

# Lab Updates

March 2009

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Laboratories

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## Thyroid Function Tests

### UMass Memorial Medical Center Laboratories

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### **T**HE THYROID IS CONTROLLED BY A TYPICAL ENDOCRINE FEEDBACK LOOP.

#### I. Overview

TSH is secreted by the pituitary and stimulates the thyroid gland to produce **both** the prohormone  $T_4$  and the active hormone triiodothyronine ( $T_3$ ).  $T_4$ , in turn, is metabolized by peripheral tissues to  $T_3$ , and both hormones feed back to the pituitary to inhibit TSH secretion. This feedback loop is very sensitive to changes in circulating thyroid hormone concentration: A twofold change induces a tenfold change in TSH, in both directions. Thus, when the hypothalamic-pituitary axis is intact, TSH is the most sensitive marker of thyroid hormone action and is, thereby, used as a screening test for thyroid status.

**A. Indications** (suspected Hyperthyroidism, Hypothyroidism, Goiter and Thyroid nodules)

#### B. Techniques and interpretations

**1. Hormone assays:** Most hormones are measured by immunoradiometric assay or, more commonly, chemoluminescence immunometric assay.

**a. The normal range for TSH** is approximately 0.35-5.00 U/ml. Eighty percent of normal people have a TSH of less than 3.0 U/ml. An assay with functional sensitivity  $< 0.05$  U/ml is attained with so called "third generation" or "ultra-sensitive" TSH assays.

(1) In **hyperthyroidism**, serum TSH is below normal and frequently < 0.1 U/ml. TSH may remain decreased for many months in treated—formerly hyperthyroid—patients; therefore, thyroid hormone levels more accurately reflect the clinical situation.

(2) Primary **hypothyroidism** is easily diagnosed by an elevated TSH. However, when hypothyroidism is caused by hypothalamic-pituitary dysfunction (secondary hypothyroidism), TSH is no longer a good marker for hypothyroidism, and circulating thyroid hormone concentrations need to be obtained. During treatment for hypothyroidism, as many as 6 weeks are needed to reach a new steady thyroid state.

b.  $T_4$  and  $T_3$  circulate tightly bound to serum proteins [thyroxine binding globulin (TBG), transthyretin (TTR), and albumin], and only the free hormone (0.03 % for  $T_4$  and 0.3 % for  $T_3$ ) is available to initiate thyroid hormone action. Changes in binding protein concentrations and

hormone affinity can alter total thyroid hormone levels **without affecting free hormone concentrations** (Table 16-2). Total serum  $T_4$  and  $T_3$  concentrations are usually measured by immunoassays, which include both bound and free hormone. A number of alternative methods have been developed to estimate free hormone concentrations.

c. **Free  $T_4$  index** (FTI or  $FT_4I$ ) is a calculated value that uses the total  $T_4$  and the  $T_3$  resin uptake test to estimate free hormone indices.

(1) The  $T_3$  resin uptake test is performed by incubating the patient's serum with radioactive  $T_3$ , then adding a resin, which traps all of the unbound radiolabeled  $T_3$ . It can be expressed directly as the percent of total counts bound to the insoluble resin ( **$T_3RU$** ) or as a ratio of the patient's  $T_3$  resin uptake to that of a pool of normal patients (**THBR**) processed identically. The ratio is by definition 1 or 100%. The resin uptake is inversely proportional to the available free binding sites on the patient's thyroid hormone binding proteins (Figure 16-4).

