

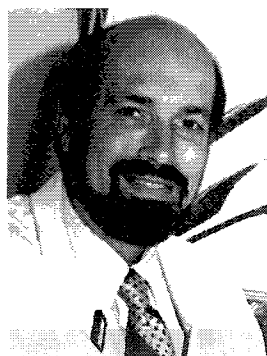
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LABORATORY AIDS IN THE DIAGNOSIS OF HYPOTHYROIDISM

MARTIN I. SURKS, M.D., F.A.C.P.



Martin I. Surks, M.D., F.A.C.P.
Head, Division of
Endocrinology & Metabolism
Montefiore Hospital and Medical Center
Associate Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Clinicians are fortunate that the recent explosive growth in our knowledge of the physiology and pathophysiology of many endocrine disorders has been rapidly translated into development of specific laboratory tests for the diagnosis and management of endocrine diseases. Nowhere is this more evident than in the laboratory diagnosis of hypothyroidism. Radioimmunoassay methods for direct measurement of the plasma concentration of the thyroid hormones, L-thyroxine (T_4) and L-triiodothyronine (T_3), and of the thyroid-stimulating hormone (TSH) which is secreted by the anterior pituitary have been introduced and are now widely employed.¹⁻³ The direct measurement of the plasma concentration of these hormones makes the laboratory diagnosis of hypothyroidism much simpler and more precise than ten years ago. It should also be far easier for the physician to detect early hypothyroidism and thus substantially to improve the quality of life of affected patients. This article will focus on those tests which are currently used for the diagnosis of hypothyroidism in the adult, describe their physiologic rationale, and attempt to provide a practical guide for the selection of the appropriate tests.

The hallmark of hypothyroidism, regardless of etiology, is a decrease in the secretion of thyroid hormones. This is reflected by a decrease in the plasma concentration of T_4 and T_3 (Figure 1, Table 1). In advanced hypothyroidism, the concentration of both plasma T_4 and T_3 is decreased to below the normal range, less than $5.0 \mu\text{g}/\text{dl}$ for T_4 and less than $90 \text{ ng}/\text{dl}$ for T_3 (Figure 1, Column C). In early hypothy-

roidism, only plasma T_4 may be decreased to below normal (Figure 1, Column B), and, in some cases, the concentration of T_4 and T_3 may be minimally decreased from the patient's own normal value but still remain within the normal range (Figure 1, Column A). Hypothyroidism is frequently a slowly progressive disease in which the thyroidal state changes from normal to one of marked hormone deficiency (Figure 2). With the use of the appropriate diagnostic tests an accurate diagnosis can be established at any time during the development of the disease. This will be discussed in greater detail later.

Plasma T_4

In the patient with symptoms and signs of hypothyroidism, the clinical diagnosis can generally be confirmed rapidly and simply by measurement of plasma T_4 . When the measurement is made by competitive-protein-binding⁴ or radioimmunoassay methods, it is specific for T_4 . A high concentration of inorganic iodide or radiopaque contrast agents used in diagnostic radiology will not result in spurious elevations in T_4 concentration as was the case when T_4 was measured as protein-bound iodine or T_4 -iodine by column. The latter methods are now largely obsolete.

A decrease in plasma T_4 confirms the diagnosis of hypothyroidism as long as the binding of T_4 by plasma thyroxine-binding proteins is not decreased as a result of other causes. Thyroid hormones are tightly bound to specific binding proteins in the plasma.⁵ If the binding of T_4 by plasma

protein is decreased, the concentration of total T_4 will fall proportionately but the free thyroxine concentration and the physiological impact of the hormone will be normal. The strength of binding by plasma proteins is assessed by tests which use radioactively labeled T_4 and T_3 . The T_3 resin uptake (T_3RU) is inversely proportional to the strength of binding. When plasma protein binding is decreased, the T_3RU is increased. The product of the total T_4 and T_3RU yields the free T_4 index, a value which is proportional to the free T_4 concentration. A great deal of confusion has arisen because of the use of isotopically labeled T_3 in measurements of the strength of plasma protein binding such as the T_3RU . The T_3RU has nothing to do with the T_3 radioimmunoassay which measures plasma total T_3 concentration.

In hypothyroidism itself, the concentration of one of the binding proteins is increased and plasma T_4 is low. These factors result in a larger than normal number of available binding sites for T_4 and an increase in the overall intensity of T_4 binding by the plasma proteins. The T_3 resin uptake is therefore decreased, and the free thyroxine concentration is particularly low.

