Background
Thyroid hormone synthesis and secretion is regulated via a negative feed-back control system, which involves the hypothalamus, anterior pituitary, and the thyroid gland. Thyrotrophin-releasing hormone (TRH) is secreted by the hypothalamus. TRH stimulates the anterior pituitary to secrete TSH, which acts on the thyroid gland to stimulate the release of T-3 and T-4. T-3 and T-4 act negatively on the anterior pituitary gland to suppress the release of TSH, thereby controlling thyroid hormone production.

Discussion
- TSH is the most sensitive test for primary hypothyroidism. However if there is a clinical picture of hypothyroidism, yet the TSH is normal then investigate other causes within the thyroid-pituitary-hypothalamic feedback axis.

  - With normal thyroid and anterior pituitary/hypothalamic function, a decreased T-3 and T-4 causes an increase in TSH, and an increase in T-3 and T-4 causes a decrease in TSH.

  - TSH is an integral part of a thyroid panel useful for the determination and potential differentiation of hypothyroidism.

  - TSH is used to diagnose primary hypothyroidism when there is a problem intrinsic to the thyroid gland itself. TSH levels will be elevated.

  - When TSH levels are decreased the problem may be reflective of a hyperthyroid state. Also consider that the problem may be due to abnormalities outside the thyroid in the pituitary-hypothalamic axis, which cause a secondary and even tertiary hypothyroidism.

  - Although sensitive it is not uncommon for a patient with a clinical picture of hypothyroidism to have completely normal serum thyroid tests. In these cases this should alert the clinician to an etiology other than an intrinsic thyroid gland dysfunction (i.e. increased tissue resistance to thyroid hormone.) Consider other low T-3 or low T-4 syndromes, such as subclinical hypothyroidism and Wilson’s syndrome. Please see the special topic on Wilson’s syndrome on page 188 for more information.
**Ranges:**

<table>
<thead>
<tr>
<th></th>
<th>Standard U.S. Units</th>
<th>Standard International Units</th>
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<tbody>
<tr>
<td>Conventional Laboratory Range</td>
<td>0.35 – 5.5 µIU/ml</td>
<td>0.35 – 5.5 mIU/l</td>
</tr>
<tr>
<td>Optimal Range</td>
<td>2.0 – 4.4 µIU/ml</td>
<td>2.0 – 4.4 mIU/l</td>
</tr>
<tr>
<td>Alarm Ranges</td>
<td>&lt; 0.3 or &gt; 10.0 µIU/ml</td>
<td>&lt; 0.3 or &gt; 10.0 mIU/l</td>
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**When would you run this test?**

1. To identify the cause of a thyroid related problem
2. As part of a thyroid screening panel

**Clinical implications**

**HIGH**

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>Additional information</th>
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<tbody>
<tr>
<td>Primary hypothyroidism</td>
<td>Hypothyroidism is a very common and often undiagnosed condition. Individual blood indices are notoriously insensitive to mild or borderline cases of primary hypothyroidism. In many cases TSH levels may be within normal limits yet the patient is suffering from all the classic signs and symptoms of low thyroid. In these cases it is often more efficacious to look at more functional criteria such as basal body temperature, Achilles return reflex, and iodine status, along with history, other blood indices, and clinical signs and symptoms. Please see the special topic on functional tests for hypothyroidism below.</td>
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**Pattern:**

If TSH levels are elevated (> 4.4), with a normal or decreased T-4 level (<6 or 7.2 nmol/L) and/or T-3 (<100 or 1.54 nmol/L), a decreased T-3 uptake (<27), and an increased cholesterol (>220 or 5.69 mmol/L) and triglyceride level (>110 or 1.24 mmol/L), primary hypothyroidism is **probable**.

Some of the clinical signs of hypothyroidism include:
### Functional Tests for Hypothyroidism

1. **Achilles return reflex**
   - A delayed Achilles return reflex is a classic sign of hypothyroidism.
   - In the absence of spinal lesions, a delayed Achilles return reflex bilaterally indicates the strong likelihood for low thyroid activity, along with the corresponding signs and symptoms.

2. **Basal Body Temperature test**
   - The basal body temperature (BBT) reflects the body’s basal metabolism, which refers to the amount of energy your body burns at rest.
   - The basal metabolism is largely determined by hormones secreted from the thyroid and to a lesser degree the adrenal glands.
   - The function of the thyroid can be observed by measuring the fluctuations of the basal body temperature over a number of days.
   - Reduced axillary temperature is also common with reduced adrenal function, a diet low in essential fatty acids, protein malnutrition and thiamine deficiency. Therefore, you should not equivocally associate a depressed temperature with a pure thyroid problem.