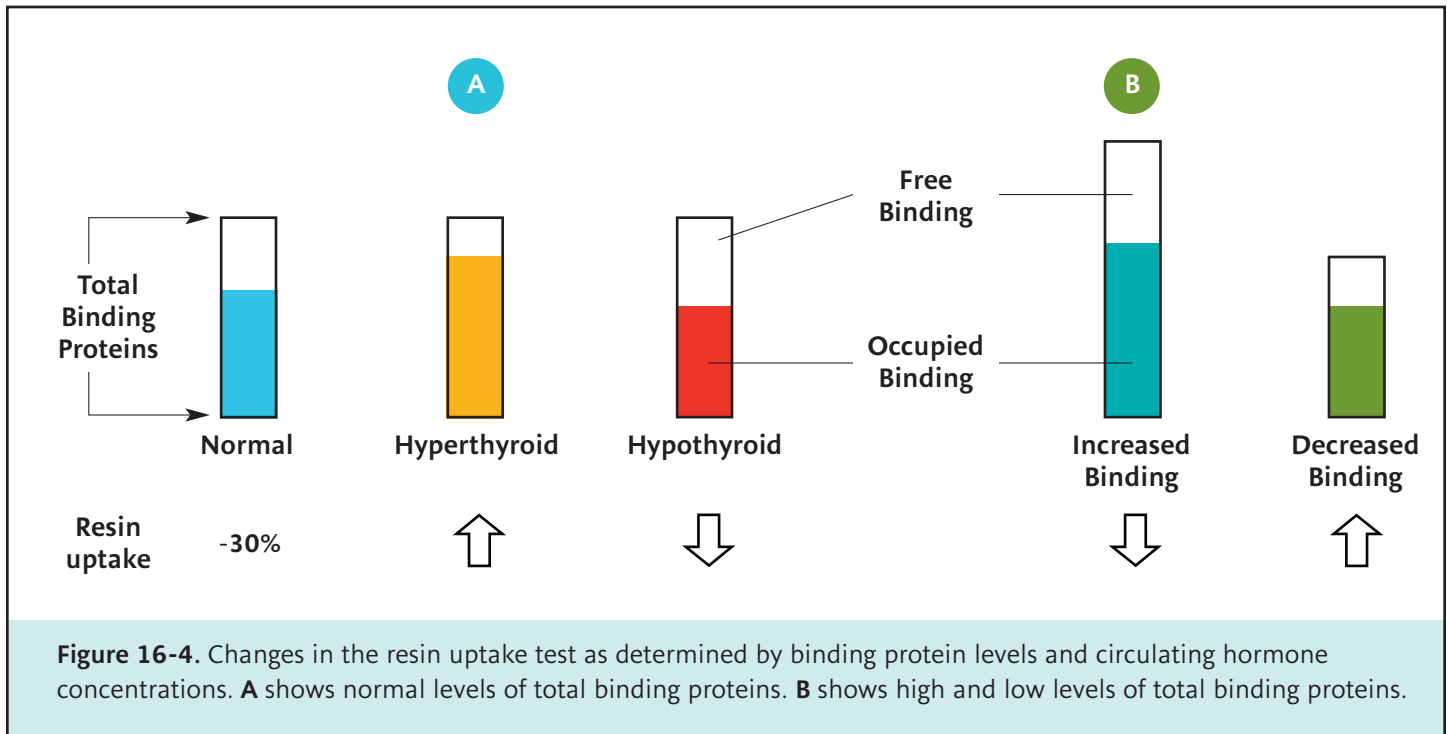
### Clinical Conditions and Drugs That Alter Thyroid Hormone Binding

Decrease thyroid hormone binding	Decrease TBG	Increase TBG
Carbamazepine Phenytoin	Testosterone	Estrogens (OCPs, pregnancy hormone-replacement therapy)
Rifampin	Corticosteroids	Infectious hepatitis
Salicylates	Severe illness	Neonatal
Euthyroid sick	Cirrhosis	Acute intermittent porphyria
Heparin (acutely)	Nephrotic syndrome Inherited	Inherited

OCPs = oral contraceptive pills; TBG = thyroxine-binding globuline

Table 16-2





**Figure 16-4.** Changes in the resin uptake test as determined by binding protein levels and circulating hormone concentrations. **A** shows normal levels of total binding proteins. **B** shows high and low levels of total binding proteins.

