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Contemporary Approach to Thyroid Disease Emphasizing Use of High-Sensitivity Thyrotropin Assays*

Carolyn S. Feldkamp, PhD,* and Malachi J. McKenna, MD†

Capabilities of new high-sensitivity immunoradiometric assays for thyroid-stimulating hormone (TSH-IRMA) to distinguish among hypothyroid, euthyroid, and hyperthyroid subjects and patient groups with low TSH for nonthyroidal causes suggested an algorithmic approach (directed TSH) to the evaluation of patients with suspected thyroid disease. Utilizing the algorithm, a TSH-IRMA result outside normal limits (0.5 to 5.0 mU/L) generates follow-up tests on the same sample. The interpretation of thyroid function tests (TSH-IRMA, thyroxine, resin uptake, free thyroxine index) and associated studies in the context of different clinical settings is reviewed. The approach is a cost-effective and efficient utilization of laboratory services. (Henry Ford Hosp Med J 1991:39:25-9)

We are living in an era of cost containment necessitating appropriate utilization of fixed resources. Tests to evaluate thyroid function have proliferated over the last three decades and are the highest volume assays performed in the Ligand Assay Laboratory at Henry Ford Hospital. In the last few years the analysis of thyroid-stimulating hormone (TSH) has been improved by the introduction of new technologies and the use of monoclonal antibodies. After evaluating a number of kits that measure TSH by the immunoradiometric methodology (TSH-IRMA), we introduced a new assay to replace conventional radiiodinunoassay (TSH-RIA) in 1987. The use of this improved TSH assay as well as the implementation of a Pathology Department Laboratory Information System with enhanced capabilities has led us to propose an algorithm which diminishes the frequency of unnecessary thyroid testing. This approach to the initial evaluation of thyroid disease, incorporating the algorithm, has been studied in different clinical settings: states of thyroid dysfunction, as well as thyromegalies, diffuse or nodular.

Patterns of Thyroid Testing

We reviewed the ordering patterns of thyroid function tests at Henry Ford Hospital and satellites in an effort to optimize laboratory testing while simultaneously maintaining quality medical care. Table 1 shows the usual frequency of thyroid tests ordered. An evaluation of the distributions of test results in the combined inpatient and outpatient population (Figs 1 and 2) revealed that in approximately 1,000 tests nearly 78% had normal TSH-IRMA and 84% had normal thyroxine (T₄). Approximately one-third of all orders included both TSH-IRMA and T₄. The current ordering pattern suggests that, departing from the past recommendations to include T₄, triiodothyronine (T₃) resin uptake (RU) ratio, and free thyroxine index (FTI) (T₄ x RU) for initial diagnosis, physicians now frequently order TSH-IRMA in addition for screening, diagnosis, and follow-up. Retrospective laboratory data are not adequate to evaluate whether the test combinations being used are appropriate for all clinical situations.

Traditional Approach to Thyroid Function Testing

A number of laboratory tests have been available for many years: total T₄; T₃ resin uptake or RU ratio (resin uptake/normal resin uptake); calculated FTI based on total T₄ and RU; total T₃; free T₄; free T₃; basal TSH-RIA; and TSH-RIA response to thyrotropin-releasing hormone (TRH) stimulation. In the past the most common approach to evaluation of thyroid function was to measure total T₄ and RU, the latter adjusting for the effects of abnormalities in binding proteins. In equivocal cases of hyperthyroidism, the TSH response to TRH was measured, with a

<table>
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<tr>
<th>Test</th>
<th>Number/Month</th>
<th>Frequency</th>
</tr>
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<tbody>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>2,800</td>
<td>7 days/week</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>2,500</td>
<td>Monday-Friday</td>
</tr>
<tr>
<td>Resin uptake</td>
<td>1,000</td>
<td>Monday-Friday</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>150</td>
<td>1 day/week</td>
</tr>
</tbody>
</table>

Table 1

Current Status of Thyroid Testing at Henry Ford Hospital

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*Parts of this paper were originally presented at Medical Grand Rounds, Henry Ford Hospital, November 1989.
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lack of response being indicative of thyrotoxicosis. In instances of suspected hypothyroidism, a single TSH-RIA was sufficient to make a diagnosis of primary hypothyroidism; a TRH stimulation was sometimes required to evaluate cases of central hypothyroidism but did not always elucidate the cause. Rarely were determinations of total T₃, free T₄, or free T₃ necessary for complete evaluation.

