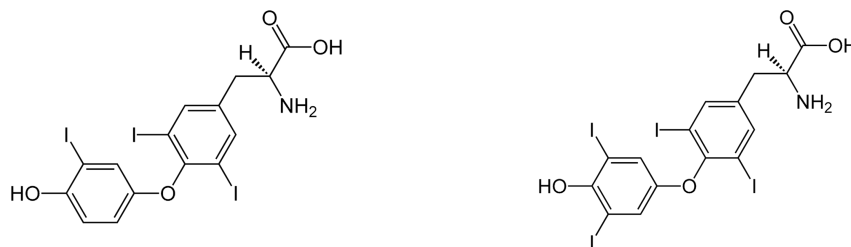


## 11. Endocrinology II MEDCHEM 535 Diagnostic Medicinal Chemistry

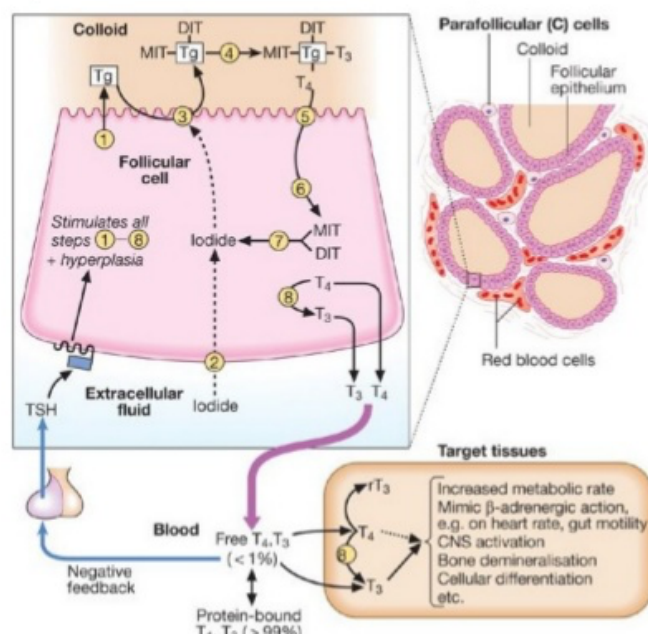
### B. Thyroid Disorders

The primary function of the thyroid gland is to produce and release the hormones triiodothyronine (T3), thyroxine (T4), and calcitonin. Calcitonin is a peptide hormone that is involved in Ca regulation. Calcitonin's actions generally oppose those of parathyroid hormone (PTH).

