her fetus can also cause transient neonatal hypothyroidism. The syndrome of inherited resistance to thyroid hormone, which is attributable to a mutant tri-iodothyronine receptor β gene in most kindreds, can interfere with thyroid hormone action in target tissues.¹² A final rare cause of hypothyroidism in neonates and young children is haemangiomas, which have such high type III deiodinase activity that thyroxine catabolism exceeds the thyroid gland's secretory capacity.¹³

Autoimmune thyroiditis

The most common cause of acquired hypothyroidism is autoimmune thyroiditis (also called Hashimoto's disease), which is seven-fold more common in women with increasing incidence during middle life.¹⁴ The role of autoimmunity in its pathogenesis is lent support by the histological finding of diffuse lymphocytic infiltration of the thyroid gland, presence of circulating thyroid autoantibodies in almost all patients,¹⁵ animal models created by immunisation with thyroid antigens,¹⁶ the finding that affected thyrocytes express the MHC class II proteins needed for antigen presentation to CD4 (helper) T lymphocytes,¹⁷ and evidence of activated CD4 T cells specific for thyroid antigens.¹⁸ There is a clear genetic predisposition to autoimmune thyroiditis, with apparent autosomal dominant inheritance of thyroid autoantibodies in the relatives of affected patients.¹⁹ A polygenic basis for autoimmune thyroiditis is suggested by linkage of the disorder to several genetic loci in affected kindreds.²⁰ Autoimmune thyroiditis is more common in geographic regions of higher dietary iodine,²¹ which has been postulated to increase thyroglobulin antigenicity;²² but the precise environmental factors inciting the condition remain unidentified.

In patients with autoimmune thyroiditis, the thyroid gland can be nonpalpable or diffusely enlarged (150–300% of normal size) with a firm consistency, irregular contour, and palpable pyramidal lobe.¹² In patients with the fibrous

Panel 1: Indications to test for hypothyroidism

Clinical symptoms and signs

- Fatigue
- Cold intolerance
- Constipation
- Impaired memory
- Slowed mental processing
- Depression
- Nerve entrapment syndromes
- Ataxia
- Muscle weakness
- Muscle cramps
- Menstrual disturbance
- Infertility
- Bradycardia
- Diastolic hypertension
- Hoarseness
- Goitre
- Periorbital oedema
- Weight gain
- Galactorrhoea

Laboratory test abnormalities

- Hypercholesterolaemia
- Hyponatraemia
- Hyperprolactinaemia
- Hyperhomocysteinaemia
- Anaemia
- Creatine phosphokinase elevation

Radiological abnormalities

- Pericardial and pleural effusions
- Pituitary gland enlargement

Risk factors for hypothyroidism

Autoimmune thyroiditis

- Established serological or tissue diagnosis
- Diffuse goitre
- Previous Graves' disease, de Quervain's thyroiditis, or painless (postpartum) thyroiditis
- Family history of autoimmune thyroid disease
- Down's syndrome
- Turner's syndrome

- Personal or family history of associated autoimmune disorders (eg, vitiligo, pernicious anaemia, adrenal insufficiency, diabetes mellitus type 1, ovarian failure, coeliac disease, Sjögren's syndrome)
- Primary pulmonary hypertension
- Multiple sclerosis

Previous thyroid injury

- Thyroidectomy or other neck surgery
- Radioactive iodine therapy
- External radiotherapy
- Exposure to polybrominated and polychlorinated biphenyls, and resorcinol

Postpartum status

Drugs impairing thyroid function

- Lithium carbonate
- Amiodarone
- Aminoglutethimide
- Interferon α
- Thalidomide
- Betaroxine
- Stavudine

Hypothalamic disorders

- Hypothalamic or suprasellar mass
- History of hypothalamic radiotherapy or surgery
- Disorders causing hypothalamic dysfunction—eg, sarcoidosis, haemochromatosis, Langerhans' cell histiocytosis

Pituitary disorders

- Known pituitary tumour
- Other elements of hypopituitarism
- Manifestations of a sellar mass (eg, headache, bitemporal haemianopsia, or diplopia)
- History of pituitary surgery or radiotherapy
- History of head trauma
- History of pituitary apoplexy, including Sheehan's syndrome
- History of other disorders causing hypopituitarism—eg, metastatic cancer and lymphocytic hypophysitis

variant, the thyroid gland is hard and markedly enlarged.²³ Rarely, the gland can be painful and tender.²⁴ Patients with autoimmune thyroiditis might be hypothyroid or euthyroid; transient thyrotoxicosis followed by hypothyroidism ("Hashitoxicosis") takes place infrequently.^{25,26} Euthyroid individuals with autoimmune thyroiditis are at increased risk of subsequently developing hypothyroidism. Detection of circulating thyroid autoantibodies confirms the diagnosis of autoimmune thyroiditis in patients with typical clinical presentations—eg, diffuse goitre with or without primary hypothyroidism.

Antimicrosomal or anti-thyroid peroxidase antibodies are present in 95% of affected individuals, whereas antithyroglobulin antibodies are present in only 60%.¹³ Immunoassay for anti-thyroid-peroxidase antibodies is the most sensitive thyroid autoantibody test;²⁷ and presence of these antibodies has been more strongly associated with an elevated serum thyrotropin concentration than have antithyroglobulin antibodies.² In the Wickham follow-up study, women with thyroid autoantibodies (11% of the population) had an eight-fold higher likelihood (95% CI 5–15) of developing overt hypothyroidism over 20 years than did antibody-negative women.²⁸ In women with both thyroid autoantibodies and isolated thyrotropin elevation,

the risk of progression to overt hypothyroidism was 38 times higher (22–65), with a 4% annual risk of developing overt hypothyroidism.

Autoimmune thyroiditis can arise in conjunction with other endocrine deficiency states in polyendocrine failure syndromes: type 1 most commonly including hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis; and type 2 most frequently including adrenal insufficiency, type 1 diabetes mellitus, and primary ovarian failure.²⁹ Patients with autoimmune thyroiditis are also at increased risk of other autoimmune disorders, including vitiligo, atrophic gastritis, pernicious anaemia, systemic sclerosis, and Sjögren's syndrome. Some researchers have shown that affected women are more likely to have spontaneous abortion, but results of other surveys have not confirmed these findings.³⁰

Acquired primary hypothyroidism

Acquired primary hypothyroidism can also result from previous thyroid injury by surgery or irradiation (after external beam radiotherapy for head and neck malignant disease),³¹ radioactive iodine therapy for thyrotoxicosis,³² accidental environmental exposure to radioiodine,³³ and experimental use of radioiodinated immunoglobulins for

cancer treatment.³⁴ Iron infiltration of the thyroid gland in haemochromatosis can cause hypothyroidism.³⁵ Toxic injury to the thyroid gland has been reported after exposure to polybrominated biphenyls and polychlorinated biphenyls. Resorcinol has been reported to cause hypothyroidism in exposed textile workers and in a patient on haemodialysis. Despite concern that environmental perchlorate exposure might cause congenital or acquired hypothyroidism, this has not been shown to happen at concentrations found in contaminated drinking water. Thalidomide causes hypothyroidism by an unknown mechanism in some thalidomide-treated patients. The antiretroviral agent stavudine has also been associated with overt and subclinical hypothyroidism.

Several drugs can cause hypothyroidism by interfering with thyroid hormone production or provoking thyroid autoimmunity. Pharmacological quantities of iodine, such as those to which patients treated with amiodarone or other iodine-containing compounds are exposed, can inhibit thyroid hormone production, especially when combined with underlying autoimmune thyroiditis, and cause hypothyroidism. In one prospective study, 22% of amiodarone-treated patients developed overt or mild hypothyroidism. Similarly, lithium interferes with glandular hormone release, causing transient thyrotropin elevation in more than a third of lithium carbonate-treated patients and persistent hypothyroidism in approximately 10%, especially those with underlying autoimmune thyroiditis. The chemotherapeutic agent aminoglutethimide inhibits thyroid hormone synthesis and can cause goitrous hypothyroidism. Treatment with interferon α can instigate thyroid autoimmunity, causing either hypothyroidism or hyperthyroidism, which is often reversed by discontinuation of the drug.

