PREFACE

Most endocrine diseases can be treated successfully, and the patient's state of well-being can usually be improved. Not surprisingly, the earlier the diagnosis is made the more positive the clinical response. *Early Diagnosis and Treatment of Endocrine Disorders* focuses on early signs and symptoms of endocrine disorders and surveys the appropriate tests to document the diseases as well as current recommendations for therapy. Each chapter reviews the pathophysiology of the endocrine disease—important for understanding each disorder as well as the rationale for early therapy—and the basis for the early recognition and treatment of each condition.

Although the practicing endocrinologist is likely to be quite knowledgeable regarding many of these diseases, *Early Diagnosis and Treatment of Endocrine Disorders* includes treatment of those conditions only recently classified as endocrine disorders, such as polycystic ovarian syndrome, obesity, and hypogonadism. The book also provides new approaches that are urgently needed to slow the epidemic of type 2 diabetes, which should be an overriding concern for all clinicians.

Until now, no other endocrinology text has focused primarily on the details of early recognition and therapy of endocrine disorders. The information in *Early Diagnosis and Treatment of Endocrine Disorders* is presented in an orderly and easy-to-follow manner, which should greatly facilitate the early recognition of endocrine diseases by medical students, house staff, primary care physicians, and endocrinologists, the four groups of clinical personnel to which this book is specifically directed.

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2 Hypothyroidism

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CONTENTS

INTRODUCTION

Early diagnosis and treatment of hypothyroidism is the exception rather than the rule. Despite its high prevalence *(1–3)* and potential consequences, hypothyroidism is typically diagnosed in clinical settings at an advanced and often long-standing stage or is incidentally detected during a wide-ranging evaluation for nonspecific complaints. Even when hypothyroidism should be anticipated, such as in patients who have received neck irradiation *(4)* or amiodarone therapy *(5)*, its recognition is often delayed. Only in neonates, for whom universal thyroid function testing is mandated in most industrialized societies, is hypothyroidism identified early and treated promptly. Application of the principles of preventive medicine to hypothyroidism has occurred slowly, except in the worldwide efforts to prevent dietary iodine deficiency disorders, including endemic goiter, hypothyroidism, and cretinism *(6)*.

Preventive interventions are categorized by the stage of disease progression that they address. *Primary prevention* refers to interventions in patients without disease, in order to decrease its incidence. *Secondary prevention* aims to identify people early in a disorder's natural history. Achieved through screening and early intervention, secondary prevention attempts to avert disease morbidity,

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complications, and mortality. *Tertiary prevention* refers to amelioration of the course of established disease and decreasing recurrent episodes of an existing illness. The success of disease prevention may be assessed based on the benefit to treated individuals or, more often, from the perspective of cumulative benefit to an entire population. Evidence-based approaches to developing preventive practices, such as systematic literature reviews, meta-analyses, and decision and cost-effectiveness analyses, can predict whether screening is likely to achieve the desired outcome and result in more good than harm *(7)*.

PRIMARY PREVENTION OF HYPOTHYROIDISM

Primary prevention of disease focuses on risk factor identification and modification. Risk factors may stem from genetic predispositions and environmental exposures. There is a genetic predisposition to the most common cause of hypothyroidism, autoimmune thyroiditis, which occurs approximately tenfold more frequently in women than men and affects approximately one in seven female children of affected women. However, autoimmune thyroiditis appears to be a polygenic disorder *(8)* for which there can currently be only general predictions of disease risk. A number of other rare monogenic disorders causing hypothyroidism have been described. Familial combined pituitary hormone deficiencies *(9)* and isolated thyrotropin (TSH) deficiency *(10)* cause central hypothyroidism. The thyroid gland may be congenitally resistant to TSH action as the result of a mutation in the TSH receptor *(11)*, its related $G_s\alpha$ subunit *(12)*, or the TSH β-subunit *(13)*. Inherited defects in thyroid hormone biosynthesis caused by mutant thyroglobulin *(14)*, sodium-iodide symporter *(15)*, thyroid peroxidase *(16)*, and pendrin *(17)* genes can produce goiter with or without hypothyroidism. Although it is theoretically possible to detect these mutations prenatally with the goal of either preventing (primary prevention) or promptly detecting and treating (secondary prevention) congenital hypothyroidism, there is no report of this actually being done. Furthermore, the rarity of these disorders, and the ease with which hypothyroidism can be treated, makes the issue of primary prevention by genetic modification clinically inconsequential.