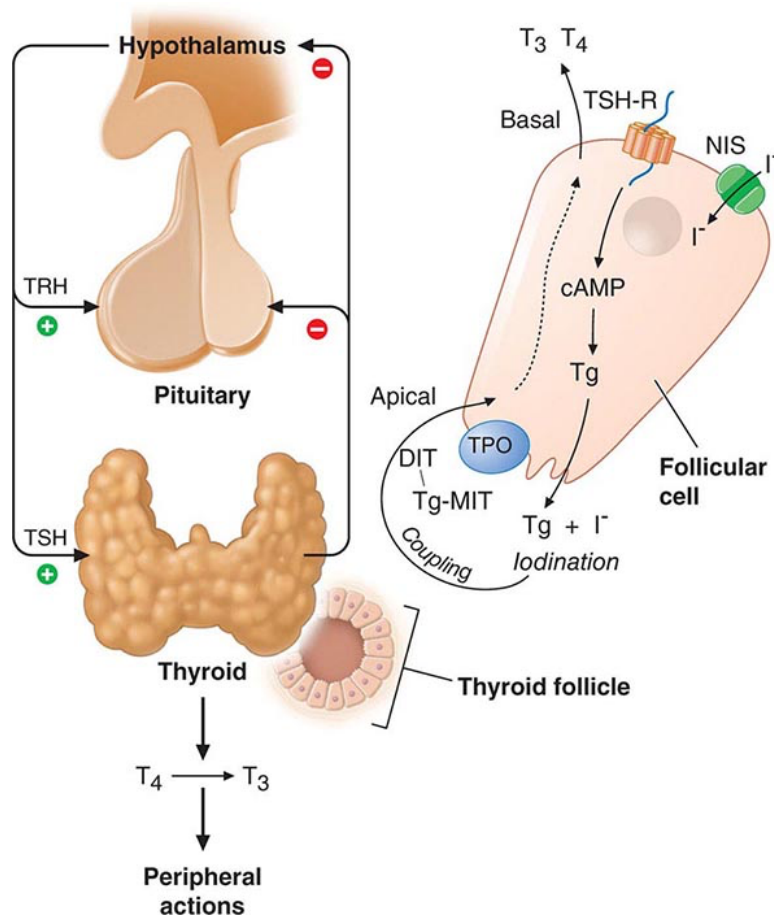


As much as 80% of the T4 that is released to the blood is subsequently converted to T3 by selenium dependent de-iodinases in peripheral organs such as the liver, kidney and spleen. Because T3 is 4-6- fold more potent than T4, some regard T4 more as a prohormone. It may be that the conversion of T4 to the more active T3 in the organs and tissues may be a targeting mechanism. RT3 (a T3 isomer) used to be used as a marker but that has fallen out of favor.