Plasma T_4 concentration is sometimes decreased in patients suffering from a variety of nonthyroidal diseases.^{6,7} Although plasma T_4 concentration may be decreased, this group of patients can be readily distinguished from patients with hypothyroidism by measurement of free T_4 . In contrast to hypothyroid patients, individuals with nonthyroidal diseases have free T_4 concentrations which are either normal or modestly increased. In nonthyroidal diseases the decrease in plasma T_4 concentration is due primarily to decreased plasma T_4 binding and does not reflect reduced thyroidal function. Similarly, decreased plasma protein binding may occur in patients with a hereditary decrease in thyroxine-binding globulin (TBG). Such patients have low plasma T_4 concentrations, normal free T_4 concentrations, and are clinically euthyroid.^{5,8}

Plasma T_3

It is somewhat paradoxical that although T_3 appears to affect most of the biological activity of the thyroid hormones, low plasma T_3 concentration does not necessarily connote a clinical hypothyroidism. Like plasma T_4 concentration, plasma T_3 concentration may fall below the normal range (90 to 180 ng/dl) because of decreased plasma-binding of T_3 in euthyroid patients with nonthyroidal diseases.⁷ In addition, it is now well documented that the plasma T_3 concentration may decrease with age.^{7,9} Thus, individuals in the seventh to ninth decades of life frequently have plasma T_3 concentrations between 70 to 90 ng/dl without hypothyroidism. Plasma T_3 may also be decreased without hypothyroidism in a variety of clinical settings including acute and chronic nonthyroidal diseases,⁷ fasting,¹⁰ and administration of pharmacological doses of glucocorticoids.¹¹ The finding of a decreased plasma T_3 concentration which cannot be explained by decreased plasma T_3 binding or advanced age in euthyroid sick patients is often termed the "low T_3 syndrome." Low T_3 values in patients with nonthyroidal disease are even more common than low T_4 values in such patients. The decrease in plasma T_3 concentration in patients with the "low T_3 syndrome" is greater than can be

CONTINUUM OF CHANGES IN PLASMA T_4 , T_3 AND TSH CONCENTRATIONS DURING DEVELOPMENT OF HYPOTHYROIDISM

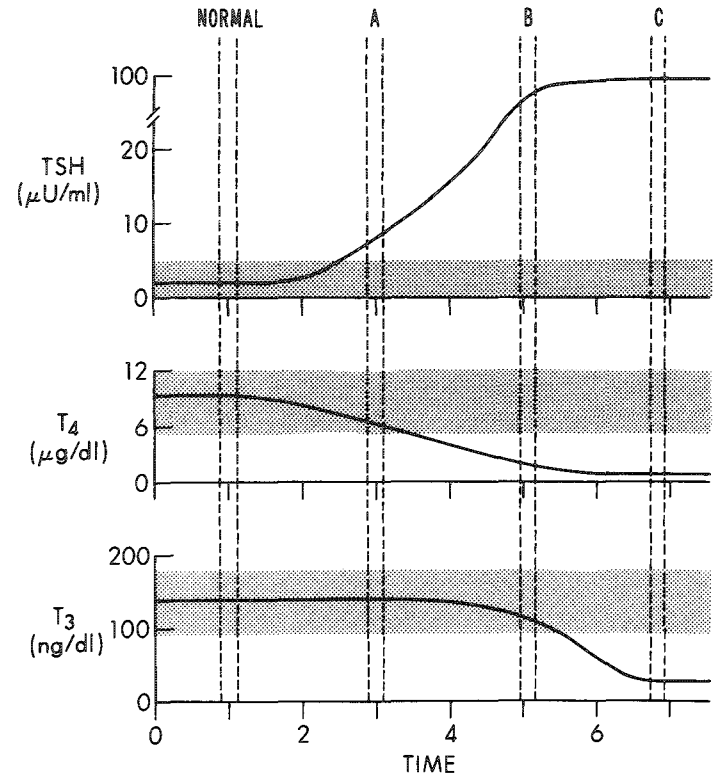


Figure 1. Continuum of changes in plasma T_4 , T_3 and TSH concentrations during development of hypothyroidism. Normal range for each hormone illustrated by the shaded area: TSH, undetectable to 5.0 μ U/ml; T_4 , 5.0 to 12.0 μ g/dl; and T_3 , 90 to 180 ng/dl. The vertical dashed lines indicate time intervals in which different constellations of laboratory findings may be found during the development of hypothyroidism. The units of the time scale are arbitrary and could represent weeks, months, or years for individual patients.