Transient primary hypothyroidism can also take place with two inflammatory conditions, subacute thyroiditis (also called de Quervain's thyroiditis) and lymphocytic thyroiditis (also called painless, silent, and postpartum thyroiditis). In both disorders, hypothyroidism lasting 2–8 weeks typically follows transient thyrotoxicosis, which is due to unregulated leakage of stored thyroxine; residual impairment of hormonogenesis is responsible for the subsequent hypothyroid phase. Subacute thyroiditis, which is believed, but not yet proven, to be a viral illness, also usually causes a painful, tender, woody hard goitre and constitutional symptoms, such as fever and malaise. Lymphocytic thyroiditis is an idiopathic disorder affecting 6% of women 2–12 months postpartum;³⁶ it rarely occurs in women without preceding pregnancy and in men. Lymphocytic thyroiditis causes modest thyroid enlargement, which is not painful or tender. Since most patients with both conditions recover to euthyroidism—about 85% with subacute thyroiditis³⁷ and 75% with lymphocytic thyroiditis—only temporary thyroxine treatment for symptomatic patients or no thyroid hormone therapy at all is generally needed.

However, women with a previous episode of postpartum thyroiditis remain at increased risk of developing hypothyroidism and should be monitored for its appearance. Reassessment of thyroid status is particularly important for women who are planning subsequent pregnancy or who are newly pregnant, since acceleration of thyroxine catabolism during gestation can lead to hypothyroidism in women with limited thyroid reserve. This is particularly important because, if untreated, even mild hypothyroidism can lead to subtle impairment of subsequent childhood neuropsychological development.³⁸ Diagnosis and management of these disorders have been discussed in several reviews.^{39–41}

Central (secondary) hypothyroidism

Central hypothyroidism can be acquired when diseases interfere with thyrotropin-releasing hormone (TRH) production by the hypothalamus or its delivery via the pituitary stalk, or with pituitary thyrotropin production. The most common causes of central hypothyroidism are pituitary adenomas and the surgery and/or radiotherapy⁴² used to treat them. Central hypothyroidism can also result from tumours impinging on the hypothalamus (eg, germinoma, glioma, and meningioma) or the pituitary stalk in suprasellar region (eg, craniopharyngioma and chordoma). Sarcoidosis,⁴³ haemochromatosis,⁴⁴ and Langerhans' cell histiocytosis can impair hypothalamic TRH production. Head trauma transecting the pituitary stalk can interrupt TRH delivery.⁴⁵ Pituitary thyrotrope function can also be affected by lymphocytic hypophysitis, infection, metastatic disease, apoplectic infarction (eg, Sheehan's syndrome) and the retinoid X receptor-selective ligand betaroxine.⁴⁶

Molecular and biochemical pathophysiology

Clinical hypothyroidism indicates a pervasive deficit in thyroid hormone actions, including modulation of calorogenesis and oxygen consumption in most tissues and additional organ-specific effects. The following description of the basis for thyroid hormone action summarises how deficient tri-iodothyronine actions at the genomic level cause biochemical, hormonal, ion transport, and mechanical changes in target tissues. Thyroxine, the principal product of the thyroid gland and circulating thyroid hormone, is converted by outer-ring monodeiodination to tri-iodothyronine in the cytoplasm and nucleus of target tissues by three distinct tissue specific deiodinases.⁴⁷ Most classic thyroid hormone actions are believed to be mediated genomically by tri-iodothyronine binding to one of the tri-iodothyronine receptor isoforms (TR α_1 , TR β_1 , and TR β_2), which are members of the nuclear receptor superfamily.⁴⁸ Tri-iodothyronine receptors possess domains for tri-iodothyronine binding, DNA binding, and coupling with another tri-iodothyronine receptor or other nuclear receptor (eg, retinoic acid X receptor) to form dimers. The receptors bind to DNA at sites with certain specific orientations of paired thyroid response elements with specific hexameric oligonucleotide sequences (eg, AGGTCA) that are typically located in the 5' regulatory regions of thyroid hormone-responsive genes. In most cases, interaction of tri-iodothyronine with its receptor prompts the binding of accessory protein cofactors that either activate or repress a specific gene's transcription⁴⁹ (as tri-iodothyronine does to the hypothalamic thyroid releasing hormone and thyrotrope thyrotropin β subunit genes).

Based on this model, some clinical manifestations of hypothyroidism are understood at the molecular level. For example, failure to stimulate the growth hormone gene in pituitary somatotrophs causes short stature in prepubertal children; a deficit in expression of the hepatic LDL receptor gene mediated by thyroid hormone regulated SREBP2 (sterol regulatory element binding transcription factor 2) decreases the rate of LDL-cholesterol clearance, causing hypercholesterolaemia; and decreased expression of myocardial sarcoplasmic reticulum ATPase and α -myosin heavy chain impairs diastolic and systolic ventricular performance, respectively. Many other clinical manifestations of hypothyroidism are not yet linked to specific genomic actions. In addition to the nuclear actions of thyroid hormone, tri-iodothyronine stimulates cellular uptake of aminoacids and glucose, augments

calcium-ATPase activity in cardiomyocytes, and alters mitochondrial ATP-generation by non-genomic mechanisms.⁵⁰ Thyroid hormone also interacts with G protein-coupled membrane receptors and activates the mitogen-activated protein kinase (MAPK) pathway; deficits in these non-genomic actions could account for some of the additional consequences of hypothyroidism.

Clinical manifestations

Symptoms and signs

Overt hypothyroidism has been associated with a familiar set of symptoms and signs, including cold intolerance, weight gain, constipation, dry skin, bradycardia, hoarseness, and slowed mental processing. In one study of patients with short-term hypothyroidism, 38% to 58% of patients had one or more of these clinical findings.⁵¹ In screened populations, however, the diagnostic accuracy of clinical findings is lower. In newly diagnosed hypothyroid patients in a case-control study, only 30% had any symptoms, whereas 17% of euthyroid controls had at least one of the same nonspecific complaints.⁵² Consequently, the positive predictive value of individual hypothyroid symptoms was only 8% to 12%. Inaccuracy in clinical diagnosis of hypothyroidism is attributable to the many medical and lifestyle causes of similar symptoms, their gradual onset, and occasionally the impaired insight that hypothyroidism itself can produce in affected patients. Symptoms that are new or arise in combination are more likely to indicate hypothyroidism. In the same case-control study, hypothyroid patients reported symptoms that had changed from the previous year more often than did euthyroid individuals; and those with seven or more new symptoms were almost nine-fold more likely to be hypothyroid than those with fewer changed symptoms (95% CI 4–20).

Atypical clinical presentations

Atypical clinical presentations of hypothyroidism⁵³ can include hypothermia,⁵⁴ congestive heart failure,^{55,56} pericardial^{57,58} and pleural effusions,⁵⁹ ileus and intestinal pseudo-obstruction,⁶⁰ and coagulopathy.⁶¹ Neurological manifestations can include depression,⁶² psychosis,^{63,64} ataxia,⁶⁵ seizures,⁶⁶ and coma.⁶⁷ Hypothyroidism has been associated with several neurocognitive deficits, particularly in memory.⁶⁸ The condition has traditionally been included in the differential diagnosis of reversible dementias and is occasionally seen in elderly patients with dementia, but thyroid hormone treatment rarely reverses dementia in these individuals.^{69,70}

Congenital hypothyroidism

Congenital hypothyroidism usually presents in severely affected infants with hypothermia, poor feeding, bradycardia, jaundice, and an enlarged posterior fontanelle and umbilical hernia; but most affected infants have no apparent clinical manifestations in the early neonatal state, justifying the practice of routine thyroid function screening.⁷¹ Additional presentations of hypothyroidism in children and adolescents can include growth failure with markedly delayed bone maturation,⁷² slipped capital femoral epiphysis,⁷³ delayed eruption of permanent teeth, muscle pseudohypertrophy,⁷⁴ unexplained anaemia, pituitary enlargement due to thyrotroph hyperplasia,⁷⁵ galactorrhoea,⁷⁶ and delayed or precocious puberty.⁷⁷

Routine laboratory abnormalities

Abnormalities in routine laboratory indices can sometimes be the first diagnostic clue to, or might be explained by,

hypothyroidism.⁷⁸ 4–14% of hypercholesterolaemic patients have been reported to have hypothyroidism,⁷⁹ a relation that is often unsuspected by primary care physicians.⁸⁰ Hyponatraemia, hyperprolactinaemia,⁸¹ hyperhomocysteinaemia,⁸² hypoglycaemia, and elevated creatine phosphokinase⁸³ (predominantly MM band) can all be caused by hypothyroidism.