## Thyroid hormone synthesis

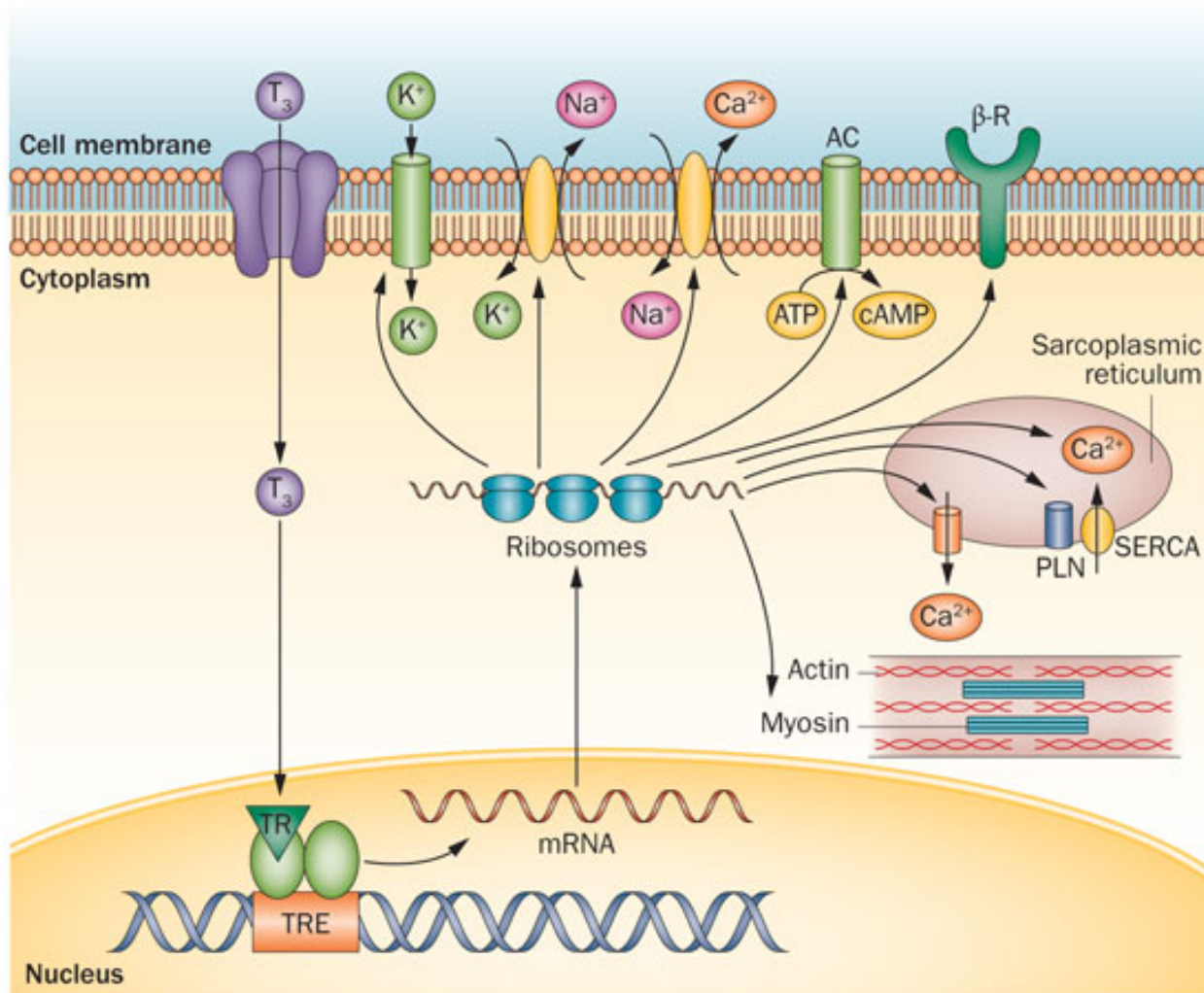


The thyroid hormones contain iodine. Iodine ( $I_2$ ) is concentrated by the thyroid as iodide ( $I^-$ ), converted to elemental iodine ( $I$ ) and attached to the non-halogenated precursors of the hormone precursors on tyrosine residues of thyroglobulin. This process is definitely totally amazing and involves a bunch of peptidases to cleave iodinated tyrosine precursors.



The thyroid hormones bind to a rather well-researched family of nuclear thyroid hormone receptors and hybrid receptors (THR/RXR) to exert their numerous effects in many tissues and organs. Total hormone release per day is T<sub>4</sub> (80  $\mu$ g) and T<sub>3</sub> (30  $\mu$ g).

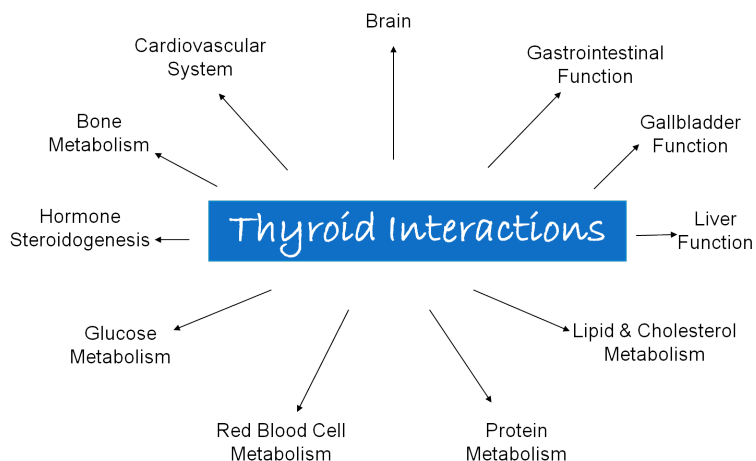
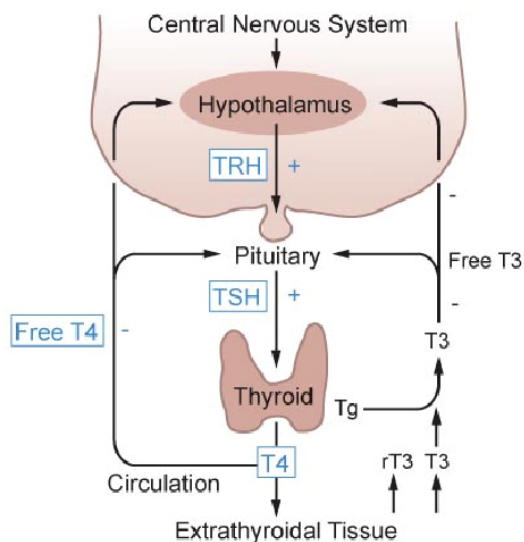
Below see the receptor system in cardiomyocytes.



The thyroid hormones are tightly bound to a serum protein called thyroxine binding protein (TBG: not to be confused with thyroglobulin above) and others (albumin and transthyretin). Very notably free (unbound) T3 and T4 hormone levels in serum are extremely low: T3 (0.2% free) and T4 (0.02% free). As far as we can tell the free T3 and T4 concentrations, rather than total, are most important in clinical tests/diagnosis/treatment. They are not easy to measure and highly amplified ELISA assays are used. Overall the tests for free hormone are less commonly used:

*Mayo: Free triiodothyronine (T3) is a second- or third-level test of thyroid function; it provides further confirmation of hyperthyroidism, supplementing the tetraiodothyronine (T4), sensitive thyrotropin (sTSH), and total T3 assays.*