The traditional approach had limitations because several conditions simulated the biochemical features of hyperthyroidism and hypothyroidism, the most common example in hospitalized patients being nonthyroidal illness (NTI), termed "euthyroid sick syndrome." Nearly all serious illnesses give rise to changes in T₄. There are two prominent abnormalities: 1) impaired 5'-monooiodination leading to impaired peripheral conversion of T₄ to T₃, and 2) an inhibition of binding of thyroid hormones to binding proteins. Initially T₃ may rise, but eventually values can be very low, the degree of change often correlating with the severity of the NTI. Total T₃ in serum is always disproportionately lower than T₄. At the same time, there is often an increase in reverse T₃, a nonfunctional metabolite, not caused by an increase in its production but rather to a decrease in its clearance from serum. The more severe the illness, the lower the T₄ becomes. The reverse T₃ level is inversely related to patient survival. TSH-RIA is usually within the normal range in NTI, although high-sensitivity assays have reported both very low values or occasional high values in the acute illness.

Close inspection of the RU result often allows discrimination between NTI and intrinsic thyroid disease. In hyperthyroidism, thyroxine-binding globulin (TBG) is saturated and few binding sites remain, so the RU is elevated. Calculated FTI is higher than total T₄. In hypothyroidism the converse is found: TBG is unsaturated, RU is low, and calculated FTI is lower than total T₄. On the other hand, for NTI, there is an apparent saturation of TBG as a consequence of putative inhibitors to binding, along with low TBG levels, and RU is elevated. Calculated FTI exceeds the measured total T₄. The main conclusion for the clinician interpreting T₄ levels in patients with severe illnesses is the importance of recognizing the direction of changes in T₄ and RU for both hyperthyroidism and NTI. In hypothyroidism the FTI is lower than the total T₄, but in NTI the total T₄ is lower than the FTI. Also, it is important to emphasize that the FTI result in NTI is frequently not corrected to the normal range.

**New Approach to Thyroid Function Testing Using TSH-IRMA**

State-of-the-art assays for TSH are variably called TSH-IRMA, "sandwich" TSH, or "high-sensitivity" TSH. The latter refers to contemporary immunoassays being able to detect TSH at concentrations which are orders of magnitude lower than concentrations measured by RIA.

Use of new TSH-IRMAs in the initial evaluation of patients offers an approach that should be superior in terms of diagnostic accuracy and cost effectiveness (1-5). The level of TSH in serum reflects the pituitary response to ambient thyroid hormone concentration. TSH measured by conventional RIA did not have the analytical sensitivity to distinguish reduction in TSH secretion from normal. The TSH-IRMA, a high-sensitivity assay, can detect very low concentrations and does make this distinction. In the natural history of primary thyroid dysfunction, serum TSH values become abnormal much sooner than serum T₃. The laboratory reference range for total T₄ is broad, and T₄ values within the normal range may be found in patients with both hyperthyroidism and NTI. In hypothyroidism the FTI is lower than the total T₄, but in NTI the total T₄ is lower than the FTI. Also, it is important to emphasize that the FTI result in NTI is frequently not corrected to the normal range.

**Principle of TSH-IRMA**

The principle of immunoradiometric assays is illustrated in Fig 3. A characteristic feature of these assays is that two different, specific (often monoclonal) antibodies directed toward two different antigenic sites on the TSH molecule are used to create
a "sandwich" with TSH between. The first antibody is often bound to a solid phase material such as a plastic bead, a magnetic particle, or the inside of a test tube that serves as a mechanism for physically separating the TSH from the sample solution. After the first antibody has extracted the analyte of interest from the sample, the second antibody directed toward a different antigenic site is added, forming the sandwich. The second antibody is labeled with some detectable moiety such as a radioactive atom like ¹²⁵Iodine, an enzyme, or a fluorescent molecule. The measured label increases linearly over a wide range of concentrations.

These assays tend to be specific because of the use of monoclonal antibodies and because only molecules which contain both antigenic sites can be detected. High sensitivity is obtained because the labels used can be detected in very low amounts and because both antibodies are in excess. Sensitivity is limited only by the amount of sample used in the measurement, nonspecific interference, and instrument noise in detection of the label. Excess reagent conditions in a chemical reaction also increase the rate of reaction. Thus, these assays are relatively fast, a few minutes of reaction time in contrast with the several days needed in the early days of RIA.

The immunoradiometric assay format can be contrasted with RIA which also uses a specific antibody-antigen reaction to measure a biological molecule. RIA uses a limited amount of a single antibody and a labeled antigen which competes with the antigen in the patient sample for binding to antibody binding sites. The measured response is inversely and nonlinearly related to concentration. Both assay types have analytical strengths and weaknesses and both have a role in the clinical laboratory, depending on the specific application.