Several environmental influences are known to be associated with hypothyroidism, including severe dietary iodine deficiency, iodine excess, certain medications, cigarette smoke, and thyroidal irradiation. Dietary iodine deficiency is the most important of these factors epidemiologically *(18)*, affecting approximately 100 million people in underdeveloped (principally mountainous) regions around the world. The spectrum of iodine deficiency disorders includes goiter, maternal and fetal hypothyroidism, and cretinism; follicular thyroid cancer is also relatively more common in regions of mild to moderate iodine deficiency *(19)*. A full discussion of this problem and of strategies for eradication of iodine deficiency is beyond the scope of this chapter, but the topic has recently been reviewed elsewhere *(6,20)*.

Paradoxically, iodine excess is also a potential cause of hypothyroidism in two settings. First, a surfeit of iodine in the diet has been associated with higher incidences of hypothyroidism, in populations both with *(21)* and without autoimmune thyroiditis *(22)*. Experimental evidence in animal models supports this relationship *(23,24)*. Second, chronic ingestion of pharmacologic amounts of iodine in the diet or in medications can provoke hypothyroidism in individuals with underlying autoimmune thyroiditis. The most important sources of iodine in this context are dietary seaweed *(25)*, naturopathic food supplements containing kelp, and the drug amiodarone, which is 40% iodine by weight. In North America, more than 20% of individuals treated with amiodarone develop hypothyroidism *(5)*.

Cigarette smoke can impair thyroid function in women with iodine deficiency or autoimmune thyroiditis *(26–28)*. One study performed in a geographic region with low dietary iodine intake suggested that in women 23% of the risk for developing autoimmune thyroiditis-related hypothyroidism could be attributed to smoking *(29)*. Although a causal relationship between cigarette smoke and hypothyroidism has not been established, it has been postulated that increased circulating thiocyanate concentrations found in smokers may inhibit iodide transport and thyroid peroxidase-catalyzed iodide organification, precipitating hypothyroidism in patients with decreased thyroid gland reserve *(30–32)*. Active smoking can also exacerbate established partial hypothyroidism, inhibiting both thyroid hormone secretion and peripheral thyroid hormone action *(33)*. Consequently, smoking cessation in both populations and individual patients can contribute to both primary and secondary prevention of hypothyroidism.

Certain industrial toxins and medications cause hypothyroidism. Exposure to polybrominated biphenyls *(34)* and polychlorinated biphenyls *(35)* precipitates hypothyroidism by structural injury to the thyroid gland. Resorcinol has been reported to induce hypothyroidism in textile workers *(36)* and in a patient on chronic hemodialysis *(37)*. The adrenolytic agent aminoglutethimide can impair thyroid gland function *(38)*. The commonly used psychotropic medication lithium carbonate frequently causes hypothyroidism by inhibiting hormone release from the gland. Almost 40% of lithium-treated patients have transient TSH elevation, and approximately 10% have sustained hypothyroidism. Again, patients with underlying autoimmune thyroiditis are the most vulnerable. The immunomodulatory agent interferon-α can induce autoimmune thyroiditis and hypothyroidism, as well as hyperthyroid Graves' disease and a transiently thyrotoxic form of thyroiditis *(39)*. Avoidance of these toxic and medicinal exposures when possible, particularly in individuals with underlying autoimmune thyroiditis, represents a form of primary prevention for hypothyroidism.