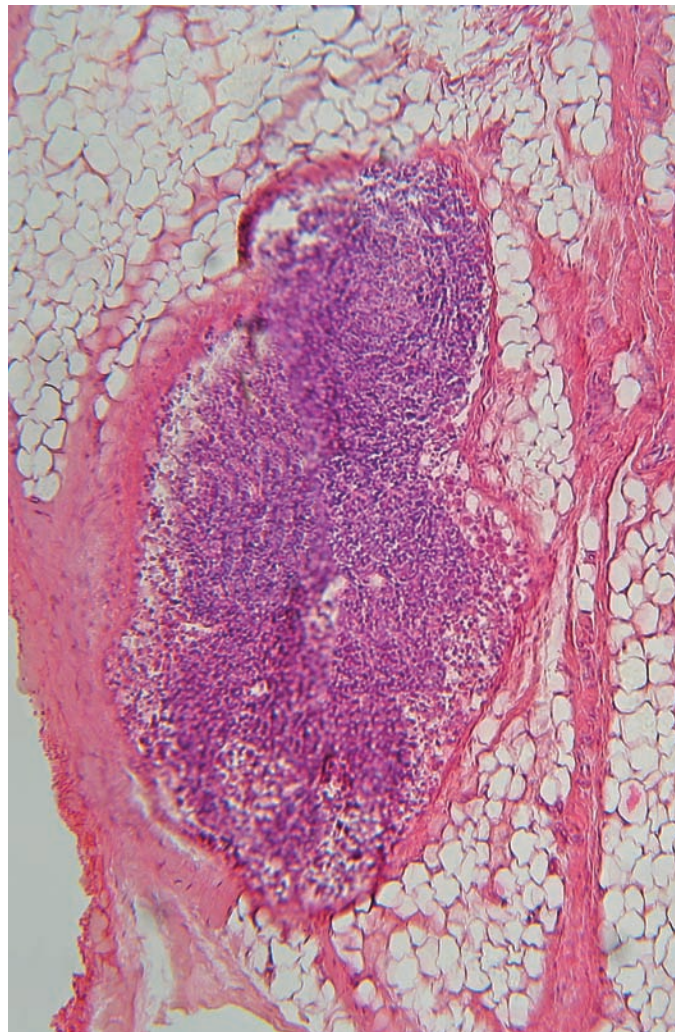
- (a) For example, when thyroid hormone secretion is increased in hyperthyroidism, the binding equilibrium is shifted such that more of the binding sites are occupied by the patient's thyroid hormone, there are fewer sites available to bind the radiolabeled  $T_3$ , and more of the available radiolabeled  $T_3$  binds to the resin.
- (b) On the other hand, if there is an increase in the concentration of binding proteins (such as the increase in TBG induced by estrogens), the binding equilibrium is unchanged but the number of unoccupied binding sites is increased and less radiolabeled  $T_3$  binds to the resin.
- (2) The FTI or FT<sub>4</sub>I is calculated as the product of the total  $T_4$  and the  $T_3$ RU or THBR respectively, and corrects for binding abnormalities as shown in Table 16-3.
- d. **Free  $T_4$  measurement** assays are quite good under conditions of normal-binding proteins, but can be misleading when binding abnormalities are present. If the free  $T_4$  measurement is at odds with the clinical impression,
- it may be necessary to obtain an FTI or even free  $T_4$  by dialysis.
- e.  $T_3$  is usually elevated with hyperthyroidism. Assessment of  $T_3$  levels is important to determine the severity of the hyperthyroidism and to monitor the response to treatment. Measurement of  $T_3$  is wasteful in patients with hypothyroidism since it is low only in severe hypothyroidism and is also decreased in patients with nonthyroidal illness in the absence of hypothyroidism.
- f. **Thyroglobulin** is a large glycoprotein that is secreted by thyroid follicular cells. It can be detected in normal serum and is increased with increased thyroid cell mass (e.g., with Graves' disease, toxic MNG, thyroid cancer) and injury (e.g., biopsy, surgery, radioactive iodine treatment, external irradiation, inflammation). Its main uses are in distinguishing factitious hyperthyroidism from other causes of low-RAIU hyperthyroidism (values are low to undetectable in the former and measurable or increased in the latter) and in identifying recurrences in patients with thyroid cancer. Normal values vary.

## Thyroid Function Test Results in Various Abnormalities of the Thyroid Gland

Clinical Status	Total T4	Resin Uptake	FTI
Hyperthyroidism	High	High	High
Excess TBG	High	Low	Normal
Hypothyroidism	Low	Low	Low
TBG deficiency	Low	High	Normal