Laboratory diagnosis

Serum thyrotropin measurement

Serum thyrotropin measurement is the first-line diagnostic test for hypothyroidism in most clinical settings, including case-finding prompted by clinical or routine laboratory findings, and patient or population screening (panel 1).^{84,85} Raised serum thyrotropin concentrations identify patients with primary hypothyroidism irrespective of its cause or severity, even those with thyroid hormone deficiency so mild that the serum thyroxine concentration remains within the reference range for a population. Normal serum thyrotropin levels in disease-free individuals, typically cited as about 0.4 mU/L to 4.0 mU/L, are distributed logarithmically, with the geometric mean thyrotropin concentration in the lower half of the reference range, 1.5 mU/L.² Consequently, even a serum thyrotropin level at the upper end of the normal range (ie, greater than 3.0 mU/L) might indicate very mild thyroid dysfunction with greater risk of progression to hypothyroidism, especially if thyroid autoantibodies are detected.

Furthermore, investigators in one study found that individuals with serum thyrotropin concentrations in the upper half of the reference range had higher mean serum cholesterol level than those with low-to-normal serum thyrotropin values.⁸⁶ As a result, some authorities have recommended lowering the thyrotropin assay's upper limit of normal even further to 2.5 mU/L.⁸⁷ When elevated serum thyrotropin is detected in a potentially hypothyroid patient or an individual in a screened population, the thyrotropin assay should usually be repeated along with measurement of serum free thyroxine. This method confirms the diagnosis for patients who will generally be committed to lifelong thyroid hormone replacement therapy, and more fully defines the severity of hypothyroidism.⁶⁹

Limitations of serum thyrotropin testing

The thyrotropin assay can be insensitive in diagnosing hypothyroidism in a few circumstances. In patients with central hypothyroidism due to hypothalamic or pituitary disorders, the amount of serum thyrotropin can be low because of decreased production, or inappropriately normal or only modestly elevated⁸⁸ as a result of synthesis of a thyrotropin molecule with reduced bioactivity.⁸⁹ Central hypothyroidism should be suspected in several circumstances: when there are persuasive clinical features of hypothyroidism despite absence of raised serum thyrotropin; when there are clinical findings suggesting other anterior pituitary hormone deficiencies or a sellar mass lesion; or when a patient has a condition known to cause hypopituitarism—eg, sarcoidosis, previous cranial injury or radiotherapy, or cancers with potential pituitary metastasis. In these settings, the serum free thyroxine concentration should be measured along with thyrotropin. The finding of a low serum free thyroxine concentration, regardless of the thyrotropin concentration, should then prompt further testing, which could include pituitary imaging, a thyroid releasing hormone stimulation test to assess thyrotropin responsiveness,⁹⁰ and other pituitary function testing. In a highly suggestive clinical setting, even serum free thyroxine levels in the lower third of the

normal range should be regarded as suggestive of mild central hypothyroidism, and might justify additional evaluation.

Conversely, there are several situations in which raised serum thyrotropin might not be indicative of hypothyroidism, including euthyroid patients with adrenal glucocorticoid insufficiency,⁹¹ renal failure,⁹² and exposure to cold temperatures.⁹³ Circulating antibodies against thyrotropin⁹⁴ or mouse immunoglobulins,⁹⁵ when used as assay reagents, can also yield falsely raised thyrotropin immunoassay readings. Two rare forms of thyrotropin-mediated hyperthyroidism, thyrotropin-secreting pituitary tumours⁹⁶ and isolated pituitary resistance to thyroid hormone,⁹⁷ can present as clinical and biochemical hyperthyroidism with an inappropriately elevated serum thyrotropin, but raised serum free thyroxine or tri-iodothyronine, or both, in these patients suggest these diagnoses.

Effects of non-thyroidal illnesses and drugs

In clinical practice, the greatest challenge in diagnosis of the condition is in patients with changes in thyroid hormone and thyroid function test results that are usually seen in severe non-thyroidal illnesses. In those with systemic illness, accompanying thyrotropin suppression can mask mild,⁹⁸ but not severe, primary hypothyroidism. Three drugs used in severely ill patients, glucocorticoids,⁹⁹ dopamine,¹⁰⁰ and dobutamine,¹⁰¹ can suppress serum thyrotropin even in patients with overt primary hypothyroidism. Conversely, patients recovering from severe illness may have a transiently raised thyrotropin concentration.¹⁰² Thus, thyroid function testing is best reserved for severely ill patients in whom there is a substantial clinical suspicion of hypothyroidism; otherwise, abnormal results are much more likely to represent false-positive than true-positive findings. A diagnostic challenge similar to nonthyroidal illnesses can arise in patients taking the anti-seizure medications phenytoin and carbamazepine, which can cause low serum total thyroxine and thyrotropin levels and be confused with central hypothyroidism.¹⁰³

Antithyroid antibodies

Laboratory tests are seldom necessary to define the underlying cause of primary hypothyroidism; the history is usually sufficient, identifying factors such as previous neck irradiation, radioiodine therapy, thyroid surgery, postpartum state, or medications inducing thyroid dysfunction. In patients with none of these findings and sustained primary hypothyroidism, the cause can usually be assumed to be autoimmune thyroiditis. Although not essential, it is sometimes helpful for the patient to have this diagnosis confirmed by detection of thyroid autoantibodies. Other uses of thyroid autoantibody screening include prediction of subsequent hypothyroidism in patients with mild hypothyroidism²⁶ and in pregnant¹⁰⁴ and postpartum women,¹⁰⁵ and for the differential diagnosis of diffuse goitre.

Management of hypothyroidism

Thyroxine pharmacokinetics

The treatment of choice for hypothyroidism is levothyroxine sodium (thyroxine), which has convenient pharmacokinetic properties, and when given in the proper dose, a high degree of effectiveness and small risk of adverse reactions.¹⁰⁶ However, thyroid hormone has a narrow toxic-to-therapeutic ratio; and despite the assumption that treatment should be straightforward, researchers in several studies—undertaken in large

populations^{2,4} and patients cared for in general³ and specialist practices¹⁰⁷—have noted that about a fifth of hypothyroid patients are receiving an inadequate thyroxine dose, and a fifth are given an excessive amount of medication (panel 2). Thyroxine is well absorbed by the proximal small bowel, circulates with a long 7-day half-life because of plasma protein binding, and is metabolised in target tissues, in part by deiodination to tri-iodothyronine.

Dose considerations and drug interactions

The optimum dose of thyroxine for hypothyroid patients is related to bodyweight (about 1.8 µg per kg in adults)¹⁰⁸ and age, with a dose requirement that is higher in infants and young children and is lower in older adults (0.5 µg per kg per day).¹⁰⁹ The thyroxine dose is generally higher in patients with previous thyroidectomy than in those with autoimmune thyroiditis, in which there may be some residual functioning thyroid tissue. The dose needed for individuals with mild hypothyroidism is usually lower as well (0.5 µg per kg per day).¹¹⁰ Thyroxine absorption can be decreased in patients with malabsorption from gastrointestinal disorders¹¹¹ or previous small bowel bypass surgery.¹¹² Several drugs (panel 2), iron¹¹³ and calcium carbonate¹¹⁴ mineral supplements, cholestyramine, aluminum hydroxide gel, sucralfate, dietary soy,¹¹⁵ and perhaps fibre^{116,117} have all been reported to interfere with thyroxine absorption.

Thyroxine disposal is accelerated by nephrotic syndrome,¹¹⁸ other severe systemic illnesses,¹¹⁹ and several anti-seizure medications (phenobarbital, phenytoin, and carbamazepine) and rifampin.¹²⁰ Pregnancy increases the thyroxine dose requirement in 75% of women,¹²¹ probably because of increased degradation by the placental deiodinase. Initiating postmenopausal hormone replacement therapy increases the dose needed in 35% of women, perhaps due to an increased circulating thyroxine-binding globulin level.¹²² Patient non-compliance with prescribed thyroxine, the most common cause of inadequate treatment, might be suspected in patients with a dose that is higher than expected, variable thyroid function test results that do not correlate well with prescribed doses, and an elevated serum thyrotropin concentration with serum free thyroxine at the upper end of the normal range, which can suggest improved compliance immediately before testing due to a lag in the thyrotropin response.

