THYROID HORMONE TUTORIAL: DRUG AND OTHER THERAPIES

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I. TREATMENT OF HYPERTHYROIDISM

The goal of treatment for hyperthyroidism is resolution of signs and symptoms, normalization of serum thyroid hormone concentrations, remission of disease, and prevention or abatement of potential long-term consequences such as atrial fibrillation and osteoporosis. The three treatment options are antithyroid drugs (ie, methimazole, and propylthiouracil [PTU]), radioiodine, and surgery. Adjunctive therapy is often used to help manage the symptoms of thyroid disease. This chapter will focus on radioactive iodine treatment, the antithyroid drugs and adjunctive therapies. Surgical procedures are discussed in the "Thyroid Surgery" Tutorial.

II. RADIOACTIVE IODINE THERAPY

The most common treatment modality for hyperthyroidism used in the United States is radioactive iodine (RAI). It is painless, effective, economical and quick. However, fears of radiation and the high incidence of hypothyroidism often deter the use of RAI. All isotopes of iodine are rapidly taken up in thyroid follicles. So far, only the isotopes ^{131}I and ^{125}I have been used consistently, and ^{131}I is regarded as the agent of choice for most forms of hyperthyroidism (Graves' disease, toxic nodules, toxic multinodular goiter). The isotope ^{131}I, which decays to ^{131}Xe mainly with the emission of 0.6 meV beta-particle and of approximately 0.3 meV gamma-rays, has a half-life of 8 days. The gamma-radiation emitted by ^{131}I can be detected by a suitably placed scintillation crystal. This is the basis for the diagnostic use of this isotope in iodine uptake and in thyroid-scanning procedures. A review of the use of ^{125}I in thyrotoxicosis has indicated that the potential advantages of the ^{125}I isotope, which are based on its lower penetrability and more localized action, have not been realized in practice. The isotope ^{125}I with a half-life of 60 days, decays to ^{125}Te by electron capture. The major component of its decay is a 27 keV X-ray, and the minor component is a 35.5 keV gamma-ray.

Organs other than the thyroid take up ^{131}I, but the thyroid is the only organ where organification occurs. The absorption and organification of ^{131}I beta-radiation by the thyroid results in highly localized destruction of those thyroid follicles. Initially RAI disrupts thyroid hormone biosynthesis followed by necrosis of follicle cells and associated blood vessels. The specificity of RAI for thyroid tissues has promoted this procedure as a therapeutic alternative to surgical removal of the gland. Advantages of RAI therapy over surgery include the simplicity of the procedure, its applicability to patients who are poor surgical risks, and the avoidance of surgical complications such as hypoparathyroidism. *The development of late hypothyroidism and the fear of chromosomal damage are arguments against the use of radioiodine in patients under age 20 years and during pregnancy or lactation. Because of it's mechanism of action RAI is absolutely contraindicated in pregnancy.*

RAI is commonly used in 1). cardiac, debilitated and older patients, 2). patients who have failed drug therapy or experience adverse reactions with the antithyroid drugs, and 3). patients who develop recurrent hyperthyroidism after surgery. The goal of RAI is to affect enough tissue to achieve euthyroidism; however, hypothyroidism and the requirement for temporary or lifelong

thyroid hormone replacement therapy may result. RAI is administered as a colorless and tasteless liquid that is well absorbed and concentrates in the thyroid. The goal of therapy is to destroy overactive thyroid cells and this is typically accomplished with 4000 to 8000 rads. In Graves' disease this involves administration of 5 to 15 mCi (80-120 μCi/g of thyroid tissue); larger thyroid glands (> 80g) may require higher doses. Patients receiving RAI should remain isolated for a suitable period of time.

With this type of RAI dosing 60% of patients achieve the euthyroid state within 6 months and virtually all patients become euthyroid within a year. If a patient remains hyperthyroid after a single RAI dose, a second dose may be administered within 6 months. Lingering symptoms of hyperthyroidism can be treated with beta-blockers or iodide reagents within 1-14 days after RAI; iodides should not be used is a second dose of RAI is planned. Hypothyroidism resulting from RAI treatment begins about 3 to 6 months after treatment and therefore these patients therefore should be monitored at monthly intervals and suspected hypothyroidism confirmed by measuring free T_4 and TSH levels. Thyroid hormone replacement therapy is then initiated to bring the TSH level into the normal range, and replacement therapy is maintained throughout life. Hypothyroidism develops in about 20% of patients 1 year after RAI. The annual rate of development is 2.5% per year thereafter, with 50% of patients hypothyroid by year 10 and 80% by year 20. Again, all patients must be monitored for hypothyroidism after RAI therapy.

The overall outcome of RAI therapy depends on a number of factors including:

- Gender: Men are more likely than women to develop hypothyroidism post-RAI:
- Race: Blacks are more resistant to RAI therapy
- Thyroid size
- Severity of disease
- The level of antibodies (TSAbs)

RAI therapy is considered safe except during pregnancy or lactation, in which cases it is contraindicated. The acute effects of RAI include thyroid tenderness and dysphagia. Concerns about the development of thyroid carcinomas and leukemia following RAI therapy have historically restricted the use of RAI in adults over the age of 20-35 years old. However, concerns about RAI-induced cancer are not supported by current literature. Some studies do suggest an increased risk of cardiovascular and cerebrovascular mortality following RAI, and an increase in bone fractures.

Some patients, particularly the elderly, debilitated and those with cardiac disease may be treated with antithyroid thionamide drugs prior to radioactive iodine therapy to minimize the risk of exacerbating the hyperthyroidism (transient increase in thyroid hormone release) following RAI treatment. It should be noted that thionamide therapy may take as long as 6 to 8 weeks to be effective. Also, in patients with underlying cardiac disease it may be necessary to use antithyroid drugs after RAI therapy. When thionamides are used they are typically withdrawn 4 days prior to RAI treatment and reinstituted 4 days after RAI therapy is concluded. Corticosteroids may also be used with RAI to blunt and delay the rise in antibodies to the TSH receptor, thyroglobulin and thyroid peroxidase, and reduce T_3 and T_4 levels following RAI. This may be of significance if these antigens contribute to overall disease-related pathology such as ophthalmopathy. Beta-

blockers may be administered any time without altering the efficacy of RAI and are often used as adjunctive therapy. Iodides should be administered 3 to 7 days prior to RAI to minimize competition for thyroid uptake.