FTI = free thyroxine index;  
TBG = thyroxine-binding globulin

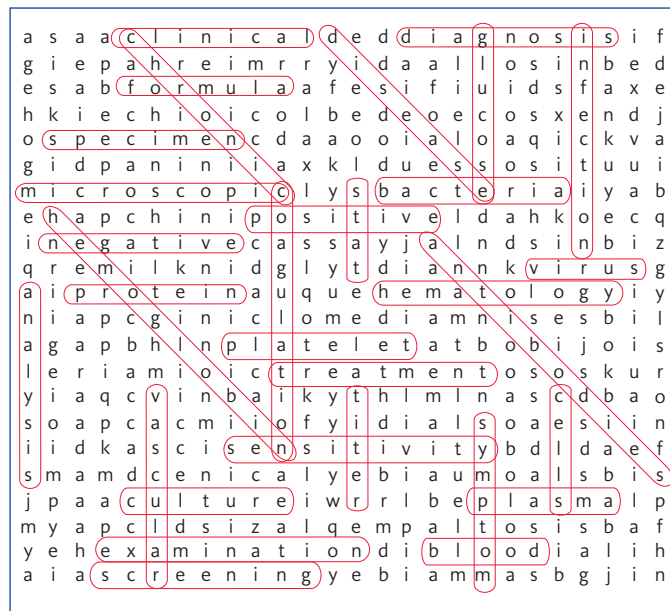
Table 16-3



**2. Antithyroid antibodies** are of two types: Those that are markers of autoimmune thyroid disease [antithyroperoxidase and antithyroglobulin antibodies and those that are mediators of autoimmune thyroid disease (anti-TSH receptor antibodies).

**a. Antithyroperoxidase** (and to a much lesser degree, antithyroglobulin) is detected in almost all patients with Hashimoto's disease and its variants, in 70% of patients with Graves' disease, and in a smaller number of patients with various other thyroid disorders such as MNG, nontoxic goiter, and thyroid carcinoma. Both are assayed by solid-phase, two-step chemoluminescence immunometric assay.

**b. Anti-TSH receptor** antibodies are of two types: stimulating and blocking. They can be identified by measuring thyroid-stimulating immunoglobulin (TSI), which will pick up only the stimulating antibodies, or TSH-binding inhibitory immunoglobulin (TEII), which will pick up both types of TSH receptor antibodies. While TSI is present in 70%-100% of patients with Graves' disease, its measurement is not usually necessary for diagnosis, but it may be helpful in prognosis because patients who have very high TSI titers that do not decrease with antithyroid drug treatment are unlikely to go into remission. Measurement of TSI is important in pregnancy, because a high titer at the end of pregnancy correlates with an increased risk of neonatal hyperthyroidism.



Solution to Lab Word Puzzle on page 6

## II. Special Notes

- A. Drugs may decrease TSH.** These include glucocorticoids and dopamine.
- B. TSH may also be suppressed during illness and increased during recovery** (to as high as 20 U/ml).
- C. Total T<sub>4</sub> and T<sub>3</sub> can be affected by alterations in hormone binding.**
- D. In patients with “T<sub>3</sub>-toxicosis,” T<sub>3</sub> (but not T<sub>4</sub>) concentrations are increased.**
- E. T<sub>3</sub> levels are decreased by drugs** such as glucocorticoids, propranolol, amiodarone, and cholecystographic agents (e.g., iopanoic acid, sodium ipodate).
- F. The presence of antithyroperoxidase antibodies will falsely decrease or increase thyroglobulin measurements** when analyzed by immunometric assays or radioimmunoassay, respectively, and will confound the usefulness of the test.

**G. Titers of antithyroglobulin antibodies do not correlate with disease severity.**

**H. Commercial assays of TSI are very variable,** and therefore when indicated, it is recommended to measure TBII, which is more sensitive, although less specific.

**Reference:** Safran, Marjorie., “Thyroid Function Tests”. *Guide to Diagnostic Testing.* pp 85-89.

*If you have questions, comments or suggestions, please contact:*  
 Dr. L. Michael Snyder, Chairman, UMass Memorial Laboratories  
 at 508-334-0280