The metabolism of other pharmacological agents can be altered in patients with hypothyroidism. The mechanism might be decreased expression of hepatic enzymes involved in drug metabolism, as seen in hypothyroid rats.^{123,124} As a result, increased sensitivity to anaesthetic¹²⁵ and sedative agents,¹²⁶ and higher serum levels of phenytoin have been reported.¹²⁷ Hypothyroidism can also cause higher serum digoxin values,¹²⁸ an effect attributed to a decreased volume of drug distribution.^{129,130} Conversely, hypothyroidism might decrease sensitivity to warfarin due to slowed metabolism of the vitamin K-dependent clotting factors,¹³¹ and restoration of euthyroidism can then increase the warfarin dose requirement.

Initiating thyroxine therapy

Physicians should usually initiate treatment with a dose at the lower end of the anticipated dose requirement—eg, 125 µg per day in a 70 kg adult. In most patients who are otherwise healthy, titration of the dose upward from a low starting dose of 25–50 µg per day is unnecessary and prolongs recovery. Laboratory monitoring of treated hypothyroid patients is appropriate 4–6 weeks after

Panel 2: Potential causes of thyrotropin elevation in thyroxine-treated patients with primary hypothyroidism

Suboptimal dosing

Inadequate prescribed dosage
Noncompliance
Dispensing error (incorrect dose or formulation change)

Progressive decrease in endogenous thyroxine production

Autoimmune thyroiditis
Previous thyroid irradiation

Reduced thyroxine absorption

Drug interactions

Iron
Calcium carbonate
Cholestyramine
Aluminum hydroxide gel
Sucralfate
Dietary soy and fibre

Comorbid conditions

Disorders causing malabsorption—eg, coeliac disease
Previous small bowel surgery

Increased thyroxine clearance

Drug interactions

Phenytoin
Carbamazepine
Phenobarbital
Rifampin

Coexisting conditions

Pregnancy
Nephrotic syndrome
Other systemic illnesses

Other

Postmenopausal hormone replacement therapy

instituting a new thyroxine dose, and yearly or when persistent symptoms suggesting thyroid hormone deficiency or excess arise. In patients with primary hypothyroidism, serum thyrotropin concentration should be assessed, with the aim of restoring the thyrotropin value to the lower half of the normal range (about 1.0 mU/L). In individuals with central hypothyroidism, serum free thyroxine concentration must be monitored, and should generally be maintained in the upper half of the normal range.

Adverse reactions and problems

Adverse reactions to thyroxine treatment are related to excessive or increased thyroid hormone action, and include symptomatic thyrotoxicosis, subclinical thyrotoxicosis with increased risks of bone loss,¹³² and atrial tachyarrhythmias.¹³³ Complications can also arise from restoration of euthyroidism in patients who have underlying ischaemic heart disease¹³⁴ and borderline adrenal cortical insufficiency; this insufficiency can arise in people with hypopituitarism and those with the type 2 polyendocrine failure syndrome (Schmidt's syndrome), which is comprised of autoimmune thyroiditis and idiopathic (autoimmune) adrenal insufficiency. A syndrome of acute sympathomimetic symptoms soon after start of thyroxine treatment has been described,¹³⁵ and could be attributable to anaemia in some cases.¹³⁶ Transient scalp hair loss can also take place during the first few weeks of hormone replacement. Allergy to commonly prescribed thyroxine formulations has not been well documented.

In addition to anticipating changing dose requirements, avoiding drug interactions, and optimising patient compliance, physicians should be aware of specific problems in management of hypothyroidism in patients with coexisting ischaemic heart disease, persistent symptoms despite normal laboratory test results, mild hypothyroidism, and complicated myxoedema.

Patients with ischaemic heart disease

Thyroxine treatment of hypothyroid patients might exacerbate myocardial ischaemia in those with underlying coronary artery disease due to positive inotropic and chronotropic effects of thyroid hormone. Starting treatment at lower doses in these patients—eg, 25 µg per day, can be justified. The traditional recommendation has been gradual titration of the thyroxine dose upward to euthyroidism in 12.5 to 25.0 µg increments at intervals of 4–6 weeks along with vigilant clinical and electrocardiographic monitoring. However, long-term suboptimal dosing increases the risk of worsening coronary atherosclerosis.¹³⁷ Starting or supplementing β-adrenergic blockade might be helpful. Hypothyroid patients can undergo coronary angioplasty¹³⁸ and even surgical bypass grafting with only slightly, if at all, increased perioperative risk.¹³⁹

Residual symptoms and tri-iodothyronine therapy

Even adequately treated hypothyroid patients more commonly have constitutional and neuropsychological complaints and a decreased sense of well-being than do euthyroid individuals.¹⁴⁰ The cause of this is unknown, and it might represent an ascertainment bias—ie, individuals with inclination to complain and seek medical care are more likely to be diagnosed with hypothyroidism. However, another postulated cause of this problem is absence of the small amount of tri-iodothyronine directly produced by the thyroid gland, in addition to the preponderance of endogenous tri-iodothyronine generated from the extrathyroidal thyroxine. Results of a clinical trial in which a fraction of the thyroxine dose was replaced by the addition of a small dose of tri-iodothyronine showed significant improvement in some symptoms.¹⁴¹ However, these findings were confounded because the ratio of tri-iodothyronine to thyroxine used was supraphysiological; thus, some patients had depression, and some were actually overtreated with a suppressed serum thyrotropin concentration.

Furthermore, researchers in two subsequent investigations have failed to confirm these findings; Sawka and colleagues¹⁴² did not record enhancement of mood or sense of well-being with tri-iodothyronine plus thyroxine treatment compared with thyroxine alone,¹⁴² and Walsh and co-workers¹⁴³ noted no improvements in well-being, cognitive function, or quality of life with combined treatment of tri-iodothyronine and thyroxine compared with thyroxine only. Also, such combined therapy has the disadvantage of a fluctuating tri-iodothyronine concentration due to its 1-day half-life, which can result in a supraphysiological tri-iodothyronine concentration during part of the day. Additionally, use of a combination of synthetic thyroxine and tri-iodothyronine formulations leads to increased complexity and expense of treatment. Thus, its benefit in routine management of hypothyroid patients remains unproven.

Mild (subclinical) hypothyroidism

Whether patients with mild hypothyroidism should be treated is controversial. Some have argued that diagnosis of mild and overt hypothyroidism satisfies criteria for

secondary prevention by early detection, either case finding based on clinical suspicion or routine screening of specific populations or even all adults.^{144,145} As noted previously, mild hypothyroidism is highly prevalent, particularly in older women, and clinical diagnosis alone is often inaccurate. The test for its diagnosis, serum thyrotropin measurement, and its treatment with thyroxine are effective, safe, and relatively inexpensive. The greatest controversy surrounds the issue of whether mild hypothyroidism has clinically important and reversible consequences in a significant enough proportion of affected patients to justify widespread screening.¹⁴⁶

The first potential benefit of thyroxine therapy is preventing patients' progression to overt hypothyroidism, especially in those with a serum thyrotropin concentration greater than 10 mU/L, aged 65 years or older, with or without thyroid autoantibodies indicative of underlying autoimmune thyroiditis.^{26,147} The second argument for intervention is reduction of future risk of cardiovascular disease, based on findings that mildly hypothyroid patients have higher mean cholesterol levels⁴ and that thyrotropin-normalising thyroxine treatment might lower serum total and LDL cholesterol concentrations.¹⁴⁸ Additionally, subtle and reversible changes in myocardial performance have been described in mild hypothyroidism.^{149,150} However, a higher risk of clinical heart disease has only been shown in some,¹⁵¹ but not other epidemiological studies,¹⁵² and cardiovascular benefit of thyroid hormone treatment has never been rigorously tested in a randomised controlled trial. Third, four small controlled, double-blinded trials have shown that thyroxine treatment produced greater improvements in mildly hypothyroid patients' symptoms and neuropsychological performance indices than did placebo,¹⁵³⁻⁵⁶ but these observations have not been

confirmed in other small studies and no large prospective randomised trial has been undertaken. Two decision and cost-effectiveness models based on these studies have suggested that the cost-effectiveness of screening for and treating mild hypothyroidism is similar to other widely accepted preventive medicine strategies.^{157,158} Nonetheless, there remains controversy about the actual benefit of such therapy for individuals with mild hypothyroidism, and by extension, of thyrotropin screening of populations to identify affected individuals.