accounted for by decreased plasma protein binding of the hormone and probably results from a decrease in production of T_3 from T_4 during T_4 metabolism. We do not yet understand why patients with the "low T_3 syndrome" remain euthyroid despite very low plasma T_3 concentration. Nevertheless, the fact that plasma T_3 concentration may be sharply decreased in a large number of apparently euthyroid patients with nonthyroidal disease and in advanced age makes the finding of a decrease in plasma T_3 concentration too nonspecific to serve as a useful routine diagnostic test for hypothyroidism.

A number of other tests have been used to aid in the diagnosis of hypothyroidism. These include assessment of the function of the thyroid gland itself with radioiodine and measures which reflect the biological activity of the thyroid hormones, such as serum cholesterol concentration and oxygen consumption. Since confirmation of clinically suspected hypothyroidism can be made readily in most patients by the direct measurement of T_4 or T_3 or both concentrations in plasma, these tests are now only infre-

PITUITARY-THYROID RELATIONSHIPS IN EUTHYROID AND HYPOTHYROID PATIENTS

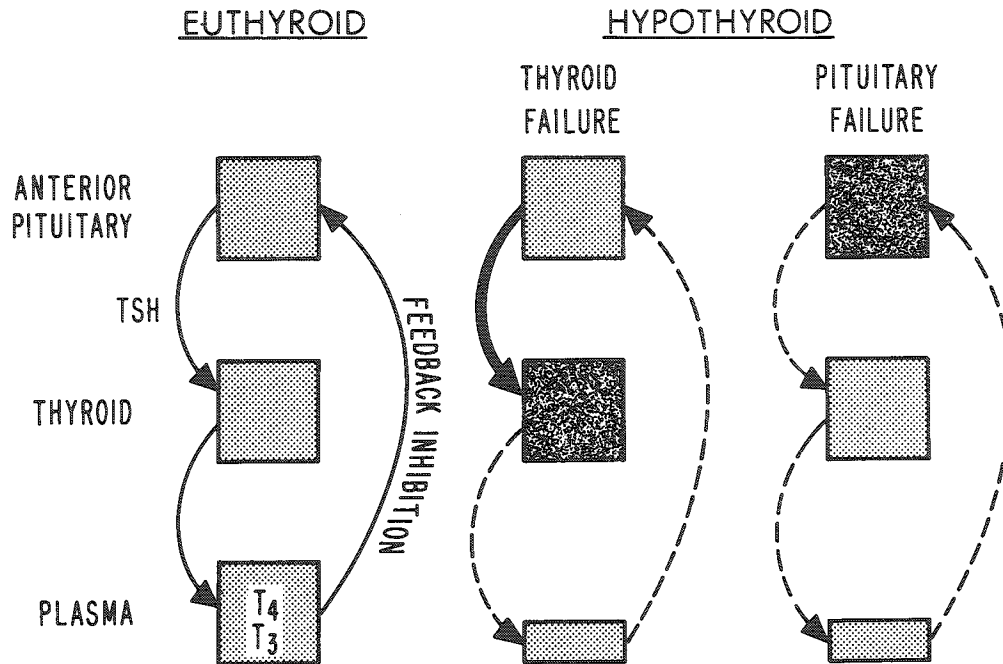


Figure 2.
Pituitary-thyroid relationships in euthyroid and hypothyroid patients.

quently used. Although hypothyroidism is accompanied by an increase in the serum cholesterol concentration, cholesterol may also be elevated in familial hyperlipidemias, diabetes mellitus and many other metabolic disorders. An increased serum cholesterol concentration alone is consistent with but clearly not diagnostic of hypothyroidism. In hypothyroid patients with elevated cholesterol concentrations, clinicians should make certain that the cholesterol concentration decreases to the normal range after adequate hormonal replacement therapy in order to exclude other contributing causes for the cholesterol elevation. The level of the enzyme creatine phosphokinase may also be elevated in hypothyroidism, but again, this increase is not specific.