## Laboratory Word Puzzle

This puzzle contains common medical/laboratory terms. The words contained within the puzzle are listed on the right. The words may appear horizontal, vertical or diagonal within the puzzle. Solution appears on page 5.

```

a s a a c l i n i c a l d e d d i a g n o s i s i f
g i e p a h r e i m r r y i d a a l l o s i n b e d
e s a b f o r m u l a a f e s i f i u i d s f a x e
h k i e c h i o i c o l b e d e o e c o s x e n d j
o s p e c i m e n c d a a o o i a l o a q i c k v a
g i d p a n i n i i a x k l d u e s s o s i t u u i
m i c r o s c o p i c l y s b a c t e r i a i y a b
e h a p c h i n i p o s i t i v e l d a h k o e c q
i n e g a t i v e c a s s a y j a l n d s i n b i z
q r e m i l k n i d g l y t d i a n n k v i r u s g
a i p r o t e i n a u q u e h e m a t o l o g y i y
n i a p c g i n i c l o m e d i a m n i s e s b i l
a g a p b h l n p l a t e l e t a t b o b i j o i s
l e r i a m i o i c t r e a t m e n t o s o s k u r
y i a q c v i n b a i k y t h l m l n a s c d b a o
s o a p c a c m i i o f y i d i a l s o a e s i i n
i i d k a s c i s e n s i t i v i t y b d l d a e f
s m a m d c e n i c a l y e b i a u m o a l s b i s
j p a a c u l t u r e i w r r l b e p l a s m a l p
m y a p c l d s i z a l q e m p a l t o s i s b a f
y e h e x a m i n a t i o n d i b l o o d i a l i h
a i a s c r e e n i n g y e b i a m m a s b g j i n
    
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- |                 |                 |
|-----------------|-----------------|
| 1. assay        | 18 stat         |
| 2. protein      | 19. microscopic |
| 3. glucose      | 20. formula     |
| 4. specimen     | 21. hemoglobin  |
| 5. screening    | 22 cells        |
| 6. diagnosis    | 23. hematology  |
| 7. negative     | 24. sensitivity |
| 8. positive     | 25. symptom     |
| 9. platelet     | 26. culture     |
| 10. examination | 27. treatment   |
| 11. infection   | 28. blood       |
| 12. bacteria    | 29. titer       |
| 13. antibodies  | 30. fluid       |
| 14. clinical    | 31. vascular    |
| 15. plasma      | 32. disease     |
| 16. chronic     | 31. virus       |
| 17. coagulation | 32. analysis    |

# Estimated Average Blood Glucose (eAG)

## *A new way to talk to patients about diabetes management*

Measurement of glycosylated hemoglobin (HgbA1c) is a fundamental component of the management of patients with diabetes mellitus. The interpretation of HgbA1c levels is not intuitively obvious to many diabetic patients, who are accustomed to thinking in terms of blood glucose levels. American Diabetes Association (ADA) has called for laboratories to express HgbA1c results as estimated average blood glucose (eAG). ADA believes that eAG will be easier for patients to understand and will lead to improved management of diabetes.

The formula we will be using to report eAG is  
**eAG (mg/dL) = 28.7 X Hemoglobin A1c – 46.7**

eAG Conversion Chart	
HgbA1c %	eAG mg/dl
6	126
6.5	140
7	154
7.5	169
8	183
8.5	197
9	212
9.5	226
10	240

It is to be noted that eAG has the same limitations as Hemoglobin A1c for patients with hemoglobinopathies. Also, the appropriateness of eAG in less-studied populations, like pregnant women, adolescents and various ethnic groups is not clear at this time and additional studies are being conducted.

**Effective March 23, 2009**, UMass Memorial Laboratories will report eAG values along with Hemoglobin A1c results.

*If you have questions, comments or suggestions, please contact:*

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via email at [Raol@ummhc.org](mailto:Raol@ummhc.org)

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### Laboratory Supply Distribution Center Updates

The Laboratory Supply Distribution Center has relocated to 640D Lincoln Street.

The new number for placing supply orders is 508-519-6015.

The new phone number for supply inquiries is 508-853-6450.

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Medical Center Laboratories**  
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## New Patient Service Center

We are one of the largest  
laboratory providers in  
New England

UMass Memorial Laboratories has opened a  
Patient Service Center (phlebotomy draw station)  
at 33 East Main St., Westborough MA.

The vision of UMass  
Memorial Laboratories is:

- To be a leading provider of laboratory services throughout New England, meeting the needs of patients and providers in the region, and
- To be one of the top ten academic medical center-based laboratories in the United States



### **Westborough PSC** **33 East Main Street, Westborough, MA**

Westborough PSC is located at 33 East Main Street, Westborough, MA. The hours are Monday through Friday 8:00am-5:00pm, closed 12:15pm-1:15pm. The phone number at Westborough PSC is 508-366-2838.