Thyroidal irradiation—either by accidental or therapeutic radioactive iodine ingestion, or by external beam radiotherapy—can cause hypothyroidism, as well as benign and malignant thyroid neoplasms. Well-defined procedures, equip-

ment, and monitoring are important to prevent and detect accidental thyroid irradiation in the setting of research laboratories, nuclear medicine departments, and nuclear reactor facilities where workers could be exposed to radioiodine. Radioiodine has proved to be among the most dangerous radioisotopes released in nuclear power plant accidents, such as the Chernobyl nuclear power station disaster. The principal thyroid problem occurring in populations exposed as children has been thyroid cancer *(40)*, but hypothyroidism may also occur with greater frequency *(41)*. Stable iodine, as potassium iodide (KI), can effectively prevent significant thyroidal irradiation and its consequences if the compound is administered before or simultaneously with radioiodine exposure *(42)*. The potential benefits of KI, logistics of distribution, and potential side effects have been the basis for lively public debate. Similarly, thyroidal radioiodine exposure associated with the investigational use of radioimmunoglobulins to treat malignancies, such as hepatoma and Hodgkin's lymphoma *(43)*, can be prevented by administering stable iodine in advance. In patients given therapeutic 131-iodine therapy for diffuse and nodular toxic goiter, hypothyroidism is an unavoidable consequence of effective therapy in most patients *(44)*, so secondary prevention in the form of early detection is appropriate (*see* next section). External beam radiotherapy for malignancies of the head and neck commonly cause hypothyroidism, but shielding of the thyroid gland would limit the treatment field, so primary prevention is not feasible.

SECONDARY PREVENTION OF HYPOTHYROIDISM: *EARLY DIAGNOSIS AND TREATMENT*

Hypothyroidism fulfills the criteria for early detection, either through testing prompted by clinical suspicion (case finding) or by routine testing of all individuals in a defined group (screening). First, hypothyroidism is highly prevalent, particularly in clinically identifiable subsets of the population, such as older women. Second, its consequences can be clinically significant—whether one considers the morbidity of subsequent myxedema or the long-term vascular effects of associated hyperlipidemia—and these consequences can be avoided by early diagnosis and therapy. Third, clinical diagnosis alone can be inaccurate. Fourth, the diagnostic test, serum TSH measurement, can successfully identify individuals with early disease, so interventions are possible before development of adverse consequences of untreated disease. Importantly, the screening test is accurate, safe, and inexpensive. Furthermore, once hypothyroidism is diagnosed, treatment is also effective, safe, and inexpensive. For all the common causes of primary hyperthyroidism, measurement of a serum TSH can establish or exclude the diagnosis in a straightforward manner. For central hypothyroidism caused by hypothalamic or pituitary disorders, a serum free thyroxine measurement (FT4) is required.

Table 1
Indications to Test for Hypothyroidism

Symptoms and Signs

Fatigue	Muscle weakness	Bradycardia
Dry skin	Muscle cramps	Diastolic hypertension
Impaired memory	Deep tendon reflex delay	Hoarseness
Slowed mentation	Cold intolerance	Periorbital edema
Depression	Constipation	Weight gain

Risk factors for thyroid failure
- Autoimmune thyroiditis
  - Established serologic or tissue diagnosis
  - Diffuse goiter
  - Family history of autoimmune thyroid disease
  - Previous Graves' disease or painless (postpartum) thyroiditis
  - Personal or family history of associated autoimmune disorders (e.g., vitiligo, pernicious anemia, adrenal insufficiency, diabetes mellitus)
  - Interferon-α therapy
- Previous thyroid injury
  - Surgery
  - Radioactive iodine
  - External radiotherapy
- Postpartum status
- Drug impairing thyroid function
  - Lithium carbonate
  - Amiodarone
  - Aminoglutethimide
- Hypothalamic or pituitary disease, known or suspected
  - Other elements of hypopituitarism
  - Manifestations of a sellar mass (headache, decreased temporal vision, or diplopia).
  - Disorders known to cause hypothalamic or pituitary dysfunction (sarcoidosis or metastatic cancer).