Radioiodine Test

A decrease in the 24-hour thyroidal radioiodine uptake also occurs in patients with hypothyroidism, but there is now a large overlap in values for radioiodine uptake between hypothyroid patients and normal individuals. This is the case because the intake of iodides from dietary sources and medications has increased greatly in the last ten years.¹² Increased dietary iodine results in a greater extrathyroidal iodide pool and a lower 24-hour thyroidal radioiodine uptake in euthyroid patients. Although the thyroidal radioiodine uptake is now generally considered to be a poor discriminator for hypothyroidism, *in vivo* tracer iodine may still be diagnostically useful in specifying mechanisms in patients with hereditary or acquired abnormalities of enzymatic steps

necessary for the biosynthesis and release of thyroid hormones. Thus, hypothyroidism may be associated with the ingestion of large amounts of inorganic iodide. This may be accompanied by thyroid enlargement and increased thyroidal uptake of radioiodine which is subsequently not converted to hormone.¹³ For most patients with hypothyroidism, however, the inconvenience, expense and radiation exposure of the 24-hour radioiodine uptake test can be avoided by reliance upon the results of serum hormone measurements.

It is important to ascertain whether thyroid hormone deficiency results from intrinsic disease of the thyroid gland itself or from a decrease in secretion of TSH from the anterior pituitary. In the great majority of patients, hypothyroidism is due to disease of the thyroid gland. However, failure to identify the pituitary or hypothalamus as the cause of hypothyroidism may lead to serious consequences for the patient. Conversely, an early diagnosis of the anterior pituitary or hypothalamic disease causing hypothyroidism may lead to effective treatment with arrest of the disease process, prevention of visual loss and, in some instances, preservation of life.

Plasma TSH

In past years, clinicians distinguished between a thyroidal and pituitary-hypothalamic etiology of hypothyroidism by demonstration of a normal response of the thyroid gland to administered TSH. A patient with hypothyroidism

who had a normal thyroidal response to TSH with increased radioiodine uptake was presumed to have a pituitary or hypothalamic basis of the hypothyroidism. The availability of a direct measurement for plasma TSH concentration by radioimmunoassay³ has supplanted this tedious TSH stimulation test.

The relationship of pituitary TSH secretion and plasma thyroid hormone concentration in the normal setting and in hypothyroidism is shown in Figure 2. In the normal individual (left panel), pituitary TSH secretion maintains thyroidal synthesis and secretion of thyroid hormones. The system is kept in balance by a very sensitive negative-feedback between plasma thyroid hormone concentrations and pituitary TSH secretion.¹⁴ Even a small decrease in plasma thyroid hormone concentration results in an increase in TSH secretion and concentration in plasma.^{15,16} Thus, hypothyroidism due to disease of the thyroid gland is always associated with an increase in plasma TSH concentration (Figure 2, middle panel). In the relatively few patients who have hypothyroidism as a result of decreased pituitary secretion of TSH, the plasma TSH concentration is either undetectable or in the low normal range (Figure 2, right panel). Limitations in the sensitivity of the TSH radioimmunoassay unfortunately do not allow reliable distinctions between low normal and absent levels of TSH. With primary pituitary-hypothalamic disease as the cause of hypothyroidism, however, TSH is never elevated. Thus, measurement of TSH concentration in a single plasma sample enables the clinician to determine whether thyroidal failure or defective function of the pituitary or hypothalamus is responsible for the hypothyroid state.

Patients with primary hypothyroidism with an elevation in plasma TSH concentration have a marked increase in the

release of TSH after administration of thyrotropin-releasing hormone (TRH).^{17,18} Since the elevation in baseline concentration of TSH itself confirms the diagnosis of hypothyroidism, TRH does not have a place in the routine diagnosis of hypothyroidism. TRH testing may occasionally be useful in localizing the site of disease in relatively few patients with hypothyroidism secondary to failure of TSH secretion.

Since the great majority of patients with hypothyroidism has disease of the thyroid gland itself, the plasma TSH measurement has become an extremely useful method both for identifying patients with hypothyroidism and for distinguishing between intrinsic thyroid disease and pituitary deficiency.^{19,20} In the author's clinic, plasma TSH as well as plasma T₄ concentrations and plasma binding measurements are carried out in a single blood sample obtained after clinical evaluation has raised the suspicion of hypothyroidism. The finding of an elevation in plasma TSH concentration and decrease in plasma T₄ concentration confirms hypothyroidism due to intrinsic disease of the thyroid gland (Table 1). An undetectable or low normal TSH concentration with decreased plasma total and free T₄ strongly suggests that hypothyroidism is due to pituitary-hypothalamic factors. Additional endocrine, neurologic and radiologic studies are then indicated to define the underlying process in greater detail.