III. ANTITHYROID DRUGS: IODINE/IODIDE AND RELATED IONS

At one time the primary therapy available for hyperthyroidism such as Grave's disease was iodide. Iodine-containing agents (eg, potassium iodide, Lugol's solution) in the short term inhibit thyroid hormone release, inhibit thyroid hormone biosynthesis and decrease the size and vascularity of the thyroid gland. The phenomenon of iodine-inhibited organification of thyroid hormones is known as the Wolff-Chaikoff effect. It is an autoregulatory mechanism to protect the gland from excess production of thyroid hormones in the presence of a large iodine load. The gland escapes this mechanism within a few days of iodine ingestion because of leakage and/or altered transport of iodine. The effects of iodides are overcome by TSH levels that increase in response to lower plasma levels of free thyroid hormone. Thus the iodide-suppressive effects on thyroid hormone release are overcome within 7 to 14 days

With the introduction of the more effective antithyroid thionamide drugs (see below), iodine agents are no longer used routinely for the long-term management of hyperthyroidism. However, due mainly to their effects on gland size and vascularity, the iodines are useful agents in preparation for thyroid surgery (Thyroidectomy in Graves' disease) or for the treatment of thyroid storm (to rapidly achieve euthyroidism). They may also be used to inhibit thyroid hormone release following RAI therapy. When initiating iodine therapy, the symptoms of hyperthryoidism improve within 2 to 7 days, and serum thyroid hormone levels are reduced for a few weeks. However, as mentioned above, the thyroid escapes the inhibitory actions of the iodides within 1-2 weeks.

Patients most likely to respond to iodides are those with high intrathyroidal iodide levels or toxic adenoma, those on lithium, and some with Hashimoto's thyroiditis. Potassium iodide is available as a saturated solution (SSKI) which contains 38-40 mg of idode per drop, or as Lugol's solution which contains 6-8 mg of iodide/drop (5% iodine and 10% potassium iodide). The typical starting dose of SSKI is 3-10 drops daily (120-400 mg) in water or juice. The dose of Lugol's solution is 5 to 10 drops orally three times daily for 10 to 14 days prior to surgery. When used to prepare a patient for thyroidectomy, these iodides should be administered 7-14 days preoperatively. As an adjunct to RAI these agents should be used 3-7 days after RAI, but not before since they may compromise radioiodide concentration in the thyroid!

The most frequent adverse reaction associated with iodine/iodide use is hypersensitivity reactions (skin rash, drug fever, etc.), salivary gland swelling, gynecomastia and iodism. Iodism, is characterized by oral (metallic taste, burning mouth and throat, sore teeth and gums) symptoms and symptoms similar to the common cold. It should be noted that large doses of iodine may exacerbate hyperthyroidism or precipitate hyperthyroidism in previously euthyroid individuals (so-called Jod-Basedow disease). Jod-Basedow disease is most common in iodine deficient areas, particularly in patients with pre-existing nontoxic goiter. Also, iodine products are contraindicated in toxic multinodular goiter.
Other large anions of molar volume comparable to iodide may be taken up into the thyroid by

way of the iodide pump. The affinity of iodide for the iodide pump is equal to that of thiocyanate but much smaller than that of the larger perchlorate and pertechnetate ions. In contrast to iodide and SCN^-, TcO_4^- and $Cl0_4^-$ do not undergo intrathyroidal metabolism after they are trapped. This property has made TcO_4^- labeled with the short-lived technetium-99^m, a widely used radioisotope for thyroid trapping and for thyroid imaging.

Perchlorate, which competitively inhibits the uptake of iodide, has been used in both diagnosis and treatment of thyroid disease. In continental Europe, Perchlorate (Irenat, Anthyrium) has been used for surgical preparation and in the long-term treatment of thyrotoxicosis. *In the United States, the use of perchlorate was drastically curtailed after aplastic anemia and severe renal damage were reported following its use.*

Diagnostically, perchlorate is used to assess the intra-thyroidal organification of iodine. When perchlorate is administered after a dose of radioactive iodine, perchlorate washes out or discharges intrathyroidal inorganic iodide but does not affect covalently bound organic iodide. When organification is inadequate, there is a sharp decrease in intrathyroidal radioactive iodine after perchlorate administration.

Additionally, lithium, and corticosteroids decrease thyroid hormone concentrations, but they are rarely prescribed for the routine treatment of hyperthyroidism. Lithium's antithyroid action is also of short duration, and its narrow therapeutic window requires extensive drug monitoring.

IV. ANTIHTYROID DRUGS: THE THIONAMIDES

A. Development and Properties of the Thionamides:

The primary antithyroid drugs used in the United States to achieve remission of thyroid disease are methimazole (Tapazole, MMI) and propylthiouracil (PTU) of the thionamide class. The are the preferred treatment for children, pregnant women and young adults with uncomplicated Graves' disease. These drugs also are used to prepare patients for therapy with radioactive iodine or surgery, and unlike surgery or radioiodine treatment, do not destroy the thyroid gland.

Mechanism of Action: The thionamides are potent inhibitors of the thyroid peroxidase enzymes (TPO) which are responsible for iodination of tyrosine residues of thyroglobulin ("organification") to form monoiodotyrosine and diiodotyrosine, and the coupling of iodotyrosine residues to form iodothyronines. Thus the thionamides ultimately prevent hormone formation. PTU, but not MMI, also inhibits the peripheral conversion of T_4 to T_3, an effect which occurs within hours of administration and may enhance the utility of this drug versus MMI in thyroid storm. These drugs have no effect on iodide trap or on thyroid hormone release. The thionamides also decrease the concentration of thyrotropin (TSH)-receptor autoantibodies (TSAbs) and increase suppressor T-cell activity, indicating possible immunosuppressive activity and a role in remission. This however, may simply be an indirect effect of reducing thyroid hormone levels.

The most clinically useful thionamides are thioureylenes, which are five- or six-membered heterocyclic derivatives of thiourea and include the thiouracil, 6-n-propyl-2-thiouracil (PTU), and the thioimidazole, 1-methyl-2-mercaptoimidazole (methimazole, Tapazole, MMI). The structural

derivation of the thiouracils is shown in Figure 1 below. The study of 6-alkylthiouracil showed maximal antithyroid activity with 6-propylthiouracil. 6-Methylthiouracil has less than one-tenth the activity of PTU. The ability of PTU to inhibit the enzyme 5'-D, i.e., the peripheral deiodination of T_4 to T_3 (in addition to its intrathyroidal inhibition of thyroid hormone formation) has made PTU the drug of choice in the treatment of emergency of thyroid storm. Single doses of PTU in excess of 300 mg are capable of almost total blockage of peripheral T_3 production.