Severe hypothyroidism

Myxoedema can become complicated by multiple organ system failure when it is profound and long term, especially in patients who are elderly and who could have other cardiac, pulmonary, neurological, renal, and infectious diseases. The syndrome of myxoedema coma represents the most extreme form of this complicated hypothyroidism,⁵⁸ and despite the best of contemporary intensive medical care, is associated with substantial mortality. In severely hypothyroid patients, these complications can be prevented by early and sustained thyroxine therapy, prompt attention to other underlying medical conditions (eg, heart and renal failure, pneumonia, and metabolic disturbances), and avoidance of sedative, anaesthetic, and analgesic medications that suppress central nervous system function, particularly ventilatory drive. Treatment entails thyroid hormone replacement and aggressive management of the individual organ system complications that can be present (panel 3). Regimens shown to be effective are either thyroxine in a large replacement dose, with or without a preceding 500 µg loading dose to replete the normal total body thyroxine pool;¹⁶³ or tri-iodothyronine in divided doses, advocated because of the anticipated impairment of thyroxine to tri-iodothyronine conversion in critically ill patients. Although no comparative trial has proven the advantage of one approach over the other, a small retrospective experience recorded a higher mortality in tri-iodothyronine-treated patients.¹⁶⁴

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References

- 1 Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf)* 1977; **7**: 115-25.
- 2 Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T4, and thyroid antibodies in the United States Population (1988-1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002; **87**: 489-99.
- 3 Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotropin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol* 1991; **34**: 77-83.
- 4 Canaris GJ, Manowitz NR, Mayor G, Ridgway C. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; **160**: 526-34.
- 5 Muller AF, Drexhage HA, Berghout A. Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antenatal and postnatal care. *Endocr Rev* 2001; **22**: 605-30.
- 6 Chopra IJ, Solomon DH, Chopra U, Yoshihara E, Terasaki PI, Smith F. Abnormalities in thyroid function in relatives of patients with Graves disease and Hashimoto's thyroiditis: lack of correlation with inheritance of HLA-B8. *J Clin Endocrinol Metab* 1977; **45**: 45-54.
- 7 Tamai H, Ohsako N, Takeno K, et al. Changes in thyroid function in euthyroid subjects with a family history of Graves disease: a follow-up study of 69 patients. *J Clin Endocrinol Metab* 1980; **51**: 1123-27.

Panel 3: Pathogenesis of general complications in management of complicated hypothyroidism

Congestive heart failure

Impaired ventricular systolic and diastolic functions,¹⁵⁹ and increased peripheral vascular resistance

Ventilatory failure

Blunted hypercapnoeic and hypoxic ventilatory drives¹⁶⁰

Hyponatraemia

Impaired renal free water excretion and syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Ileus

Bowel hypomotility⁵⁴

Medication sensitivity

Reduced clearance rate and increased sensitivity to sedative, analgesic, and anaesthetic agents

Hypothermia and lack of febrile response to sepsis

Decreased calorogenesis

Delirium, dementia, seizure, stupor, and coma

Decreased CNS thyroid hormone actions, and encephalopathy due to hyponatraemia and hypercapnoea

Adrenal insufficiency

Associated intrinsic adrenal or pituitary disease, or reversible impairment of hypothalamic-pituitary-adrenal stress response¹⁶¹

Coagulopathy

Acquired von Willebrand syndrome (type 1), and decreased factors VIII, VII, V, IX, and X¹⁶²