The determination of plasma TSH concentration is also useful in the diagnosis of patients with the low T₃ syndrome. Such patients may have decreased plasma T₄ as well as T₃ (Table 1) but plasma TSH generally remains within the normal range.⁷ Occasionally intermediate values of TSH may be observed (5 to 12 μU/ml). Since the precise level of TSH which delineates hypothyroidism has not been established,

TABLE 1. Plasma Hormone Concentration and Binding.

	Total Hormone			Plasma Protein Binding*	Free Hormone		
	T ₄ (μg/dl)	T ₃ (ng/dl)	TSH (μU/ml)		Free T ₄ (ng/dl)	Free T ₄ ** Index	Free T ₃ ** Index
Normal Range	5-12	90-180	0-10		1-2.3	5-12	90-180
Hypothyroidism							
Thyroid disease	↓	↓	↑	↑	↓	↓	↓
Pituitary-Hypothalamic disease	↓	↓	N or ↓	↑	↓	↓	↓
Low T₃ syndrome							
Nonthyroidal disease	N or ↓	↓	N	↓	N or ↑	N or ↓	↓

Changes in hypothyroidism are representative of those patients with severe disease.

of the total hormone and an inverse measure of protein binding. The range of the indexes is adjusted to correspond to the range of the total hormone in plasma.

*Plasma protein binding is inversely related to the T₃ resin uptake (T₃RU) or the free thyroxine or dialyzable fraction as determined by equilibrium dialysis.

The normal range for all measurements are those from the author's institution. These values may vary slightly among different medical centers or commercial laboratories.

**Both free T₄ and free T₃ indexes are measures designed to be proportional to the free T₄ and free T₃ concentrations respectively and represent the product

we choose not to make a diagnosis of hypothyroidism in such patients. TSH values greater than 15 μ U/ml, however, are clearly diagnostic of primary thyroidal failure.

Progressive Thyroid Failure

The feedback inhibition of TSH secretion by thyroid hormones (Figure 2) is sufficiently sensitive to permit the diagnosis of subclinical hypothyroidism. As small a decrease in plasma T_4 concentration as 1 μ g/dl or 20 ng/dl of T_3 can result in a measurable increase in plasma TSH concentration.^{15,16} An increase in plasma TSH can therefore occur with only a minimal decrease in thyroid function, with a plasma T_4 and T_3 concentration state within the value of normal population range, and in the absence of clinical symptoms. This constellation of laboratory findings (Figure 1, Column A) is probably the earliest indication of thyroidal deficiency. As these changes are probably progressive in most cases, they should prompt the physician to follow his patient closely, watching for the development of clinically symptomatic hypothyroidism. Alternatively, he may wish to initiate hormonal replacement therapy in the anticipation of progressive thyroid failure. The next stage in the continuum of thyroid failure is a decrease in plasma T_4 concentration to below the lower limit of normal, maintenance of plasma T_3 concentration within the normal range, and an elevation in the serum TSH (Figure 1, Column B). At this stage, the patient most often still remains clinically euthyroid, and the thyroid gland, under the influence of the very high plasma TSH concentration, preferentially synthesizes and secretes T_3 . This is in contrast to the normal thyroid gland which secretes predominantly T_4 .^{21,22} With further progression of thyroid disease, T_3 secretion also decreases and plasma T_3 concentration falls below the normal range (Figure 1, Column C). The fall in plasma T_3 concentration is accompanied by development of the typical symptoms and signs of hypothyroidism.

The ability to document subclinical hypothyroidism by finding an elevation in plasma TSH concentration also enables clinicians to use measurements of plasma TSH to screen patients at high risk for the development of hypothyroidism. The finding of an elevation in plasma TSH concentration in such patients documents the presence of subclinical hypothyroidism and enables the initiation of hormonal replacement therapy before the disease becomes clinically significant. In the author's clinic, euthyroid patients who have chronic thyroiditis or who have had radioiodine or surgical therapy for Graves' disease are recalled annually for clinical evaluation and measurement of plasma T_4 and TSH concentrations. Routine screening of these populations at high risk for the development of hypothyroidism is especially important since hypothyroidism characteristically develops insidiously. Indeed, patients may suffer years of discomfort and disability before they or their physicians are alerted to the possible presence of this disease. Judicious use of the available highly specific measurements of the concentration of thyroid hormones and TSH in plasma should lead to the diagnosis and management of hypothyroidism before the clinical manifestations of the disease become significant.

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