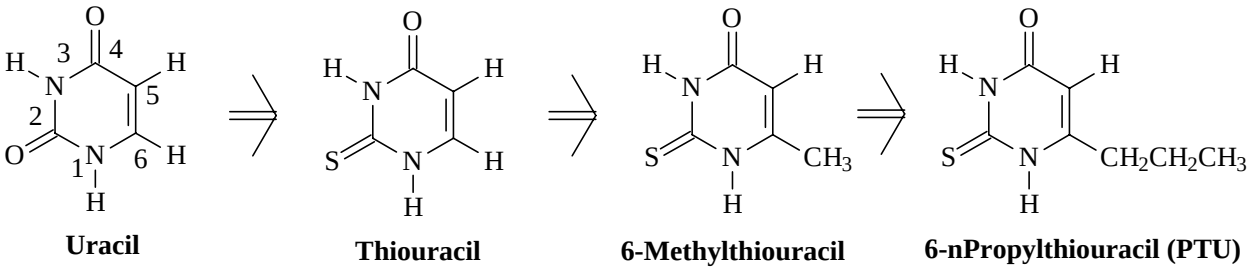


Figure 1: PTU and the thiouracils

A number of studies have defined the structure-activity relations of thiouracils and other related compounds as inhibitors of outer-ring deiodinase. The C_2 thioketo/thioenol group and an unsubstituted N, position are essential for activity. The enolic hydroxyl group at C_4 in PTU and the presence of alkyl group at C_5 and C_6, enhance the inhibitory potency.

The structural derivation of the thioimidazoles are shown in Figure 2 below. Methimazole has more thyroid peroxidase inhibitory activity and is longer-acting than PTU but, in contrast to PTU, is not able to inhibit the peripheral deiodination of T_4 presumably because of the presence of the methyl group at N_1 position.

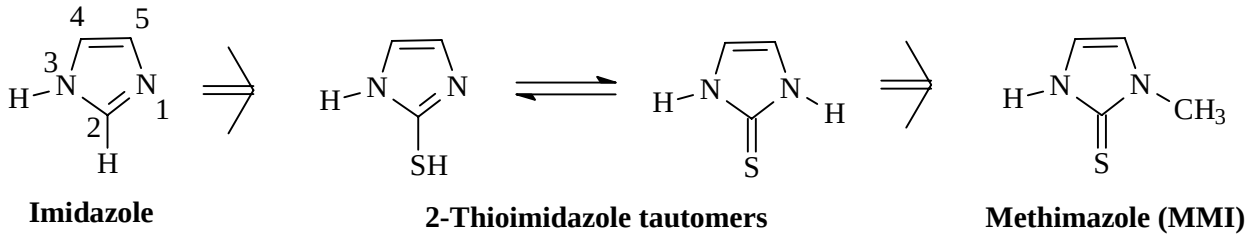
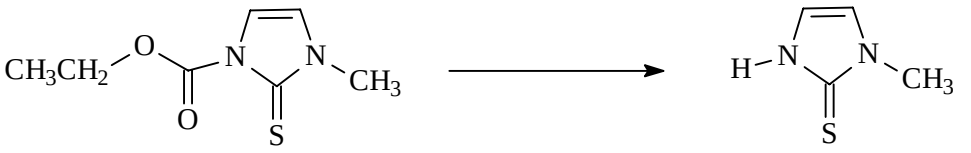


Figure 2: Methimazole and the thioimidazoles

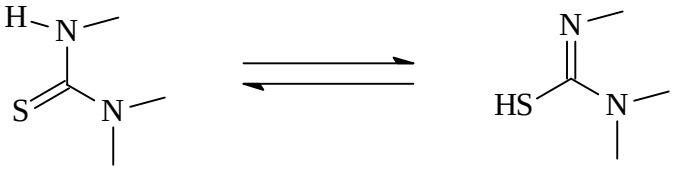
Efforts to improve the taste and decrease the rate of release of MMI led to the development of 1-carbethoxy-3-methylthioimidazole (carbimazole). Carbimazole, the prodrug derivative of methimazole, gives rise to methimazole in vivo and is used in the same dosage (Figure 3):



Carbimazole **Methimazole (MMI)**

Figure 3: Carbimazole as a methimazole prodrug

Chemically the grouping R-CS-N- has been referred to as thioamide, thionamide, thiocarbamide, and if R is N, as it is in PTU and MMI, as thioureylene. This structure may exist in the thioketo or thioenol tautomeric forms (Figure 4). PTU and MMI are extensively taken up by the thyroid gland and act as substrates for and inhibitors of thyroid peroxidase (TPO). The thioureylenes have been described as potent inhibitors of thyroidal iodination and suggested that a thioureylene such as propylthiouracil (PTU.SH) would prevent the formation of a TPO-iodine complex when the thioureylene-to-iodide ratio was high and compete with thyroglobulin tyrosyl residues (TG.Tyr) when the PTU.SH-to-iodide ratio was low. In the course of the reaction, the thioureylene



Thioketo **Thioenol**

Figure 4: Tautomeric forms of the thioureylene moiety

PTU.SH would be oxidized, possibly to a dimer such as PTU.SS.PTU. Because of the rapid reaction of sulfenyl iodide with thioureylenes, a TPO sulfenyl iodide intermediate (TPO.SI) has been proposed to be a part of the reaction:

TPO.SI + PTU.SH → TPO.SH + PTU.SI
PTU.SI + PTU.SH - PTU.SS.PTU + HI

Thioureylene drugs also effectively prevent the coupling of thyroglobulin residues, which yields iodinated thyronines. This effect has been related to an alteration of the conformation of TG brought on by the binding of the thioureylene to TG (i.e., the formation of a compound such as TPO.S.S.PTU). After the observation that PTU inhibited the peripheral deiodination of T_4, attempts to relate deiodinase inhibitory activity to structural parameters were undertaken. These studies emphasized the need for tautomerization to a thiol form and for the presence of a polar hydrogen on the nitrogen adjacent to the sulfur-bearing carbon. A study of the relation of chemical structure to 5'- D inhibitory activity related to similar studies of structural requirements for TPO inhibition could prove fruitful in the design of improved antithyroid drugs.