**Precision profile and sensitivity**

In any chemical assay there is some error associated with measurement, and immunoassays are no exception. Typically a measurement error is expressed as coefficient of variation (CV), i.e., standard deviation divided by the mean of the measurement. For immunoassays, CV increases at very high and low concentrations. Sensitivity in an analytical sense means how low a concentration can be measured before the error is intolerable. A precision profile (Fig 4) is a graph of measured CV versus concentration. The working range of an assay can be defined as the range of concentration with CV less than a predefined level. Typically a CV of 10% or less is considered desirable for immunoassay. As assay sensitivity improves, the precision profile shifts to the left. The difference between IRMAs (second- and third-generation assays) compared to RIA (first-generation immunoassay) is illustrated in Fig 5 (6).

An alternative method of expressing analytical sensitivity is to define the "least detectable dose" (LDD). LDD is defined as the lowest concentration that is not zero at a 95% confidence level. That is, the measured response is > 2 standard deviations from that of a sample with none of the analyte of interest. The CV for a zero standard in the LDD experiment is usually quite low since the measurement is made on a single laboratory-prepared zero standard, and thus it may give an overly optimistic estimate of the sensitivity of an assay. Also, use of LDD does
Clinical application of highly sensitive TSH

TSH-IRMA defines the lower reporting range. Results below the lower reporting limit are considered undetectable. Third-generation assays are being developed to detect even lower concentrations. Experience with TSH-IRMA has led many laboratories to define "laboratory sensitivity" as a concentration somewhere below the LDD also have significant measurement error which may overlap the 95% confidence limits of the zero. Not reflect that very low concentrations in patient samples near the LDD also have significant measurement error which may overlap the 95% confidence limits of the zero.

To confirm the diagnostic specificity and sensitivity of the TSH-IRMA and to establish an effective lower reporting limit, we reviewed the clinical status of 52 patients (Table 2) whose TSH-IRMA concentrations fell between the LDD (0.04 mU/L) and the previous lower reporting limit of < 0.2 mU/L. The patients were classified by TSH-IRMA concentration as < 0.1 mU/L or between 0.1 and 0.2 mU/L.

All of the patients with Graves' disease (six in this group) had TSH-IRMA < 0.1 mU/L. As expected, many of the patients in the group were being treated with thyroxine; their TSH-IRMA results varied from the LDD to 0.2 mU/L. Six patients, all with low but detectable TSH, had a NTI or were receiving therapy known to lower TSH-IRMA such as glucocorticoids or dopamine. Though in this limited study all patients with NTI fell in a detectable range (0.1 to 0.2 mU/L), others have reported undetectable TSH-IRMA in NTI (6.9%) and a poor correlation between FTI and TSH concentration in this group. When an even more sensitive assay was used, there appeared to be meaningful distinction between hyperthyroid patients (< 0.1 mU/L) and patients with either NTI or who were receiving thyroxine (> 0.1 mU/L).

Proposed algorithm for thyroid function testing

The following advancements have allowed us to propose an algorithm for thyroid function testing:

1. TSH-IRMA, a highly sensitive technique, allows measurement of hormone levels lower than those detectable by conventional RIA.

2. The lower reporting range of TSH, less than 0.1 mU/L, identifies a category of patients with TSH lower than normals, herein designated as low (0.1 to 0.4 mU/L), in addition to the undetectable category.

3. The laboratory computer system permits automatic ordering of subsequent tests based on the results of the initial TSH assay.

A computer-directed algorithm for thyroid testing, termed directed TSH (DRTSH), is defined in Fig 6. Initially, TSH-IRMA is measured. If the result falls within specified limits, the results are reported and no further testing is done. Although the normal range is 0.4 to 5.5 mU/mL, the cut-off limits for the purpose of the algorithm were set to overlap with the extremes of normal range, i.e., 0.5 to 5.0 mU/L. If the results are < 0.5 mU/L or > 5.0 but < 10.0 mU/L, total T₄ and RU will be determined on the same specimen and reported along with a calculated FTI (T₄ x RU). This conservative approach may generate some additional follow-up testing but reduces the concern about missing appropriate follow-up in borderline cases. An upper limit of 10.0 mU/L was chosen because TSH higher than 10 mU/L rarely occurs with conditions other than hypothyroidism. The follow-up tests often clarify the cause of the low or high TSH and may identify the need for additional studies.

Fig 6, which depicts the use of TSH-IRMA as a screening test, indicates possible interpretation of test results. A normal TSH-IRMA value indicates normal function and precludes the need for further tests. An "abnormal" result (outside preset limit) suggests a potential need for further testing, namely total T₄ and RU. High TSH-IRMA in conjunction with low FTI is not a diagnostic criterion for hyperthyroidism. A figure illustrates the proposed algorithm for thyroid function testing.