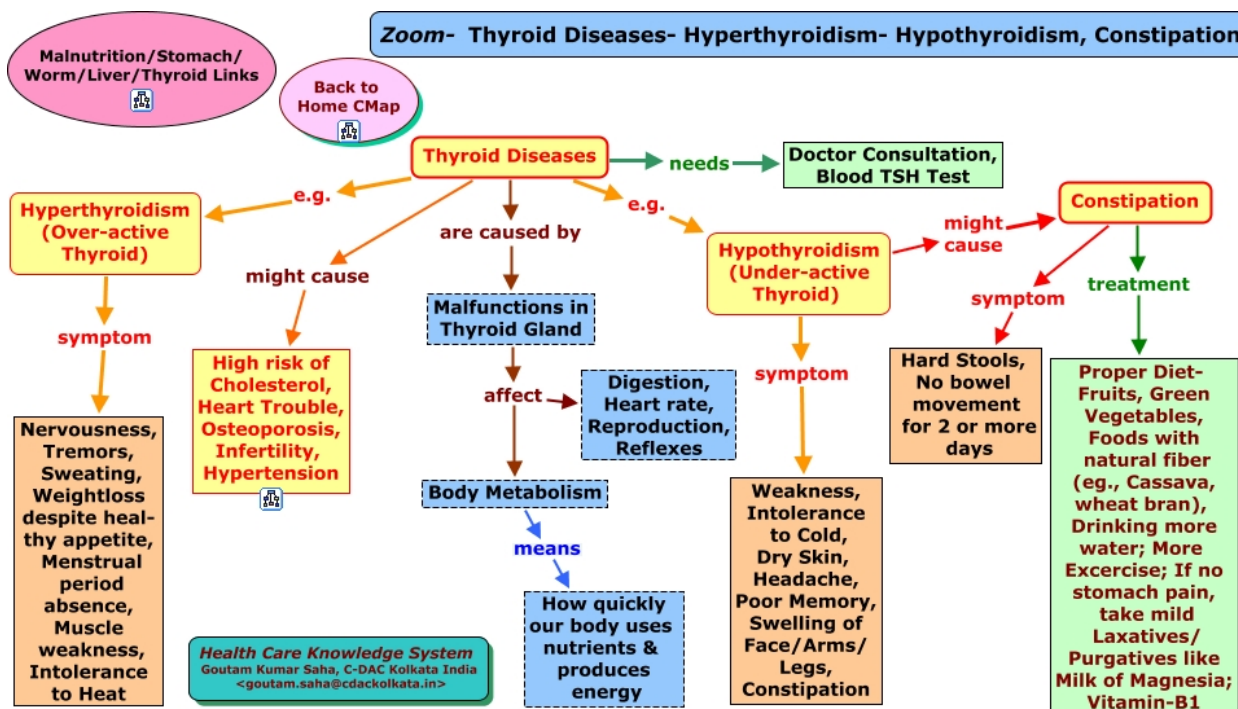
T3 and T4 in serum are feedback inhibitors of the stimulatory TRH and TSH hormones released from the hypothalamus and pituitary. This arrangement is called the



Diseases of the thyroid are classified as hyperthyroidism and hypothyroidism.

The following diagram summarizes symptoms of these two diseases. They can be further sub-classified as primary and secondary disorders. In addition a number of other lab tests are employed to diagnose other disorders that are affected in hypo- and hyperthyroidism..... so it is complicated. As with the corticosteroids the signaling hormones TSH (thyroid stimulating hormone) and to a lesser extent TRH (thyroid releasing hormone) can be measured in diagnosis and employed as tools to diagnose disease.

While we won't go into it in detail the concentrations of the serum binding proteins can be used in diagnosis.



### Thyroid function tests

a. Serum Thyroxine (T4) note the difference between free and total below and the difference in units!!!. The test for total T4 is still the most common test. It is high in 90% of hyperthyroid cases and low in 85% of hypothyroid cases.

Total [Ref range 4-12.5  $\mu\text{g/dL}$ ] (still standard screening test)