B. Pharmacokinetics of the Thionamides

PTU is usually dosed on a schedule of two to four times a day, although some evidence shows that single-daily dosing may be adequate in some patients. The pharmacokinetic and biodisposition properties of PTU and MMI are shown in the Table below. Both drugs are well absorbed from the GI tract giving peak plasma levels within 1-2 hours. PTU has a significantly shorter plasma half-life than MMI, but both drugs are actively concentrated by the thyroid and thus plasma half-life does not correlate with duration of therapeutic effect, and once daily dosing may be effective. Both drugs are metabolized and only small amounts of the parent drug (PTU, 35%; MMI, 10%) appear in the urine unchanged. PTU is more highly bound (60-80%) by plasma proteins than MMI and thus MMI is reported to distribute across placental membranes and into breast milk more readily than PTU. Therefore PTU historically has been preferred over MMI in pregnant or breast feeding patients. However, current studies indicate that both drugs can penetrate placental tissues and achieve adequate concentrations to elevate TSH levels and lower T_4 in the fetus. In one study mean fetal TSH was elevated to 10.2 mIU/mL, whereas maternal TSH was 0.8 mIU/mL, indicating subclinical hypothyroidism in the fetus. The degree to which these drugs cross the placenta probably varies throughout pregnancy and thus caution should be exercised with use of any antithyroid treatment during pregnancy.

Comparison of Propylthiouracil and Methimazole

Parameter	Propylthiouracil	Methimazole
Water Solubility	Relatively low	Higher
Relative Potency	1	10
Oral Bioavailability	>80%	>80%
Time to PPL	1-2 hr	1-2 hr
Serum half-life	1-2.5 hr	6-9 hr
Intrathy half-life	??	20 hr
Thyroid/Blood ratio	100/1	100/1
Protein Binding	60-80%	Low
Urinary Excretion	35%	10%
Rel. Placental Conc.	1	4
Rel Breast Milk Conc.	1	10

C. Thionamide Dosage:

PTU is available as 50 mg tablets and MMI as 5 mg and 10 mg tablets (reflecting the difference in their potency). The initial dose of MMI typically is administered orally in three doses totaling 30 to 60 mg daily; typically MMI doses >40 mg/day are not necessary. The initial dose of PTU ranges from 300 to 600 mg daily (sometimes 800 mg/day), usually in 3-4 divided doses (i.e. 100 mg orally three times daily); higher doses and dose frequency are used in thyroid storm. Both drugs can also be given as a single dose, although there is some controversy regarding the efficacy of PTU when given once daily. MMI is more likely to be effective when administered as a single dose and this can improve compliance. Generally patients with severe hyperthyroidism may respond better to larger doses (PTU, 600 to 900 mg/day; MMI, 30 to 60 mg/day) and divided doses. The maximum MMI dose is 120 mg/day, and the maximum PTU dose is 1,200

mg/day. Dosages for pediatric patients are based on weight.

In most patients the symptoms of hyperthryoidism and circulating thyroid hormone levels return to normal levels within 4 to 8 weeks of initiating thionamide therapy. The onset of action of these drugs is slow because they block the biosynthesis rather than the release of thyroid hormones! The actual rate of return to the euthyroid state depends on the severity of the disease, the size of the thyroid gland, the antithyroid drug dosing regimen and patient compliance. The dose may be reduced after 4 to 6 weeks as the patient improves. Doses may be adjusted every 4 to 6 weeks thereafter until maintenance doses are attained: these typically are 5 to 30 mg daily of MMI or 50 to 300 mg daily of PTU. Changes in dose require an adequate interval (month) to allow for endogenous T_4 levels to reach their new steady state. It should ne noted that true resistance to the thionamides is quite rare and therefore most cases of therapeutic failure are linked to poor patient compliance (dosing regimen, adverse effects, etc.).

To induce long-term remissions, patients should remain on continuous thionamide therapy for 6 to 12 months and often for as long as 2 years. Some clinicians have advocated shorter term therapy (<6 months or until the patient is euthyroid) to improve compliance and save money, but remission rates in patients treated with short-term therapy have been disappointing. Patients are treated until a euthyroid state is achieved, spontaneous remission of Graves' disease occurs, or both. The optimal duration of therapy is unclear: the time to remission is unpredictable and, despite development of apparent complete remission on drug therapy, relapse is common (relapse rates range from 14% to 75% and plateau at 5 years). Antithyroid drug therapy is associated with permanent remissions in about 40-50% of patients, but some of these may have resulted from spontaneous remission. Typically patients who respond favorably to the thionamides are those who are older patients (>40 years old), with a low T_4/T_3 ratio (<20), a small goiter (<50g), short duration of disease (<6 months), no previous history of relapse with antithyroid drugs, duration of therapy (>1 year) and low TSAb titers. Patients who enter remission should be monitored at least annually. Although the T_4 suppression test and radioactive iodine uptake can be used to predict patients likely to maintain remission, these tests are rarely used in practice. A T_3 suppression test of 20% or less is a good indicator of prolonged remission, and some clinicians recommend treating patients with thionamides until this is achieved. Thionamide therapy can be reinstituted if hyperthyroidism reappears after a period of remission. Also, thionamides can be continued indefinitely if tolerated and the patient refuses other therapeutic approaches (surgery, RAI). Non-responsiveness to thionamides may indicate resistance, but other factors, such as noncompliance, insufficient dosing, or a dosing interval that provides too few doses per day, should also be considered. In the event of relapse, RAI therapy is preferred to a second course of thionamide therapy.

In the past some clinicians advocated concurrent administration of thyroxine with thionamides in Graves' and other hyperthyroid patients since it was believed this combined therapy resulted in a greater reduction in thyroid gland autoantibodies and improve remission rates. More recent studies, however, have not confirmed this combination therapy is superior to thionamides alone.

Monitoring: Thyroid function tests and resolution of signs and symptoms of hyperthyroidism are used to monitor thionamide therapy. Before these drugs are administered, baseline free T_4 and TSH levels should be determined. Also a baseline WBC count with differential should be

obtained to differentiate between the leukopenia associated with hyperthyroidism from drug-induced leukopenia and agranulocytosis (see Adverse Reactions below. Some symptoms, such as muscle-related complaints, may continue for months despite normalization of thyroid function tests. Thyroid function tests should be monitored every 4 to 6 weeks, and 4-6 weeks whenever there is a change in the thionamide dosing regimen . During therapy, the serum T_4 and T_3 levels should normalize; however, the serum thyrotropin (TSH) levels may remain suppressed for several months longer and, therefore, should not be used as a sole laboratory monitoring parameter. The patient should also be monitored for adverse drug effects (see below). Relatively minor adverse effects for both MMI and PTU include urticarial rash and pruritus, and both of these effects may resolve with continued therapy; if the rash or pruritus does not resolve, the patient may be switched to the other drug, although cross-reactivity is possible. Once the patient is euthyroid on maintenance doses of thionamides, thyroid function tests can be performed every 3-6 months. It should be noted that thionamide therapy can restore glycemic control in patients with diabetes

D. Adverse Effects

The incidence of minor adverse reactions to PTU and MMI is relatively low, ranging from 5-16%, and is dose dependent. Pruritic maculopapular rashes, arthralgias, fever and benign transient leukopenia (WBC < 4000/mm) are the most common minor ADRs and occur with greater frequency in children and at higher doses. It should be noted that patients with Graves' disease may have pruritus and pain associated with pretibial myxedema or dermopathy and not necessarily induced by the thionamide drug. Drug-related rashes (5-6%) typically occur early in therapy and may resolve spontaneously with continued thionamide therapy. If rashes persist they can be treated with antihistamines or topical corticosteroids. If the rash is urticarial or associated with other systemic manifestations of a rug reaction (fever, arthralgias), thionamide therapy may need to be discontinued.