3. **Iodine skin test**
   - The iodine skin test is a functional assessment for iodine status in the body.
   - By painting the skin with a 2% solution of iodine we can see how quickly the body absorbs the available iodine.
   - The quicker the iodine fades, the greater the deficiency can be assumed to be.
Drug causes of ↑
- Prescription Lithium therapy
- Potassium iodide
- TSH injections

Other conditions associated with increased TSH levels include
- Hashimoto’s thyroiditis
- Sub acute thyroiditis
- Liver/biliary dysfunction due to conjugation problems
- Severe debilitating illness
- Thyrotoxicosis
- Thyrotropin producing tumor

LOW

<table>
<thead>
<tr>
<th>Clinical Implication</th>
<th>Additional information</th>
</tr>
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<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Although less common than hypothyroidism, the following pattern may help elucidate a developing or existent hyperthyroid state.</td>
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</tbody>
</table>

**Pattern:**
If TSH is low (<2.0) with an increased T-3 (>230 or 3.53 nmol/L), T-3 uptake (>37), FTI and/or T-4 (>12 or 154.4 nmol/L), then hyperthyroidism is **probable**. Consider running thyroid antibody studies to rule out Hashimoto’s thyroiditis and Grave’s disease. Please see the special topic below for more details on thyroid antibody studies.

Rule-out food allergy/sensitivities, environmental sensitivities, recent immunizations/inoculations, viral infections, and other auto-immune problems in any cases of suspected hyperthyroidism. Some of the clinical signs of hyperthyroidism include:
1. Difficulty gaining weight, even with large appetite
2. Nervous, emotional, can't work under pressure
3. Inward trembling
4. Flush easily
5. Fast pulse at rest
6. Intolerance to high temperatures
### Thyroid Antibody Studies

Consider running anti-thyroid antibody studies (i.e. anti-thyroglobulin antibody, thyroid anti-microsomal and thyroid peroxidase antibody) with known or suspected thyroid abnormality. Differentiation between multiple auto-immune conditions (i.e. Hashimoto’s, Grave’s disease and sub-acute thyroiditis) is based upon these antibody titers. With Hashimoto’s and Grave’s disease the titers will be significantly elevated. With sub-acute thyroiditis, the levels are usually slightly increased.

| **Secondary Hypothyroidism** (Anterior Pituitary Hypofunction) | Thyroid hypofunction is often secondary to an anterior pituitary hypofunction (Secondary Hypothyroidism). If the subjective indications of thyroid hypofunction are present along with a decreased T-3 uptake (<27) and normal T-4, T-3, and FTI, with the TSH <2.0, Anterior Pituitary Hypofunction should be considered.  
If serum triglycerides are elevated (>110 or 1.24 mmol/L) and the total cholesterol levels are decreased (<150 or 3.9 mmol/L), then secondary hypothyroidism is probable.  
Anterior pituitary hypofunction is a common problem and one that is frequently mistaken for thyroid hypofunction (the subjective indications are usually identical and the patient's axillary temperature will frequently be below normal).  
Some of the common clinical indications of an anterior pituitary dysfunction include:  
1. Decreased libido  
2. Weight gain around hips or waist  
3. Menstrual irregularities  
4. Delayed sexual development (after age 13)  
5. Unresponsive thyroid treatment  
6. Hypoglycemia due to concomitant adrenal insufficiency |
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<tr>
<td><strong>Tertiary hypothyroidism</strong> (Hypothalamus hypofunction)</td>
<td>A decreased TSH level (&lt;2.0) may be due to an inadequate secretion of Thyroid Releasing Hormone (TRH) from the hypothalamus. Please see the special topic below on the differentiation of hypothyroid classification for more details.</td>
</tr>
<tr>
<td><strong>Heavy metal body burden (e.g. lead)</strong></td>
<td>Consider a heavy metal body burden with a thyroid condition that is unresponsive to treatment. Specific metals include</td>
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</table>
aluminum, mercury, and cadmium that act as disruptors to thyroid receptor activity. Other standard laboratory signs useful in elucidating a potential heavy metal body burden include MCHC, MCH, and uric acid.

