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Nonthyroid Influences on Thyroid Function

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Nonthyroid Influences on Thyroid Function

INTRODUCTION

In the majority of cases, abnormal results on thyroid function testing are traced to an underlying primary thyroid disease, most commonly hypothyroidism resulting from autoimmune destruction of the thyroid gland or hyperthyroidism resulting from Graves' disease, toxic multinodular goiter, or exogenous thyroid hormone administration. However, many other factors, both exogenous and endogenous, may affect thyroid function and should be considered in the differential diagnosis.

Worldwide, the most frequent cause of thyroid dysfunction remains iodine deficiency, resulting in endemic goiter and cretinism.¹ Lesser degrees of iodine deficiency, common even in the developed world, may also affect the thyroid, contributing to the development of multinodular goiter² and altering the spectrum of thyroid cancer toward the more aggressive follicular phenotype.³ At the opposite end of the spectrum, excessive iodine intake also may trigger thyroid disease. In the United States, iodine-induced thyroid disease is seen increasingly in the context of cardiac arrhythmia treated with amiodarone. In addition to containing large amounts of inorganic iodide, amiodarone may have a direct impact on the deiodination of thyroid hormones, altering triiodothyronine (T₃) bioavailability and complicating the interpretation of thyroid function tests.⁴

Circulating thyroid hormone concentrations usually are stable and controlled within a very narrow range that remains essentially unchanged from early childhood. However, conditions unrelated to the thyroid may alter thyroid hormone production and metabolism, sometimes in complex ways, even in the absence of thyroid disease.⁵ This so-called *nonthyroidal illness* (also known as *euthyroid sick syndrome*) accompanies many conditions that may occur at all stages of life. The severity of the disruption of thyroid hormones correlates with the severity of illness and in some conditions may predict mortality.⁵ Whether intervention directed at the pituitary-thyroid axis might affect outcomes in these conditions remains unknown, as it is unclear whether the alterations in thyroid hormones represent a physio-

logic adaptation to disease or a separate pathologic process contributing to poor outcomes.

The ability to accurately determine the thyroid status of an individual has been dramatically advanced in the last 20 years by the routine availability of sensitive and accurate tests for all of the major hormones in this system. Increasingly, thyroid function tests have been used as screening tests for patients with minimal or absent symptoms of thyroid disease.⁶ Accurate interpretation of these tests depends on an intact feedback mechanism among the thyroid, pituitary, and hypothalamus. Alterations in sensitivity to thyroid hormone, which can result from inherited abnormalities of the thyroid hormone receptor, cause a physiologic adaptation that results in increased production of thyroid hormone under the stimulation of thyroid-stimulating hormone (TSH).⁷ A new steady state arises in which circulating thyroid hormone concentrations are elevated above their normal ranges but the TSH level is normal, reflecting the true thyroid status of the patient. These patients generally are euthyroid but their increased circulating thyroid hormone concentrations may be easily interpreted as hyperthyroidism. By recognizing this syndrome of thyroid hormone resistance, inappropriate therapy can be avoided.⁷

IODINE-INDUCED THYROID DISEASE

Although iodine deficiency is common worldwide, it is rare in most of the developed world, including the United States. Nevertheless, it remains the most common cause of mental retardation worldwide, a condition that continues to frustrate the best efforts of public health officials. Although the remedy of population-based iodine supplementation is cheap, simple, and effective, prevention remains an elusive goal.¹

In contrast, iodine excess is largely a problem of the developed world, often reflecting the consequences of iodine supplementation in a population previously deficient in iodine or the impact of individual choice or medical necessity. Among the most common causes of excessive iodine intake is the use of the antiarrhythmic