Benign transient leukopenia (WBC $<4000/mm^3$) occurs quite frequently (12% adults) and is more common in children (25% children). A baseline white blood cell count (WBC) will help determine if any later alterations in WBCs are due to drug therapy or a result of the hyperthyroidism disease state. Typically leukopenia is not predictive of agranulocytosis (see below), and thus continued thioanmaide therapy is not contraindicated if the patient is leukopenic. Other relatively minor adverse effects include hypoprothrombinemia, and gastrointestinal disturbances (4-5%). For all the minor ADRs, thionamide therapy can be continued. One thionamide may be substituted for the other, but the incidence of cross-reactivity relative to minor ADRs is about 50%.

The incidence of serious adverse effects with MMI or PTU is estimated to be 1 to 5%. The most serious adverse effect associated with both PTU and MMI therapy is idiosyncratic agranulocytosis (granulocyte counts $<500/mm^3$) with an incidence of 0.5 to 6%. It is characterized by fever of more than 101°F for 1-2 days, malaise, sore throat, gingivitis, oropharyngeal infection or other symptoms of infection. Death can result from overwhelming infections in patients with agranulocytosis. The onset of agranulocytosis is almost always within 3 months, and patients more than 40 years of age appear to be at greater risk; however, definitive risk factors have not been identified. An autoimmune etiology has been suggested because

antineutrophil antibodies and lymphocyte sensitization have been detected in many patients. Others have suggested that the agranulocytosis is a direct toxic reaction to drug accumulation in granulocytes. The reaction appears to be dose dependent, because it occurs more frequently in patients on higher doses of MMI or PTU; some studies suggest it may be a dose-related effect for MMI, but not PTU. Patients should be counseled to notify their physician immediately if they experience symptoms characteristic of agranulocytosis, and thionamide therapy should be discontinued until the results of a WBC count and differential are available. While weekly monitoring of WBC with a differential during the first 3 months of thionamide therapy may identify some asymptomatic patients with agranulocytosis, routine WBC counts typically are not done because the onset of this reaction is so rapid. If agranulocytosis is diagnosed the thionamide should be discontinued and the patient monitored for symptoms of infection which can be treated with antibiotics. Glucocorticoids and colony-stimulating factors have been used with some success to restore cell counts to normal in thionamide-induced agranulocytosis. If the patient recovers, a normal granulocyte may occur in about 3 weeks. The patient should not be treated with any thionamide in the future.

Other serious but rare adverse effects include cholestatic jaundice (especially higher doses of MMI), hepatitis (especially PTU), lupus-like syndrome, vasculitis, glomerulonephritis, polyarthritis, thrombocytopenia, and aplastic anemia. PTU may cause a transient (within first 2 months) increase in liver transaminases in about 30% of patients and while this should be monitored it does not necessarily require discontinuation of therapy. Elevated liver enzymes typically normalize within 3 months of therapy, particularly if PTU doses are reduced. Overt hepatotoxicity has been reported for both drugs, usually within the first 3 months of therapy (<2%) and may include symptoms such as nausea, vomiting, diarrhea, fatigue and abdominal tenderness. If the symptoms of severe hepatitis appear (usually within 3 months), the drug should be discontinued and this typically results in resolution of symptoms. Rarely thionamide therapy has been associated with the development of lupus or lupus-like syndromes including symptoms such as skin ulcers, splenomegaly, migratory polyarthritis, pleuritis and pericarditis and renal abnormalities. Based on these potentially severe adverse reactions, all patients receiving thionamide drugs require close monitoring. Patients should be counseled to report jaundice, malaise, dark urine, or symptoms of lupus. Also, patients who experience a severe adverse reaction to one thionamide should not be switched to another because of the likelihood of cross-sensitivity and possible fatality. Patients who experience severe adverse reactions may require surgery or RAI to treat their hyperthyroidism.

Pregnancy: Propylthiouracil may cause hypoprothrombinemia, therefore concomitant warfarin therapy may lead to bleeding. Although methimazole and propylthiouracil both cross the placenta, these drugs have been used during pregnancy to treat hyperthyroidism. These drugs should also be used cautiously in the nursing mother.

Long-Term Therapy: Antithyroid drug therapy is continued for 6 to 24 months or longer, until the patient is asymptomatic and euthyroid. Longer treatment (eg, 24 months) with antithyroid drugs may favor long-term remission of Graves' disease; however, the factors affecting long-term remission are not fully elucidated. After therapy for hyperthyroidism, some patients develop hypothyroidism; these patients will require either temporary or lifelong thyroid hormone replacement therapy. Pharmacists can assist their patients first by helping them recognize the

signs and symptoms of hyperthyroidism and refer them to their primary care physician or endocrinologist, and, second, by providing pharmaceutical care for the patient receiving antithyroid drugs. Patients receiving either methimazole or propylthiouracil should receive instructions on proper administration, potential adverse effects (especially agranulocytosis and hepatitis), and the importance of adherence to therapy. Propylthiouracil should be taken with food or milk to minimize stomach upset.