- 8 Delange F, de Benoist B, Pretell E, Dunn JT. Iodine deficiency in the world: where do we stand at the turn of the century? *Thyroid* 2001; **11**: 437–47.
- 9 LaFranchi S. Congenital hypothyroidism: etiologies, diagnosis, and management. *Thyroid* 1999; **9**: 735–40.
- 10 Gillam M, Kopp P. Genetic regulation of thyroid development. *Curr Opin Pediatr* 2001; **13**: 358–63.
- 11 Gillam M, Kopp P. Genetic defects of thyroid hormone synthesis. *Curr Opin Pediatr* 2001; **13**: 364–72.
- 12 Weiss RE, Refetoff S. Resistance to thyroid hormone. *Rev Endocr Metab Disord* 2000; **1**: 97–108.
- 13 Huang SA, Tu HM, Harney JW, et al. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med* 2000; **343**: 185–89.
- 14 Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. *N Engl J Med* 1996; **335**: 99–107.
- 15 Amino N, Hagen SR, Yamada N, Refetoff S. Measurement of circulating thyroid microsomal antibodies by the tanned red cell haemagglutination technique: its usefulness in the diagnosis of autoimmune thyroid diseases. *Clin Endocrinol (Oxf)* 1976; **5**: 115–25.
- 16 Stafford EA, Rose NR. Newer insights into the pathogenesis of experimental autoimmune thyroiditis. *Int Rev Immunol* 2000; **19**: 501–33.
- 17 Hanafusa T, Pujol-Borrell R, Chiovato L, Russell RCG, Doniach D, Bottazzo GF. Aberrant expression of HLA-DR antigen on thyrocytes in Graves disease: relevance for autoimmunity. *Lancet* 1983; **2**: 1111–15.
- 18 Weetman AP, McGregor AM. Autoimmune thyroid disease: further developments in our understanding. *Endocr Rev* 1994; **15**: 788–830.
- 19 Phillips D, McLachlan S, Stephenson A, et al. Autosomal dominant transmission of autoantibodies to thyroglobulin and thyroid peroxidase. *J Clin Endocrinol Metab* 1990; **70**: 742–46.
- 20 Allen EM, Hsueh W-C, Sabra M, et al. A genome-wide scan for autoimmune thyroid disease in the Old Order Amish: replication of loci on chromosomes 5q11.2-q14.3. *J Clin Endocrinol Metab* 2003; **88**: 1292–96.
- 21 Boukis MA, Koutras DA, Souvatzoglou A, Evangelopoulou A, Vrontakis M, Mouloupoulos SD. Thyroid hormone and immunological studies in endemic goiter. *J Clin Endocrinol Metab* 1983; **57**: 859–62.
- 22 Rose NR, Rasooly L, Saboori AM, Burek CL. Linking iodine with autoimmune thyroiditis. *Environ Health Perspect* 1999; **107** (suppl 5): 749–52.
- 23 Katz SM, Vickery AL Jr. The fibrous variant of Hashimoto's thyroiditis. *Hum Pathol* 1974; **5**: 161–70.
- 24 Zimmerman RS, Brennan MD, McConahey WM, Goellner JR, Gharib H. Hashimoto's thyroiditis: an uncommon cause of painful thyroid unresponsive to corticosteroid therapy. *Ann Intern Med* 1986; **104**: 355–57.
- 25 Mallya RK, Isaacs AJ, Bayliss R. Hashimoto's thyroiditis presenting as T3 toxicosis. *BMJ* 1978; **2**: 1535–36.
- 26 Reinwein D, Benker G, Konig MP, Pinchera A, Schatz H, Schleusener A. The different types of hyperthyroidism in Europe: results of a prospective survey of 924 patients. *J Endocrinol Invest* 1988; **11**: 193–200.
- 27 Roti E, Gardini E, Minelli R, Bianconi L, Braverman LE. Prevalence of anti-thyroid peroxidase antibodies in serum in the elderly: comparison with other tests for anti-thyroid antibodies. *Clin Chem* 1992; **38**: 88–92.
- 28 Vanderpump MPJ, Tunbridge WMG, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol* 1995 **43**: 55–68.
- 29 Neufeld M, Maclaren NK, Blizzard RM. Two types of autoimmune Addison's disease associated with different polyglandular autoimmune (PGA) syndromes. *Medicine* 1981; **60**: 355–62.
- 30 Abramson J, Stagnaro-Green A. Thyroid antibodies and fetal loss: an evolving story. *Thyroid* 2001; **11**: 57–63.
- 31 Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 2000; **85**: 3227–32.
- 32 Becker DV, Hurlley JR. Complications of radioiodine treatment of hyperthyroidism. *Semin Nucl Med* 1971; **1**: 442–60.
- 33 Goldsmith JR, Grossman CM, Morton WE, et al. Juvenile hypothyroidism among two populations exposed to radioiodine. *Environ Health Perspect* 1999; **107**: 303–08.
- 34 Order SE, Sleeper AM, Stillwagon GB, Klein JL, Leichner PK. Current status of radioimmunoglobulins in the treatment of human malignancy. *Oncology (Huntingt)* 1989; **3**: 115–20.
- 35 Edwards CQ, Kelly TM, Ellwein G, Kushner JP. Thyroid disease in hemochromatosis. Increased incidence in homozygous men. *Arch Intern Med* 1983; **143**: 1890–93.
- 36 Amino N, Mori H, Iwatani Y, et al. High prevalence of transient postpartum thyrotoxicosis and hypothyroidism. *N Engl J Med* 1982; **306**: 849–52.
- 37 Fatourechi V, Aniszewski JP, Eghbali Fatourechi GZ, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota Study. *J Clin Endocrinol Metab* 2003; **88**: 2100–05.
- 38 Klein RZ, Mitchell ML. Maternal hypothyroidism and cognitive development of the offspring. *Curr Opin Pediatr* 2002; **14**: 443–46.
- 39 Ross DS. Syndromes of thyrotoxicosis with low radioactive iodine uptake. *Endocrinol Metab Clin North Am* 1998; **27**: 169–85.
- 40 Walfish PG. Thyroiditis. *Curr Ther Endocrinol Metab* 1997; **6**: 117–22.
- 41 Lazarus JH. Thyroid dysfunction: reproduction and postpartum thyroiditis. *Semin Reprod Med* 2002; **20**: 381–88.
- 42 Rose SR. Cranial irradiation and central hypothyroidism. *Trends Endocrinol Metab* 2001; **12**: 97–104.
- 43 Bell NH. Endocrine complications of sarcoidosis. *Endocrinol Metab Clin North Am* 1991; **20**: 645–54.
- 44 McNeil LW, McKee LC Jr, Lorber D, Rabin D. The endocrine manifestations of hemochromatosis. *Am J Med Sci* 1983; **285**: 7–13.
- 45 Segal-Lieberman G, Karasik A, Shimon I. Hypopituitarism following closed head injury. *Pituitary* 2000; **3**: 181–84.
- 46 Sherman SI, Gopal J, Haugen BR, Chiu AC, Whaley K, Nowlakha P, Duvic M. Central hypothyroidism associated with retinoid X receptor-selective ligands. *N Engl J Med* 1999; **340**: 1075–79.
- 47 Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev* 2002; **23**: 38–89.
- 48 Yen PM. Physiological and molecular basis of thyroid hormone action. *Physiol Rev* 2001; **81**: 1097–142.
- 49 Koenig RJ. Thyroid hormone receptor coactivators and corepressors. *Thyroid* 1998; **8**: 703–13.
- 50 Davis PJ, Davis FB. Nongenomic actions of thyroid hormone. *Thyroid* 1996; **6**: 497–504.
- 51 Ladenson PW, Braverman LE, Mazzaferri EL, et al. Comparison of recombinant human thyrotropin administration to thyroid hormone withdrawal for radioactive iodine scanning in patients with thyroid carcinoma. *N Engl J Med* 1997; **337**: 888–96.
- 52 Canaris GJ, Steiner JF, Ridgway EC. Do traditional symptoms of hypothyroidism correlate with biochemical disease? *J Gen Intern Med* 1997; **12**: 544–50.
- 53 Tachman ML, Guthrie GP. Hypothyroidism: diversity of presentation. *Endocr Rev* 1984; **5**: 456–65.
- 54 Reuler JB. Hypothermia: pathophysiology, clinical settings, and management. *Ann Intern Med* 1978; **89**: 519–27.
- 55 Zondek H. Das Myxödemherz. *Münch Med Wochenschr* 1918; **65**: 1180–83.
- 56 Ladenson PW, Sherman SI, Baughman KL, Ray PE, Feldman AM. Reversible alterations in myocardial gene expression in a young man with dilated cardiomyopathy and hypothyroidism. *Proc Natl Acad Sci USA* 1992; **89**: 5251–55.
- 57 Quin JD, McDonald A, Russell R, Thomson JA. Hypothyroidism presenting with cardiac tamponade. *Scott Med J* 1994; **39**: 82.
- 58 Lin CT, Liu CJ, Lin TK, Chen CW, Chen BC, Lin CL. Myxedema associated with cardiac tamponade. *Jpn Heart J* 2003; **44**: 447–50.
- 59 Gottehrer A, Roa J, Stanford GG, Chernow B, Sahn SA. Hypothyroidism and pleural effusions. *Chest* 1990; **98**: 1130–32.
- 60 Boruchow IB, Miller LD, Fitts WT Jr. Paralytic ileus in myxedema. *Arch Surg* 1966; **92**: 960–63.
- 61 Edson JR, Fecher DR, Doe RP. Low platelet adhesiveness and other hemostatic abnormalities in hypothyroidism. *Ann Intern Med* 1975; **82**: 342–46.
- 62 Jackson IM. The thyroid axis and depression. *Thyroid*. 1998; 951–56.
- 63 Asher R. Myxoedematous madness. *BMJ* 1949; **2**: 555.
- 64 Logothetis J. Psychotic behavior as the initial indicator of adult myxedema. *J Nerv Ment Dis* 1963; **136**: 561.
- 65 Price TR, Netsky MG. Myxedema and ataxia: cerebellar alterations and "neural myxedema bodies". *Neurology* 1966; **16**: 957–62.
- 66 Woods KL, Holmes GK. Myxoedema coma presenting in status epilepticus. *Postgrad Med J* 1977; **53**: 46–48.
- 67 Nicoloff JT, LoPresti JS. Myxedema coma: a form of decompensated hypothyroidism. *Endocrinol Metab Clin North Am* 1993; **22**: 279–90.
- 68 Nickel SN, Frame B. Neurological manifestations of myxedema. *Neurology* 1958; **8**: 511.
- 69 Clarnette RM, Patterson CJ. Hypothyroidism: does treatment cure dementia? *J Geriatr Psychiatry Neurol* 1994; **7**: 23–27.
- 70 Dugbartey AT. Neurocognitive aspects of hypothyroidism. *Arch Intern Med* 1998; **158**: 1413–18.
- 71 Foley TP Jr. Congenital hypothyroidism. In: Braverman LE, Utiger RD, eds. *The thyroid: a fundamental and clinical text*. 8th edn. Philadelphia: Lippincott Williams and Wilkins, 2000; 977–82.