Routine laboratory test abnormalities
- Hypercholesterolemia
- Anemia
- Hyponatremia
- Hyperprolactinemia
- ↑Creatine phosphokinase

Suspicion that a patient has hypothyroidism can be based on the presence of clinical findings, recognition of risk factors for thyroid gland failure, or abnormalities in routinely measured laboratory parameters (Table 1). Case finding is particularly important in populations at high risk of developing hypothyroidism,

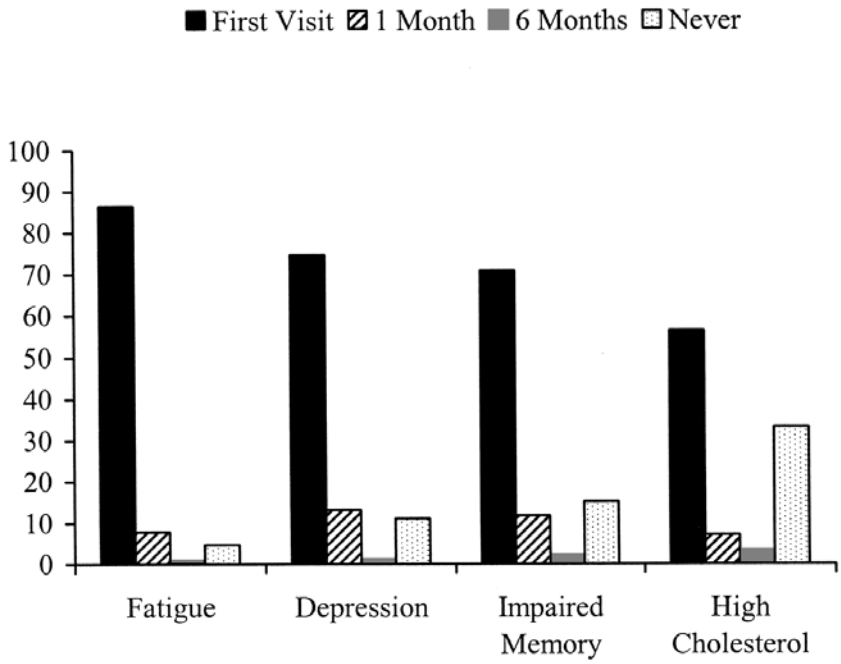

Fig. 1. TSH testing by physicians in hypothetical patients with symptoms and hypercholesterolemia potentially attributable to hypothyroidism. (Adapted from ref. *48*.)

e.g., patients who have been treated with lithium carbonate, amiodarone, or thyroid irradiation. Various strategies have been described for systematic follow-up of patients at risk of developing hypothyroidism after radioiodine therapy *(45–47)*.

The extent to which practicing physicians actually consider the diagnosis of hypothyroidism in patients with nonspecific clinical and laboratory findings is unknown. However, a recently published survey of 1721 primary care physicians revealed the frequency with which TSH testing was employed in the differential diagnosis of hypothetical patients who had potential manifestations of hypothyroidism—either one of three nonspecific symptoms or hypercholesterolemia *(48)* (Fig. 1). Seventy-five to 87% of physicians requested a serum TSH measurement, among other investigations, at the first visit in symptomatic patients, but only 56% of physicians ordered a TSH at the first visit in the hypercholesterolemic patient. Familiarity with managed care guidelines regarding the evaluation of hypercholesterolemic patients for secondary causes of hyperlipidemia was associated with a significantly higher rate of TSH testing.

The argument for population screening for hypothyroidism is particularly persuasive in neonates, since untreated thyroid hormone deficiency can lead to

irreversible abnormalities in neuropsychological development. The rationale and procedures for neonatal thyroid function screening have been reviewed elsewhere *(49)*. Guidelines for hypothyroidism screening in adults have been articulated by several professional societies *(50)* (Table 2). The cost-effectiveness of TSH screening every 5 years has been shown to be as favorable as, or even more favorable than, screening for hypertension, breast cancer, and hypercholesterolemia *(51)*.