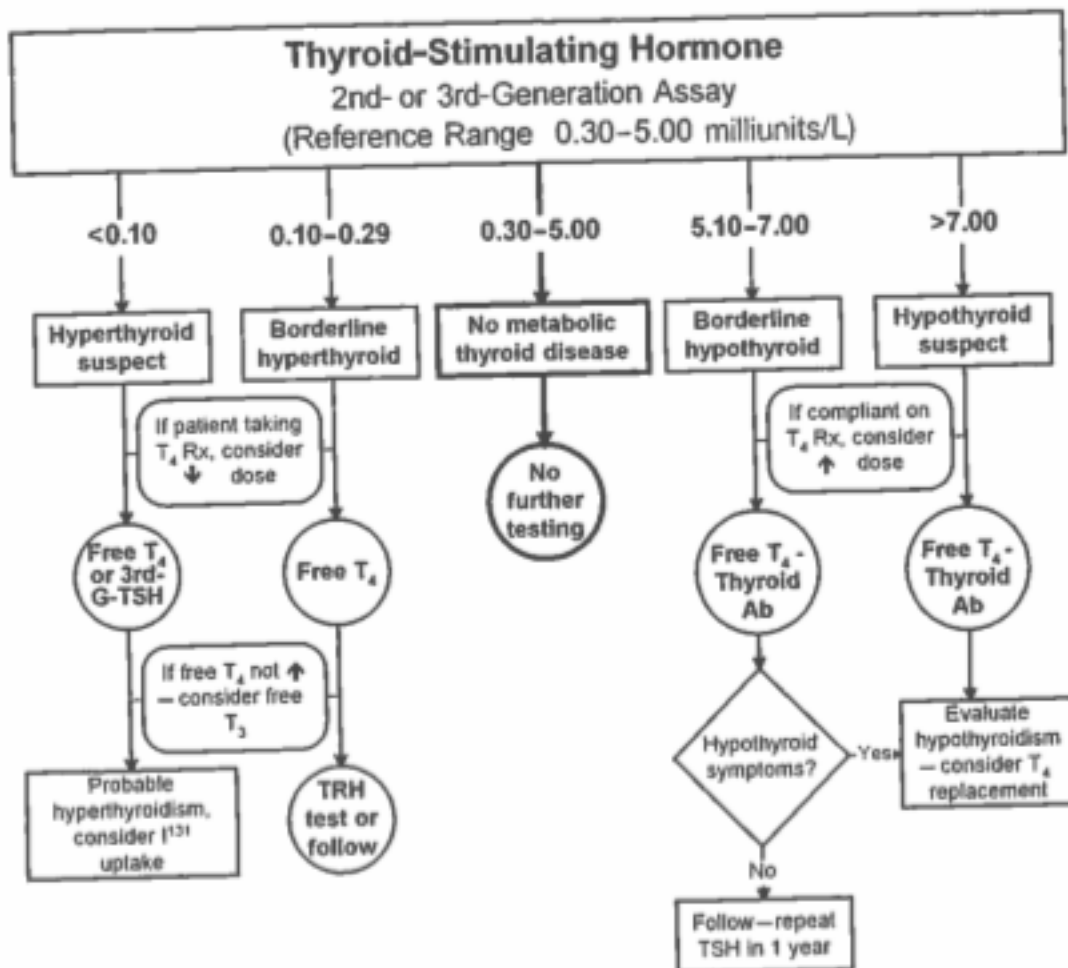
Free [Ref range 0.8-1.5 ng/dL] (twice the price, note unit change)

b. Serum T3

Total [Ref range 78-195 ng/dL] (still standard screening test)

Free [Ref range 2.3-3.9 pg/mL] (note unit change)

c. TSH (Thyroid Stimulating Hormone) [Ref Range 0.25-6.7 mU/L]. Most testing laboratories now use 2<sup>nd</sup> or 3<sup>rd</sup> generation tests that can detect TSH levels below 0.1 mU/L which is very important in hyperthyroidism. Note that this test, sometimes in combination with total T4, is used to figure out the dose of levothyroxine (T4) to be used in the treatment of primary hypothyroidism. It is also used to monitor compliance in thyroxine therapy (Think about this). Algorithms employing TSH levels are often used to drive further diagnosis and treatment.



d. Anti-thyroid antibodies in blood (Iodine peroxidase ab, thyroglobulin ab detect ) are used as well.

e. T3 uptake test (25% to 38%) (Also called the thyroid hormone binding ratio) This test uses radiolabeled T3 and a binding resin to determine total binding capacity of the serum proteins. A low value indicates a high level of TBG and is consistent with hypothyroidism. A high value indicates a low level of TBG and is consistent with hyperthyroidism.

f. Thyroid Function tests:

-Radioactive iodine uptake is the percent of a standard dose of  $^{123}\text{I}$  that is taken up by the thyroid. Used to be a standard but not used much anymore. A low test indicates hypothyroidism. A high uptake is seen in thyrotoxicosis.