- 72 Foley TP. Acquired hypothyroidism in infants, children, and adolescents. In: Braverman LE, Utiger RD, eds. *The thyroid: a fundamental and clinical text*. 8th edn. Philadelphia: Lippincott Williams and Wilkins, 2000; 983–88.
- 73 Hirano T, Stamelos S, Harris V, Dumbovic N. Association of primary hypothyroidism and slipped capital femoral epiphysis. *J Pediatr* 1978; **93**: 262–64.
- 74 Najjar SS. Muscular hypertrophy in hypothyroid children: the Kocher-Debré-Sélemelaigne syndrome. *J Pediatr* 1974; **85**: 236.
- 75 Vagenakis AG, Dole K, Braverman LE. Pituitary enlargement, pituitary failure, and primary hypothyroidism. *Ann Intern Med* 1976; **85**: 195–98.
- 76 Van Wyck J, Grumbach M. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. *J Pediatr* 1960; **57**: 416.
- 77 Barnes ND, Hayles AB, Ryan RJ. Sexual maturation in juvenile hypothyroidism. *Mayo Clin Proc* 1973; **48**: 849–56.
- 78 Ladenson PW. Diagnosis of hypothyroidism. In: Braverman LE, Utiger RD, eds. *The thyroid: a fundamental and clinical text*. 8th edn. Philadelphia: Lippincott Williams and Wilkins, 2000; 848–52.
- 79 Diekman T, Lansberg PJ, Kastelein JJ, Wiersinga WM. Prevalence and correction of hypothyroidism in a large cohort of patients referred for dyslipidemia. *Arch Intern Med* 1995; **155**: 1490–95.
- 80 Meyer CM, Ladenson PW, Scharfstein JA, Danese MD, Powe NR. Evaluation of common problems in primary care: effect of physician, practice and financial considerations. *J Man Care* 2000; **6**: 457–72.
- 81 Fish LH, Mariash CN. Hyperprolactinemia, infertility, and hypothyroidism. A case report and literature review. *Arch Intern Med* 1988; **148**: 709–11.
- 82 Morris MS, Bostom AG, Jacques PF, Selhub J, Rosenberg IH. Hyperhomocysteinemia and hypercholesterolemia associated with hypothyroidism in the third US National Health and Nutrition Examination Survey. *Atherosclerosis* 2001; **155**: 195–200.
- 83 Beyer IW, Karmali R, Demeester-Mirkine N, Cogan E, Fuss MJ. Serum creatine kinase levels in overt and subclinical hypothyroidism. *Thyroid* 1998; **8**: 1029–31.
- 84 Ross DS. Serum thyroid-stimulating hormone measurement for assessment of thyroid function and disease. *Endocrinol Metab Clin North Am* 2001; **30**: 245–64.
- 85 Spencer CA, Takeuchi M, Kazaryan M. Current status and performance goals for serum thyrotropin (TSH) assays. *Clin Chem* 1996; **42**: 140–45.
- 86 Michalopoulou G, Alevizaki M, Pipingos G, et al. High serum cholesterol levels in persons with 'high-normal' TSH levels: should one extend the definition of subclinical hypothyroidism? *Eur J Endocrinol* 1998; **138**: 141–45.
- 87 Laboratory support for the diagnosis and monitoring of thyroid disease. In: Demers LM, Spencer CA, eds. *National Academy of Clinical Biochemistry*, 2002. Available at http://www.nacb.org/lmpg/thyroid_lmpg_pub.stm (accessed Dec 16, 2003).
- 88 Faglia G, Bitensky L, Pinchera A, et al. Thyrotropin secretion in patients with central hypothyroidism: evidence for reduced biological activity of immunoreactive thyrotropin. *J Clin Endocrinol Metab* 1979; **48**: 989–98.
- 89 Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G, Weintraub BD. Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism. Effect of treatment with thyrotropin-releasing hormone. *N Engl J Med* 1985; **312**: 1085–90.
- 90 Spencer CA, Schwarzbein D, Guttler RB, LoPresti JS, Nicoloff JT. Thyrotropin (TSH)-releasing hormone stimulation test responses employing third and fourth generation TSH assays. *J Clin Endocrinol Metab* 1993; **76**: 494–98.
- 91 Topliss DJ, White EL, Stockigt JR. Significance of thyrotropin excess in untreated primary adrenal insufficiency. *J Clin Endocrinol Metab* 1980; **50**: 52–56.
- 92 Kaptein EM. Thyroid hormone metabolism and thyroid diseases in chronic renal failure. *Endocr Rev* 1996; **17**: 45–63.
- 93 Reed HL, Silverman ED, Shakir KM, Dons R, Burman KD, O'Brian JT. Changes in serum triiodothyronine (T3) kinetics after prolonged Antarctic residence: the polar T3 syndrome. *J Clin Endocrinol Metab* 1990; **70**: 965–974.
- 94 Akamizu T, Mori T, Kasagi K, et al. Anti-TSH antibody with high specificity to human TSH in sera from a patient with Graves disease: its isolation from, and interaction with, TSH receptor antibodies. *Clin Endocrinol (Oxf)* 1987; **26**: 311–20.
- 95 Kahn BB, Weintraub BD, Csako G, Zweig MH. Facititious elevation of thyrotropin in a new ultra-sensitive assay: implications for the use of monoclonal antibodies in "sandwich" immunoassay. *J Clin Endocrinol Metab* 1988 **66**: 526–33.
- 96 Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD. Thyrotropin-secreting pituitary tumors. *Endocr Rev* 1996; **17**: 610–38.
- 97 Beck-Peccoz P, Chatterjee VK. The variable clinical phenotype in thyroid hormone resistance syndrome. *Thyroid* 1994; **4**: 225–32.
- 98 Borst GC, Osburne RC, O'Brian JT, Georges LP, Burman KD. Fasting decreases thyrotropin responsiveness to thyrotropin-releasing hormone: a potential cause of misinterpretation of thyroid function tests in the critically ill. *J Clin Endocrinol Metab* 1983; **57**: 380–83.
- 99 Re RN, Kourides IA, Ridgway EC, Weintraub BD, Maloof F. The effect of glucocorticoid administration on human pituitary secretion of thyrotropin and prolactin. *J Clin Endocrinol Metab* 1976; **43**: 338–46.
- 100 Kaptein EM, Kletzky OA, Spencer CA, Nicoloff JT. Effects of prolonged dopamine infusion on anterior pituitary function in normal males. *J Clin Endocrinol Metab* 1980; **51**: 488–91.
- 101 Lee E, Chen P, Rao H, Lee J, Burmeister LA. Effect of acute high dose dobutamine administration on serum thyrotrophin (TSH). *Clin Endocrinol* 1999; **50**: 487–92.
- 102 Hamblin PS, Dyer SA, Mohr VS, et al. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. *J Clin Endocrinol Metab* 1986; **62**: 717–22.
- 103 Smith PJ, Surks MI. Multiple effects of 5,5'-diphenylhydantoin on the thyroid hormone system. *Endocr Rev* 1984; **5**: 514–24.
- 104 Ginoer D, Riahi M, Grun JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab* 1994; **79**: 197–204.
- 105 Hayslip CC, Fein HG, O'Donnell VM, Friedman DS, Klein TA, Smallridge RC. The value of serum antimicrosomal antibody testing in screening for symptomatic postpartum thyroid dysfunction. *Am J Obstet Gynecol* 1988; **159**: 203–09.
- 106 Toft AD. Thyroxine therapy. *N Engl J Med* 1994; **331**: 174–80.
- 107 Ross DS, Daniels GH, Gouveia D. The use and limitations of a chemiluminescent thyrotropin assay as a single thyroid function test in an out-patient endocrine clinic. *J Clin Endocrinol Metab* 1990; **71**: 764–69.
- 108 Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism. Role of triiodothyronine in pituitary feedback in humans. *N Engl J Med* 1987; **316**: 764–70.
- 109 Sawin CT, Geller A, Hershman JM, Castelli W, Bacharach P. The aging thyroid: the use of thyroid hormone in older persons. *JAMA* 1989; **261**: 2653–55.
- 110 Ayala A, Danese MD, Ladenson PW. When to treat mild hypothyroidism. *Clin Endocrinol Metab* 2000; **29**: 399–416.
- 111 Farthing MJ, Rees LH, Edwards CR, Byfield PG, Himsworth RL, Dawson AM. Thyroid hormones and the regulation of thyroid function in men with coeliac disease. *Clin Endocrinol (Oxf)* 1982; **16**: 525–35.
- 112 Azizi F, Belur R, Albano J. Malabsorption of thyroid hormones after jejunoileal bypass for obesity. *Ann Intern Med* 1979; **90**: 941–42.
- 113 Campbell NR, Hasinoff BB, Stalts H, Rao B, Wong NC. Ferrous sulfate reduces thyroxine efficacy in patients with hypothyroidism. *Ann Intern Med* 1992 **15**; **117**: 1010–13.
- 114 Singh N, Singh PN, Hershman JM. Effect of calcium carbonate on the absorption of levothyroxine. *JAMA* 2000; **283**: 2822–25.
- 115 Bell DS, Ovalle F. Use of soy protein supplement and resultant need for increased dose of levothyroxine. *Endocr Pract* 2001; **7**: 193–94.
- 116 Liel Y, Harman-Boehm I, Shany S. Evidence for a clinically important adverse effect of fiber-enriched diet on the bioavailability of levothyroxine in adult hypothyroid patients. *J Clin Endocrinol Metab* 1996; **81**: 857–59.
- 117 Chiu AC, Sherman SI. Effects of pharmacological fiber supplements on levothyroxine absorption. *Thyroid* 1998; **8**: 667–71.
- 118 Collins MT, Remaley AT, Csako G, Pucino F, Skarulis MC, Balow JE, Sarlis NJ. Increased levothyroxine requirements presenting as "inappropriate" TSH secretion syndrome in a patient with nephrotic syndrome. *J Endocrinol Invest* 2000; **23**: 383–92.
- 119 Kaptein EM, Grieb DA, Spencer CA, Wheeler WS, Nicoloff JT. Thyroxine metabolism in the low thyroxine state of critical nonthyroidal illnesses. *J Clin Endocrinol Metab* 1981; **53**: 764–71.
- 120 Isley WL. Effect of rifampin therapy on thyroid function tests in a hypothyroid patient on replacement L-thyroxine. *Ann Intern Med* 1987; **107**: S17–18.
- 121 Mandel SJ, Larsen PR, Seely EW, Brent GA. Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med* 1990; **323**: 91–96.
- 122 Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. *N Engl J Med* 2001; **344**: 1743–49.
- 123 Ram PA, Waxman DJ. Thyroid hormone stimulation of NADPH P450 reductase expression in liver and extrahepatic tissues.