TERTIARY PREVENTION OF HYPOTHYROIDISM: *AVOIDING COMPLICATIONS*

Potential complications of recognized hypothyroidism and its treatment are preventable with sustained thyroxine therapy and appropriate clinical and laboratory monitoring. Myxedema coma is a life-threatening syndrome of multisystem organ failure resulting from prolonged profound thyroid hormone deficiency, usually with superimposed sepsis, drug intoxication, or an ischemic vascular event *(52)*. Anecdotally, the hypothyroid patient who is elderly or has a history of previous noncompliance, other systemic illness, alcohol abuse, social isolation, and economic deprivation is at greatest risk. A second potential complication in hypothyroid patients who are suboptimally treated is persistence of risk factors for atherosclerosis. In this setting, the serum low-density lipoprotien cholesterol *(53)* concentration may remain elevated. In one small trial of patients with treated hypothyroidism and ischemic heart disease undergoing follow-up coronary catheterization after angioplasty, the patients with inadequately treated hypothyroidism (i.e., persistently elevated serum TSH concentrations) had a significantly higher rate of progression of their coronary arterial lesions than did patients on an optimal thyroxine replacement dose *(54)*.

For patients with treated hypothyroidism, tertiary prevention includes avoiding complications of thyroid hormone therapy. The first of these is iatrogenic thyrotoxicosis, which in one large population survey was found to occur in more than one-fifth of thyroid hormone-treated patients *(2)*. Appropriate dose selection and adjustment with TSH monitoring can avoid this problem *(55)*. Even the appropriate restoration of euthyroidism with thyroxine can also be associated with two unusual complications that should be anticipated and (when they are probable) prevented. First, ischemic heart disease can be exacerbated by thyroid hormone's positive chronotropic and inotropic actions, which have been reported to cause angina, myocardial infarction, dysrthythmia, and death *(56)*. Consequently, in patients with known coronary artery disease, prominent risk factors for it, or age older than 65 years, treatment should be initiated with a low dose of thyroxine, e.g., 0.025 mg/d. Second, institution of thyroid hormone replacement alone can provoke adrenal insufficiency in patients with associated borderline adrenal cortical function caused by autoimmune adrenalitis in patients with

Table 2
Clinical Practice Guidelines for Thyroid Function Testing and Screening

Guideline	*Methods used to analyze evidence*	*Organization, year*	*Summary of relevant recommendations*
American Thyroid Association guidelines for the detection of thyroid dysfunction *(58)*	Narrative literature review Expert opinion[a]	American Thyroid Association, 2000	Screening with serum thyrotropin (TSH) every 5 yr for women and men over age 35 yr Screening for individuals with symptoms and risk factors Addition of serum free thyroxine (FT4) when pituitary or hypothalamic disease suspected
Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism *(59)*	Narrative literature review Expert opinion[c]	Royal College of Physicians of London Society for Endocrinology, 1996	General testing of population unjustified Screening for congenital hypothyroidism Screening patients after thyroid surgery, radioactive iodine treatment, or longstanding lithium treatment; low threshold for screening patients on amiodarone Consideration of screening patients with type I diabetes during first-trimester pregnancy by measuring antithyroid antibody Biochemical confirmation of hypothyroidism with serum TSH and total thyroxine (T4) or FT4

Laboratory medicine practice guidelines for the diagnosis and monitoring of thyroid disease testing *(60,61)*	Narrative literature review Expert opinion[c]	American Association of Clinical Chemists American Association of Clinical Endocrinologists American Thyroid Association Endocrine Society National Academy of Clinical Biochemistry, 1990 (update in progress)	Serum TSH for evaluating patients with stable thyroid status; FT4 in patients during first 2–3 mo treatment of thyroid dysfunction Prepregnancy or first-trimester pregnancy screening with serum TSH In patients receiving amiodarone, baseline TSH, thyroid peroxidase antibody, FT4, and FT3; biannual screening of TSH, FT4, and FT3 Assessment of thyroid status (using FT4 or T4 and TSH) in hospitalized patients, when clinical suspicion high
Newborn screening for congenital hypothyroidism: recommended guidelines *(62)*	Narrative literature review Expert opinion[c]	American Academy of Pediatrics, 1993	Screening within first week of life either with filter paper blood spot primary T4 and backup TSH; or primary TSH with backup T4; or combined primary TSH and T4 Cord serum measurements in offspring of mothers with thyroid abnormalities Confirmatory serum measurements, serial serum T4 and TSH, as well as consideration of thyroid scan in infants with abnormalities Confirmation after age 3 yr with discontinuation of levothyroxine for 30 d, followed by serum TSH, T4

(continued)