-TRH releasing hormone test; Here the serum TSH levels before and after a dose of TRH are compared. A significant rise ( $>5 \mu\text{U/mL}$ ) in TSH is expected in the euthyroid patient. Interpretation of this test is somewhat complicated depending on the baseline TSH levels.

**2. Hypothyroidism:** Generally body metabolism slows down. The disease can be acquired or inherited. Symptoms include lethargy, fatigue, cold intolerance, dry skin, constipation, depression and puffy face. Roughly 11 million patients in the US are hypothyroid, 70% are female and symptoms usually arise in the 3<sup>rd</sup> to 6<sup>th</sup> decade of life. In neonates maternal hypothyroidism can cause mental retardation. Hb, HCT and glucose are often low in this disease. A number of other tests can be high including AST, LDH, TG and cholesterol. A number of non-thyroid diseases can cause low T4 even though the thyroid gland is functioning normally. Examples are liver and kidney diseases, trauma and cardiovascular disease. In some cases serum binding proteins (TBG) levels are low with gives and overall low total T4.

a. Primary hypothyroidism is 85% of total cases. Hashimoto's disease is either an inherited or acquired disorder and involves auto-immune antibodies that inhibit synthesis of thyroxine. The antigen involved here is the iodine peroxidase. Hypothyroidism is also seen in regions with low iodine in the diet.

Hypothyroidism is often seen as the result of radioactive iodine therapy in the treatment of hyperthyroidism.

Here treatment for hypothyroidism may be preferable to treatment for hyperthyroidism. Amiodarone (antiarrhythmic drug) blocks synthesis of the hormones and is a major cause of hypothyroidism though the use of this drug is declining.

b. Lab tests will show high TSH in primary disease ( $>5 \text{ mU/L}$ ), low T4 and free T4. TRH challenge will produce an exaggerated response. Additional tests for antithyroid antibodies in serum is also useful for further diagnosis.

c. The treatment is levothyroxine (synthetic T4) which is one of the most prescribed drugs in the United States. Interestingly TSH concentrations can be used to monitor therapy. Resolution of symptoms takes weeks to months.

**3. Hyperthyroidism:** Elevated body metabolism is observed.: Incidence is 2% of the female population and 0.2-0.3 % of males. Elevated T4 and T3 are seen in tests for the hormones. TSH levels are suppressed ( $<0.3 \text{ mUnits/L}$ ) due to feedback inhibition. Ultralow levels of TSH can now be reliably determined with the newer TSH tests.



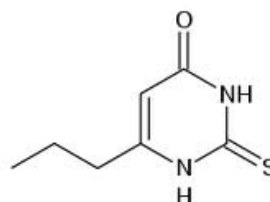
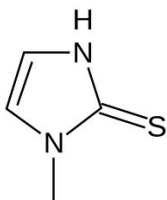
a. Primary hyperthyroidism is most common. The most common cause is Grave's disease which is an autoimmune disease of the thyroid. There is a 25% chance that an identical twin will also have the disease. In this disease the thyroid becomes enlarged and the eyes bulge. Here we will also see antibodies to TBG in the serum. The list of symptoms long and unpleasant. Hyperthyroidism can also be caused by adenomas. A number of drugs can cause low T4 and T4F including aminoglutethimide, lithium carbonate, 6-mercaptopurine, phenobarbital, antacids, glucocorticoids and phenobarbital.



b. Lab tests show low TSH and high or normal T4. High T4 is primary hyperthyroidism and further tests for antibodies and thyroglobin are indicated. Normal T4 with normal T3 is subclinical or can be associated with pregnancy (euthyroid). Elevated T3 is observed and can be of diagnostic use. Additional tests include imaging and biopsy.

c. Treatment of hyperthyroidism includes the following based on differential diagnosis.

(a) Methimazole is an orally administered drug that inhibits the peroxidase that activates iodide ( $I^-$ ) to allow iodination of tyrosines. Propylthiouracil has the same mechanism of action but is less effective.



(b) Surgery when the goiter is large or when cancer is suspected. Thyroidectomies may or may not be bilateral.



c. Radioactive iodine ( $^{131}\text{I}$ ) (RAI) is used when surgery or drug therapy is not successful or contraindicated. This therapy takes months to years to achieve a final stable effect and replacement therapy with levothyroxine must be initiated when hypothyroidism emerges.