- Regulation by multiple mechanisms. *J Biol Chem* 1992; **267**: 3294–301.
- 124 O'Leary KA, Li HC, Ram PA, McQuiddy P, Waxman DJ, Kasper CB. Thyroid regulation of NADPH:cytochrome P450 oxidoreductase: identification of a thyroid-responsive element in the 5'-flank of the oxidoreductase gene. *Mol Pharmacol* 1997; **52**: 46–53
- 125 Murkin JM. Anesthesia and hypothyroidism: a review of thyroxine physiology, pharmacology, and anesthetic implications. *Anesth Analg* 1982; **61**: 371–83.
- 126 Bolon M, Bastien O, Flamens C, Bouliou R. Prolonged sedation due to an accumulation of midazolam in an intensive care patient with hypothyroidism. *Eur J Clin Pharmacol* 2000; **56**: 771–72
- 127 Sarich TC, Wright JM. Hypothyroxinemia and phenytoin toxicity: a vicious circle. *Drug Metabol Drug Interact* 1996; **13**: 155–60.
- 128 Doherty JE, Perkins WH. Digoxin metabolism in hypo- and hyperthyroidism. Studies with tritiated digoxin in thyroid disease. *Ann Intern Med* 1966; **64**: 489–507
- 129 Shenfield GM, Thompson J, Horn DB. Plasma and urinary digoxin in thyroid dysfunction. *Eur J Clin Pharmacol* 1977; **12**: 437–43.
- 130 O'Connor P, Feely J. Clinical pharmacokinetics and endocrine disorders. Therapeutic implications. *Clin Pharmacokinet* 1987; **13**: 345–64.
- 131 Rice AJ, McIntosh TJ, Fouts JR, Brunk SF, Wilson WR. Decreased sensitivity to warfarin in patients with myxedema. *Am J Med Sci* 1971; **262**: 211–15
- 132 Quan ML, Pasieka JL, Rorstad O. Bone mineral density in well-differentiated thyroid cancer patients treated with suppressive thyroxine: a systematic overview of the literature. *J Surg Oncol* 2002; **79**: 62–69.
- 133 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**: 1249–52.
- 134 Keating FR, Parkin TW, Selby JB, Dickinson LS. Treatment of heart disease associated with myxedema. *Prog Cardiovasc Dis* 1961; **3**: 364–81.
- 135 Ladenson, PW. Problems in the management of hypothyroidism. In: Braverman LE, ed. *Diseases of the thyroid*, 2nd edition. Totowa: Humana Press, 2002.
- 136 Shakir KM, Turton D, Aprill BS, Drake AJ 3rd, Eisold JF. Anemia: a cause of intolerance to thyroxine sodium. *Mayo Clin Proc* 2000; **75**: 189–92.
- 137 Perk M, O'Neill BJ. The effect of thyroid hormone therapy on angiographic coronary artery disease progression. *Can J Cardiol* 1997; **13**: 273–76.
- 138 Sherman SI, Ladenson PW. Percutaneous transluminal angioplasty in hypothyroidism. *Am J Med* 1991; **90**: 367–70.
- 139 Ladenson PW, Levin AA, Ridgway EC, Daniels GH. Complications of surgery in hypothyroid patients. *Am J Med* 1984; **77**: 261–66.
- 140 Saravanan P, Chau W-F, 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. *Clinical Endocrinol* 2002; **57**: 577–85.
- 141 Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med* 1999; **340**: 424–29.
- 142 Sawka AM, Gerstein HC, Marriott MJ, MacQueen GM, Joffe RT. Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. *J Clin Endocrinol Metab* 2003; **88**: 4551–55.
- 143 Walsh JP, Shiels L, Lim EM, et al. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. *J Clin Endocrinol Metab* 2003; **88**: 4543–50.
- 144 McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab* 2001; **86**: 4585–90.
- 145 Ladenson PW, Singer PA, Levy EG, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Intern Med* 2000; **160**: 1573–75.
- 146 Chu JW, Crapo LM. The treatment of subclinical hypothyroidism is seldom necessary. *J Clin Endocrinol Metab* 2001; **86**: 4591–99.
- 147 Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly, microsomal antibodies as discriminant for therapy. *JAMA* 1987; **258**: 209–13.
- 148 Danese MD, Ladenson PW, Meinert CL, Powe, NR. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab* 2000; **85**: 2993–3001 .
- 149 Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. *Ann Intern Med* 2002; **137**: 904–14.
- 150 Brenta G, Mutti LA, Schnitman M, Fretes O, Perrone A, Matute ML. Assessment of left ventricular diastolic function by radionuclide ventriculography at rest and exercise in subclinical hypothyroidism, and its response to L-thyroxine therapy. *Am J Cardiol* 2003; **91**: 1327–30.
- 151 Hak AE, Pols HAP, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: The Rotterdam Study. *Ann Intern Med* 2000; **132**: 270–78.
- 152 Vanderpump MP, Tunbridge WM, French JM, et al. The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. *Thyroid* 1996; **6**: 155–60.
- 153 Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC. L-thyroxine therapy in subclinical hypothyroidism: a double-blind, placebo-controlled trial. *Ann Intern Med* 1984; **101**: 18–24.
- 154 Nystrom E, Caidahl K, Fager G, Wikkelso C, Lundberg PA, Lindstedt G. A double-blind crossover 12-month study of L-thyroxine treatment of women with "subclinical" hypothyroidism. *Clin Endocrinol (Oxf)* 1988; **29**: 62–76
- 155 Jaeschke R, Guyatt G, Gerstein H, et al. Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med* 1996; **11**: 744–49.
- 156 Monzani F, Gel Guerra P, Caraccio N. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Invest* 1993; **71**: 367–71
- 157 Danese MD, Powe NR, Sawin CT, Ladenson PW. Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. *JAMA* 1996; **276**: 285–92.
- 158 Bona M, Santini F, Rivolta G, Grossi E, Grilli R. Cost effectiveness of screening for subclinical hypothyroidism in the elderly: a decision-analytical model. *Pharmacoeconomics* 1998; **14**: 209–16.
- 159 Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med* 2001; **344**: 501–09.
- 160 Zwillich CW, Pierson DJ, Hofeldt FD, Lufkin EG, Weil JV. Ventilatory control in myxedema and hypothyroidism. *N Engl J Med* 1975; **292**: 662–65.
- 161 Bigos ST, Ridgway EC, Kourides IA, Maloof F. Spectrum of pituitary alterations with mild and severe thyroid impairment. *J Clin Endocrinol Metab* 1978; **46**: 317–25.
- 162 Michiels JJ, Schroyens W, Berneman Z, van der Planken M. Acquired von Willebrand syndrome type 1 in hypothyroidism: reversal after treatment with thyroxine. *Clin Appl Thromb Hemost* 2001; **7**: 113–15.
- 163 Holvey DN, Goodner, CJ, Nicoloff JT, Dowling JT. Treatment of myxedema coma with intravenous thyroxine. *Arch Intern Med* 1964; **113**: 89–100.
- 164 Yamamoto T, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. *Thyroid* 1999; **9**: 1167–74.