V. ADJUNCTIVE DRUG THERAPY IN HYPERTHYROIDISM

Some patients suffering from hyperthyroidism may benefit from symptom relief provided by adjunctive drug therapy. Many of the clinical manifestations of hyperthyroidism are caused by adrenergic overstimulation resulting from over-expression of beta-adrenergic receptors and β-receptor stimulation. These symptoms include palpitations, anxiety and nervousness, tremor, heat intolrance, etc. Attempts to decrease such symptoms therefore have focused on application of adrenergic blocking agents. Reserpine and guanethidine, both depletors of catecholamines, clonidine, β-blockers and calcium channel blockers have been used effectively to decrease the adrenergic symptoms of thyrotoxicosis. Propranolol (or IV esmolol) has become the drug of choice in adjunctive therapy because: 1). most of these effects are mediated by beta-receptors, 2). Propranolol has a more favorable side effect profile, and 3). There have been some reports suggesting that propranolol decreases T_3 plasma levels by blocking the peripheral deiodination of T_4; but the contribution of this action to overall efficacy is minimal and appears to be mediated by the stereoisomeric form (D-isomer) that is devoid of beta-receptor blocking activity.
Beta-blockers are used in the following circumstances:

- As adjuncts to thionamides, RAIs or iodides in Grave's disease or toxic nodules
- As adjuncts in treatment of thyroid storm
- As adjuncts preparation for thyroid surgery
- As primary therapy for thyroiditis (including pregnancy) and iodine-induced hyperthyroidism

Initial doses of 20-40 mg of propranolol four times daily typically are effective to control the adrenergic manifestations of hyperthyroidism (monitor heart rate, <100 beats/min). Caution is advised when dosing with beta-blockers because their pharmacokinetics may be highly variable in diferent patients, and they are cleared more rapidly by hyperthyroid versus euthyroid patients. Thus younger and more severely thyrotoxic patients may require higher doses; patients with severe thyroid symptoms may require dosages as high as 240 to 480 mg/day. Beta-blockers are contra-indicated in congestive heart failure patients (unless caused solely by tachycardia) and patients who have developed cardiomyopathy, heart failure, sinus bradycardia, patients receiving MAO inhibitors or TCADs. These agents also are relatively contraindicated in patients who have diabetes mellitus, asthma, obstructive lung disease, or sinus bradycardia. Non-selective beta-blockers should be used with caution in patients with asthma, COPD and diabetes (type 1), and in pregnancy since they may prolong gestation and labor.

Calcium channel blockers such as diltiazem and verapamil (but not the dihydropyridines!) can be used as adjunctive therapy, particularly if beta-blockers are contraindicated (eg, patients with asthma). Diltiazem appears comparable to propranolol in controlling the hypertension and tachycardia associated with hyperthyroidism. Diltiazem 120 mg every 8 hours is reported to

reduce heart rate by 17%.

It should be noted that none of these adjuncts alter the course of disease; they only provide symptom relief! For example, beta-blockers do not block all peripheral effects of excess thyroid hormone and they have minimal effects on urinary excretion of ions (calcium, phosphorus) and amino acids and creatinine. Also, beta-blockers do no reduce TSAb levels or prevent thyroid storm. Thus, beta-blockers should not be used alone to treat hyperthyroidism.

VI. DRUGS USED IN HYPOTHYROIDISM (*Thyroidomimetics*)

Hormone replacement is the established therapy for the treatment of various forms of hypothyroidism, from the complete absence of thyroid function seen in myxedema to the simple goiter and cretinism. The goal of therapy is clinical and biochemical euthyroidism and prevention of long-term consequences as a result of associated pathologies such as hypercholesterolemia. Thyroid hormone preparations for replacement therapy are available in several different forms. The choices in replacement therapy include biologic preparations, such as desiccated thyroid or synthetic crystalline thyroid hormone products.

A. Desiccated Thyroid

Desiccated thyroid (eg, Armour Thyroid, Thyroid USP) contains natural T_4 and T_3 derived from animal (hog, beef, or sheep) thyroid glands. These preparations are essentially acetone powders of animal thyroid gland compressed into oral tablets. A diluent is usually present because the preparations (especially those of porcine origin) commonly exceed the 0.17 to 0.23% iodine content required by the United States Pharmacopeia. Because the iodine of desiccated thyroid is in the form of the iodinated tyrosyl and thyronyl residues of the precipitated thyroglobulin, the preparation owes its efficacy to the hormones that are eventually liberated by intestinal proteases. In desiccated preparations, T_3 and T_4 may be present in a ratio approximately that found in humans. Desiccated preparations are less expensive than synthetic hormones but have been shown to produce variable T_4/T_3 blood levels because of inconsistencies between and within animal sources of the thyroid gland. The concern with thyroid extracts is the potential variance in potency, and the excess of T_3 in some of these extracts, which may cause adverse cardiovascular effects. Also the animal protein–derived product may cause allergic reactions in some patients. Yet a recent study reported improved neuropsychological function for patients receiving the combination product compared to the synthetic product levothyroxine. The usual starting dose is 30 mg daily. The dose is titrated with increments of 15 mg every 2 to 3 weeks until a maintenance dose of 60 to 120 mg/day is achieved.

B. Liotrix

Synthetic, crystalline thyroid hormones are more uniformly absorbed than biologic preparations and contain more precisely measured amounts of active ingredient in their dosage forms. Of present interest are T_4 (levothyroxine), T_3 (liothyronine), d-T_4 (dextrothyroxine), and T_4-T_3 mixtures referred to as liotrix. The synthetic combination product liotrix (Thyrolar, Euthyroid) provides T_4 and T_3 in a fixed ratio of 4:1. Thus allergenicity and uniform potency are not an issue. These synthetic combination products are associated with excessive T_3 serum levels for

several hours after each dose, which may cause adverse cardiac effects. The initial dose of Liotrix is 30 mg daily and may be increased by 15-mg increments every 2 to 3 weeks until the patient is euthyroid; the maintenance dose is 60 to 120 mg daily. Liotrix appears to offer no clinical advantage over levothyroxine and should not be recommended as initial therapy unless a patient has already been stabilized on one of these products.

C. Liothyronine

Liothyronine (Cytomel, others) is synthetic T_3; therefore, it has uniform potency and is free of antigenicity. Liothyronine has a faster onset and a shorter duration of action (half-life of 1.5 days) compared with levothyroxine (discussed below and see Table). During the dosing interval, T_3 serum levels fluctuate widely and may lead to cardiac adverse effects. In thyroid cancer patients, liothyronine has been used for short-course therapy prior to radioactive iodine; however, it is not used as first-line therapy for hypothyroidism because it appears to be associated with a higher incidence of iatrogenic hyperthyroidism compared with levothyroxine. The initial dose is 25 μg/day, titrated by 12.5 to 25 μg every 1 to 2 weeks until the patient is euthyroid; the maintenance dose is generally 25 to 75 μg/day. Dividing the daily dose into two or three doses may minimize the wide fluctuations in serum T_3 levels. Liothyronine appears to offer no clinical advantage over levothyroxine and should not be recommended as initial therapy unless a patient has already been stabilized on one of these products.