Table 2 *(continued)*

Guideline	*Methods used to analyze evidence*	*Organization, year*	*Summary of relevant recommendations*
Periodic Health Examinations: Summary of AAFP Policy Recommendations and Age Charts *(63)*	Systematic literature review performed by U.S. Preventive Services Task Force Expert opinion[c]	American Academy of Family Physicians, 1996, 2001	Screening patients over age 60 yr recommended
Screening for congenital hypothyroidism *(64)*	Systematic literature review[b]	Canadian Task Force on Preventive Health Care, 1994, 1998	Good evidence to support screening on all newborns during first week of life using routine TSH followed by T4 if necessary
Screening for congenital hypothyroidism *(65)*	Systematic literature review[b]	U.S. Preventive Services Task Force, 1996	Good evidence to support screening on all newborns, including those born at home, optimally between d 2 and 6 Choice of screening test determined by state requirements
Screening for thyroid disease *(66)*	Systematic literature review Meta-analysis of observational trials[b]	American College of Physicians- American Society of Internal Medicine, 1997	Screening women older than 50 yr with a sensitive TSH; FT4 when TSH is undetectable or ≥ 10 mU/L Poor evidence to support screening women younger than age 50 and men Careful follow-up of patients with mild hypothyroidism
Screening for thyroid disease *(67)*	Systematic literature review[b]	U.S. Preventive Services Task Force, 1996	Fair evidence to support exclusion of routine screening of thyroid disease in asymptomatic adults in periodic health examination

			Despite insufficient evidence, recommend low threshold for screening with serum TSH in high-risk patients, including elderly, postpartum women, and persons with Down's syndrome
Screening for thyroid disorders and thyroid cancer in asymptomatic adults *(68)*	Systematic literature review adapted from U.S. Preventive Services Task Force[b]	Canadian Task Force on Preventive Health Care, 1994, 1999	Poor evidence to support screening of asymptomatic adults High level of clinical suspicion should be maintained in perimenopausal and postmenopausal women
Subclinical hypothyroidism during pregnancy *(69)*	Narrative literature review Expert opinion[c]	American Association of Clinical Endocrinologists, 1999	Routine screening with serum TSH reasonable early in pregnancy Screening with TSH recommended in women considering pregnancy Screening with serum TSH recommended in pregnant women with: goiter, antithyroid antibodies, family history of thyroid disease, autoimmune endocrine disease, symptoms suggestive of hypothyroidism, history of levothyroxine treatment

[a]Self-funded.
[b]Governmental funding.
[c]Not specified.

autoimmune thyroiditis (*see* next paragraph) and in patients with hypopituitarism. Therefore, in patients with clinical features suggesting primary adrenal insufficiency (e.g., weight loss, hyperpigmentation, nausea, or vomiting) or pituitary disease (e.g., visual field deficits, diplopia, or hypogonadism), the possibility of hypoadrenalism should be excluded by adrenocorticotropic hormone stimulation testing.

Although autoimmune thyroiditis is not a complication of hypothyroidism *per se*, patients affected with it are also at risk of developing a relatively small set of associated autoimmune disorders. The polyglandular autoimmune syndrome type II includes hypothyroidism, primary adrenal insufficiency, and type I diabetes *(57)*. Less commonly, hypothyroidism may occur in the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (or polyglandular autoimmune syndrome type I). Autoimmune thyroid disorders are associated with increased risk of developing pernicious anemia and gastric achlorhydria caused by intrinsic factor and parietal cell autoimmunity. Patients with autoimmune thyroiditis should be monitored for vitamin B12 deficiency with periodic complete blood counts and, whenever the disorder is seriously suspected, serum vitamin B12 measurement. Vitiligo, leukotrichia (prematurely gray hair), and alopecia areata have also been associated with autoimmune thyroiditis; although these disorders are often distressing, their prevention is not currently possible.

In conclusion, hypothyroidism occurs commonly, generates morbidity and mortality, and may be prevented at all stages of disease progression. Once hypothyroidism has been identified and treated with thyroxine, special attention to optimal dose management, complications of therapy, and the potential development of associated diseases can improve the clinical course and quality of life for affected individuals.

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