### Table 2
Clinical Interpretation of Low TSH Levels

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Note: For clinical classification of patients with low TSH-IRMA concentrations, patients were grouped into those with Graves' disease, those being treated with L-thyroxine for replacement or suppression, and those who had a nonthyroidal illness lowering TSH-IRMA. LDD was 0.04 mU/L; the lower reporting limit was 0.1 mU/L; n = 52.

### Clinical Interpretation of Low TSH Levels

Not reflect that very low concentrations in patient samples near the LDD also have significant measurement error which may overlap the 95% confidence limits of the zero.

Experience with TSH-IRMA has led many laboratories to define "laboratory sensitivity" as a concentration somewhere below the LDD and the low end of the euthyroid range. This defines the lower reporting range. Results below the lower reporting range are considered undetectable. Third-generation assays are being developed to detect even lower concentrations, having reported LDD of 0.003 mU/L and CV of 3.9% at 0.05 mU/L.

Clinical application of highly sensitive TSH

TSH-IRMA distinguishes between hyperthyroid and euthyroid individuals (1-5,7). In addition, the increased sensitivity also allows identification of patients who are not clinically hyperthyroid but have decreased but detectable TSH (0.1 to 0.4 mU/L). A variety of conditions can account for these test results, and careful interpretation by the physician is required.

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typical of primary hypothyroidism. In the rare instance of high TSH with high FTI, test results suggest either a thyroid hormone resistant state or TSH-secreting tumor. Low TSH-IRMA with high or high-normal FTI is consistent with hyperthyroidism, thyroiditis, or therapy with L-thyroxine. Low TSH-IRMA with low-normal or low FTI is consistent with a NTI or central hypothyroidism. Hypothyroidism due to hypothalamic or pituitary disease is rare compared to the prevalence of NTI. TSH-IRMA concentration in this setting may be either low or within the normal range; in the latter instance the result would not generate follow-up tests and the correct diagnosis could be missed. Should both TSH-IRMA and T4 be low, NTI must be distinguished from central hypothyroidism. RU should give diametric results in central hypothyroidism and NTI and thus readily distinguish between the two. The diagnosis of central hypothyroidism may be corroborated with other endocrine studies of hypothalamic-pituitary function.

Employing this new approach to thyroid function testing is not without limitations (Table 3) (4). The major caveat is the likelihood of not detecting hypothyroidism due to hypothalamic-pituitary disease. Also, TSH-producing pituitary adenomas resulting in hyperthyroidism may have a normal TSH-IRMA value. Although thyroid dysfunction due to disease of the hypothalamic-pituitary area is rare, in clinical practice the diagnosis must not be missed. Certain medications such as steroids and dopamine can lower serum TSH. Acute psychiatric illnesses, mainly of the psychotic type, are also associated with low TSH-IRMA values; indeed, a state of transient hyperthyroidism may occur. Finally, NTI, particularly when severe, may lead to lowering of TSH-IRMA values. There may be other circumstances of low TSH-IRMA yet to be identified as experience with the new assays accumulates. In order to facilitate interpretation of TSH-IRMA values below the lower limit of normal, we favor distinction between two categories: "low" when the value is below the lower limit of normal but above the undetectable level, and "undetectable" when the result is below the lower reporting limit. It is our experience that undetectable values are almost always associated with hyperthyroidism. On the contrary, low TSH values may be caused by a variety of conditions but rarely, if ever, by hyperthyroidism. Testing the TSH response to TRH stimulation continues to have significance in the evaluation of difficult cases.

Adopting this approach to thyroid function testing requires an understanding of the benefits and limitations. Undoubtedly, diagnostic accuracy and efficiency of testing are substantially improved. Nonetheless, at the end of the day, clinical judgment is required when reaching a diagnosis.

**Advantages and Cautions to Use of the Algorithm**

The algorithm cannot be understood as one-step diagnosis. Rather, it is an efficient method of obtaining appropriate laboratory tests. Although frank hypothyroidism and the euthyroid state may be relatively easy to identify, thyroid tests must still be interpreted in concert with one another and in the clinical context. Physicians must distinguish between low and undetectable TSH-IRMA and be aware of nonthyroidal conditions and therapies which may affect TSH-IRMA results. In particular, patients with severe NTI may have abnormal thyroid function tests which may not be resolved until the underlying disease is improved.

**Conclusion**

Thyroid disease in all its forms is common in clinical practice. The internist has a vast array of tests available for use in guiding management. Adopting DRTSH diminishes the number of unnecessary tests. Some cases, despite a reliable approach, remain inscrutable and require expert evaluation. By choosing this simplified approach to the use and interpretation of thyroid function tests, the physician can identify cases that need more detailed study. The algorithm is by no means a substitute for sound clinical judgement; findings in an individual case must always be tempered by a physician’s intuition and experience.

**Acknowledgments**

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**References**