One of the significant effects of toxic metals is the impact they have on red blood cells especially hemoglobin. If MCH (<28) and MCHC (<32) is decreased with a decreased uric acid (<3.5 or 208 µmol/dL), suspect a heavy metal body burden. Confirm with a hair analysis or toxic element testing via blood or urine. The serum levels of the metals may also be increased, but in sub-acute conditions the serum levels may be normal. The hair and urinary/blood tests will frequently reflect the increase before it is seen outside the reference range in the serum.

<table>
<thead>
<tr>
<th>Drug causes of ↓</th>
<th>T-3 treatment</th>
<th>Heparin</th>
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<tbody>
<tr>
<td></td>
<td>Aspirin</td>
<td>Dopamine</td>
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<td></td>
<td>Corticosteroids</td>
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<tr>
<th>Other conditions associated with decreased TSH levels include</th>
<th>Protein malnutrition</th>
<th>Pregnancy</th>
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<tbody>
<tr>
<td></td>
<td>Hashimoto’s thyroiditis</td>
<td>Sub acute thyroiditis</td>
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**Differentiation of hypothyroid classifications**

A decreased TSH level may be due to an inadequate secretion of Thyroid Releasing Hormone (TRH) from the hypothalamus. Clinically an intravenous injection of TRH is administered to try to stimulate the production of TSH from the pituitary.

- **In primary hypothyroidism** there is an exaggerated TSH response after administration of TRH.
- **In secondary hypothyroidism** due to anterior pituitary hypofunction there is no significant rise in TSH levels after administration of TRH.
- **In tertiary hypothyroidism** due to a hypothalamic hypofunction there will be a delayed rise in TSH of approximately 30 minutes after administration of TRH.
**Interfering Factors:**

<table>
<thead>
<tr>
<th>Falsely increased levels</th>
<th>Falsely decreased levels</th>
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<tbody>
<tr>
<td>• Administration of radioisotopes within one week prior to testing</td>
<td>• Please see drug causes of decrease above</td>
</tr>
<tr>
<td>• Please see drug causes of increase above</td>
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</tbody>
</table>

**Related Tests:**

T-3 uptake, thyroxine (T-4), free thyroxine index, thyroid binding globulin (TBG), serum triglycerides, serum cholesterol, thyrotrophin releasing hormone (TRH), serum calcium, serum phosphorous, serum potassium, serum sodium, RBC magnesium, HCT, HGB, serum albumin
Considerations when Interpreting a Thyroid Test or Panel

- The thyroid is a complex endocrine gland that works in concert with many other endocrine glands with hormonal mediators. Support the whole system as well as the specific organ or gland.

- When addressing any endocrine dysfunction, **always support the key essentials** to normal function first (nutritional deficiencies, fatty acid metabolism, protein/albumin availability, liver activity, hidden infections etc.).

- **Liver conjugation** problems can significantly impair hormone levels from the thyroid, gonads, or adrenal cortex. Therefore, attention should be paid to optimizing liver function prior to exhausting specific endocrine causes or treatments.

- Thyroid hormone activity, along with other hormones, is extremely sensitive to **stress and toxins** such as halogens, toxic metals, drugs etc., which interfere with the synthesis, transport, and utilization of T-4 (thyroxine) and T-3 (triiodothyronine).

- Thyroiditis is the most common thyroid condition, leading to either hypothyroidism (Hashimoto’s and sub-acute thyroiditis) or hyperthyroidism (Grave’s disease). Hypothyroidism due to thyroiditis is the most common. Thyroiditis can present with normal, elevated, or decreased levels of thyroid hormone at any time.

- Functional chemistry analysis for thyroid status should consist of TSH, T-3, T-4, T-3 uptake, and free T-3 & T-4 levels. In our opinion these are the most useful tests to order.

- Multiple tests found on a thyroid panel taken independently are often misleading and inadequate in determining thyroid status. TSH, FTI, T-3 uptake, T-3, T-4, Free T-3 and T-4 are best analyzed collectively with attention to specific patterns.

- FTI (Free thyroxine Index) is a test that is often included in thyroid panels. It is an estimate calculated from total T-4 and T-3 uptake. It is usually proportional to actual free T-4 but is an imperfect measurement as it is quite possible to obtain a normal FTI with an abnormal T-3 uptake or T-4. An increased FTI is usually associated with hyperthyroidism, while a low level is associated with hypothyroidism. Although a part of many panels, this test is **not** recommended as it has been replaced by more accurate tests, such as free T-3 or thyroxine-binding globulin.