Comparison of Levothyroxine (T_4) and Liothyronine (T_3):

Hormone	Ratio Released from Thyroid	Biologic Potency	Half-Life	PPB
Levothyroxine	20	1	6-7 days	99%
Liothyronine	1	4	< 2 days	99%

D. Levothyroxine

Levothyroxine (Synthroid, others) is synthetic T_4 hormone and is the levo-isomer of thyroxine which is the physiologically active stereoisomeric form. Levothyroxine provides a "pool" of hormone that is readily and consistently converted to the active form, T_3. This conversion allows for some level of physiologic regulation of the formation of active hormone. This conversion and because of its firmer binding to carrier proteins, levothyroxine has a slower onset of action and half-life (7 days) than has crystalline T_3 or than a desiccated thyroid preparation. Its administration leads to greater increase in serum T_4 but to a lesser increase in serum T_3 than that of thyroid, USP. Average bioavailability in current preparations is 80%, but is reduced (and unreliable) in the presence of GI diseases or other drugs (see the chapter "Thyroid Disorders" in the *Pharmacotherapy: a Pathophysiologic Approach*).

Levothyroxine is generally considered the drug of first choice for thyroid hormone replacement and suppressive therapy because of its consistent potency, lack of antigenicity, natural replacement of T_3, and prolonged duration of action as well as chemical stability and low cost. It does, however, have a relatively slow onset of action of 3 to 5 days.
Levothyroxine sodium is manufactured by several pharmaceutical companies. When levothyroxine came to the market (prior to 1962), manufacturers were not required to undergo

the FDA's new drug approval (NDA) process, an approval process that confirms that an agent is safe and effective and meets FDA standards for manufacturing, processes, potency, and stability. However, in 1997, after receiving reports of potency and stability problems-tablets having less active ingredient than indicated, tablets from different manufacturers and tablets from different lots from the same manufacturer lacking consistency, and the failure of the medication to maintain its potency through the expiration date-the FDA issued a mandate requiring that all manufacturers of levothyroxine have a complete and approved NDA by August 2000; that date, however, was extended to August 2001. To date, only Watson Pharmaceuticals/Jerome Stevens' levothyroxine sodium product has received an NDA. Approval of other manufacturers' levothyroxine may follow. Based on the FDA mandate, any levothyroxine without an NDA by the stated deadline will be subject to regulatory action, unless the FDA has determined, based on a submitted citizen petition, that a particular levothyroxine product is not subject to the new drug requirements of the act.

Bioequivalence of the various levothyroxine products remains controversial and cannot be assumed. Levothyroxine is considered a narrow therapeutic index drug because small variances in drug levels could affect a patient's health. Complications that could occur if dosage strength is inconsistent from the same manufacturer or when a patient is switched to another brand include.
For example if a levothyroxine product is less potent or has lower bioavailability, a suboptimal response (hypothyroidism) may result. If the a levothyroxine product is more potent or has higher bioavailability, toxic manifestations of hyperthyroidism may result. Thus, patients should be instructed to notify their physicians of any changes in their health and to not change brands of levothyroxine without consulting their physician and pharmacist. To prevent undertreatment or overtreatment, patients should be controlled and maintained on one brand of thyroid replacement therapy, cautioned not to change brands, and monitored over time.

Pharmacists should be aware of the expiration date of levothyroxine lots because of the inherent instability of levothyroxine in the presence of light, temperature, air, and humidity. Pharmacists also should counsel patients to be aware of the expiration date for this product and should guide them on the proper storage of the drug.

Levothyroxine Dosing: Patients receiving levothyroxine replacement therapy should be instructed to take their medication each day in the morning, preferably before breakfast because absorption is increased on an empty stomach.

The initial dose of levothyroxine in the treatment of hypothyroidism is dependent on patient age, the presence of disease-related disorders (cardiovascular status), and the severity and duration of hypothyroidism. The usual levothyroxine starting dose in young patients with long standing disease or adults over 45 years old is 50 μg daily. This is increased to 100 μg daily after 1 month of therapy. The average maintenance dose for most adults should be in the range of 110 to 120 μg/day. Pregnant women may require a 20% to 50% increase in dosage to achieve normal thyrotropin (TSH) serum levels. It should be noted that in the past, higher doses of levothyroxine were used, but they may be unnecessary and may be associated with adverse effects such as exacerbation of osteoporosis in women.
Treatment of congenital hypothyroidism requires full doses of thyroid hormone as soon after birth as possible to prevent neurologic damage and impaired development. If treatment is delayed

beyond 6 months after birth, full neurologic development is impaired and regression of neurologic deficits is not possible. The dosage of levothyroxine for congenital hypothyroidism is initially based on weight and is usually 10 μg/kg/day, but can range as high as 15 μg/kg/day. The dose is titrated to maintain T_4 levels of more than 10 μg/dL. The dose is decreased as the child ages, so that, by about age 15 years, adult maintenance doses are used. If hypothyroidism develops in children older than age 2 or 3 years, it will not be associated with neurologic deficits, if treated with thyroid hormone.

Dose requirements are usually reduced in the older patient because of an age-associated decrease in T_3 clearance. For patients older than age 50 years with cardiovascular disease or with long-standing hypothyroidism, the initial dosage of levothyroxine is 25 μg/day which then may be titrated upward in 25 μg increment at monthly or longer intervals. Caution should be exercised in dosing in some patients because excessive levothyroxine can exacerbate angina and stress the cardiovascular system.

It must be stressed that thyroxine replacement is lifelong and individualization of therapy is important for efficacy. Thus all patients should be monitored for resolution of clinical signs and symptoms, as well as for maintenance of normal TSH levels as a measure the adequacy of replacement. M*any clinicians now consider serum TSH levels to be the most sensitive and specific monitoring parameter for adjustment of levothyroxine dosing.* Typically patients are monitored every 4 to 8 weeks and the thyroxne doses titrated by 25 to 50 μg increments until resolution of symptoms and normalization of thyroid function tests. TSH assays need not be repeated until 4 to 6 weeks after initiating therapy or with dosage changes, because of the long half-life of levothyroxine. Inadequate dosing will be reflected by continued signs and symptoms of hypothyroidism, a low T_4 level, and an elevated thyrotropin (TSH) level during periodic evaluation;. Patient compliance is probably best monitored by measuring T_4 levels. If poor patient compliance is not suspected, then levothyroxine doses are increased and the patient reevaluated at the next clinic visit in 4 to 8 weeks.

With levothyroxine therapy, plasma TSH levels begin to decrease within hours and are usually normalized within 2 weeks; however, it may take up to 6 weeks in some cases. And patients should note improvement in some symptoms (eg, weight, facial edema, palpitations speech, skin temperature, mental alertness, and physical activity) within 2 to 3 weeks, although other symptoms (eg, hoarseness, skin and hair changes) will take longer to resolve. Once the patient is euthyroid, the frequency of thyroid function test monitoring may be reduced to every 6 to 12 months. In general, many patients remain stabilized on the same dose for years. However, physiologic changes over time (aging) or changes in concomitant drug therapy may lead to changes in levothyroxine dose.

Levothyroxine may also be used as TSH suppressive therapy in the treatment of nodular thyroid disease and diffuse goiter, patients who have undergone thyroid irradiation and patients with thyroid cancer. The rationale for levothyroxine in these cases is the reduction of TSH secretion which promotes the growth and function of abnormal thyroid tissue. The doses employed for these indications vary according to desired plasma level of TSH.

Drug and Disease Interactions: Mucosal diseases (i.e diabetes) and co-administration of drugs such as bile acid sequestrants (cholestyramine), sucralfate, aluminum antacids, iron supplements

(ferrous sulfate), soybean fiber and dietary suplements may impair the absorption of levothyroxine from the GI tract. Drugs that induce non-deiodinative metabolism such as rifampin, carbamazepine and phenytoin may increase the clearance of levothyroxine. Other drugs, such as amiodarone, may block the metabolic conversion of levothyroxine to T_3.

Adverse Reactions: With appropriate dosing and monitoring, especially during initiation of therapy, there are relatively few serious ADRs associated with thyroid hormone replacement therapy. Excessive levothyroxine therapy will lead to clinical manifestations of hyperthyroidism including tachycardia, weight loss, tremor, irritability, nervousness, excessive perspiration and heat intolerance and cardiovascular complications such as congestive heart failure, angina and myocardial infarction. Therefore, thyroid function tests should be performed periodically even after the patient has been stabilized on a maintenance dose and some patients should have their doses held for a week and then therapy restarted at a lower dose. Hyperthyroidism is a known risk factor for osteoporosis, and long-term, excessive levothyroxine therapy may also be associated with decreased bone mineral density caused by hyperremodeling of cortical and trabecular bone. These effects appear to depend on age and sex, with postmenopausal women being more susceptible than men or premenopausal women. Although the actual risk of osteoporosis is not proven, excessive levothyroxine doses should be avoided and regular monitoring performed. Finally, as mentioned previously, allergic reactions are extremely rare with the synthetic thyroid hormone replacement agents available today.

E. Patient Counseling Tips for Levothyroxine Therapy

Patients receiving levothyroxine for the first time should be counseled to know the specific brand they will be receiving to maintain consistency with future refills. Levothyroxine should be taken orally once daily. Patients should be counseled on the time frame for symptom relief, and they should understand that thyroid hormone replacement therapy is usually lifelong and requires periodic laboratory tests. In addition, patients should learn the common symptoms of hyperthyroidism (eg, sweating, nervousness, tremors, diarrhea) to understand when their levothyroxine dose may need to be adjusted and to monitor for improvement. The patient counseling tips for this drug can be summarized as follows:

- Explain to the patient that his or her physician has prescribed this medication to control the signs and symptoms of thyroid disease. Outline the following guidelines to help ensure that patients receive optimal benefit from the medication.
- The name of the medication is levothyroxine. The medication should be stored in a cool, dry place out of the reach of children.
- This medication is made by several different manufacturers and the patient should receive the same brand of medication each time the prescription is refilled.
- The medication should be taken at the same time each day.
- Do not use more or less of the medication than the prescribing physician ordered.
- If you miss a dose, you should take it as soon you remember it, unless it is time for the next dose. In this instance, you should simply take the next scheduled dose. Do not double the dose.
- Do not discontinue using this medication without first checking with your physician.
- If your problem is related to a lack of thyroid hormones, you will most likely have to take this

medication for the rest of your life.
- If you have signs and symptoms of hypothyroidism, it may take two or three weeks for them to diminish.
- Notify your physician immediately if you experience chest pain, palpitations or a rapid pulse. These could indicate that the dose of your medication is too high and needs to be adjusted.
- This medication may cause other, less serious side effects such as sweating, nervousness, hand tremors, headache or diarrhea. These may also indicate that your dose needs to be adjusted, and you should report these side effects to your physician.
- It is very important to keep scheduled appointments with your physician in order to check your progress while using this medication.
- Tell all of your other healthcare professionals that you are taking levothyroxine, especially before having any kind of surgery (including dental) or emergency treatment.
- Consult with your physician or pharmacist before taking other prescription or nonprescription medications.

VII. GOITROGENS AND OTHER SUBSTANCES THAT AFFECT THYROID AND THYROID HORMONE FUNCTION

The degree to which drugs affect the patient clinically depends on the individual patient's pituitary-thyroid function and their ability to compensate for the changes. In most cases, of drug interaction described below the patient experiences alterations in thyroid function test results without developing clinically relevant disease. The key is to recognize that patients who are receiving these drugs and who develop signs or symptoms of thyroid disease may have an etiology that can be addressed (ie, drug discontinuation). It is also important to know which drugs affect the results of laboratory thyroid tests for appropriate interpretation.

A. Pharmacologic Interactions with "Conventional Drugs"

Lithium salts have been used as safe adjuncts in the initial treatment of thyrotoxicosis. Lithium is concentrated by the thyroid gland with a thyroid-to-serum ratio of more than 2:1, suggesting active transport. Lithium ion inhibits adenylate cyclase, which forms Camp, the mediator formed in response to TSH and is a stimulator of the processes involved in thyroid hormone release from the gland. Inhibition of hormone secretion by lithium has proved a useful adjunct in treatment of hyperthyroidism. However, hypothyroidism develops in up to 15% of patients treated with lithium and occurs most commonly occurs in patients with underlying thyroid disorders. Lithium treatment may also predispose patients to develop thyroid antibodies. Thyroid function tests (eg, TSH) should be undertaken before beginning lithium therapy and repeated annually unless the patient develops symptoms of hypothyroidism or does not respond adequately to lithium therapy.

The ability of oxidation products of 3,4-dihydroxycinnamic acid to prevent the binding of TSH to human thyroid membranes suggests that other oxygenated phenols may interfere with thyroid hormone function in more than one way. Examples of iodinated drugs affecting thyroid function are the antiarrhythmic agent amiodarone and the radiocontrasting agents iopanoic acid (Telepaque) and ipodoic acid (Oragrafin). All of these compounds interfere with the peripheral deiodination of T_4 and are being tested as adjuncts in the treatment of hyperthyroidism. Amiodarone is high in iodine content (each 200-mg tablet contains 75 mg of elemental iodine)

and is associated more often with hypothyroidism than with hyperthyroidism; however, either can occur. For patients who develop hyperthyroidism, the amiodarone dose should be decreased, and, if necessary, the drug should be discontinued. Amiodarone-induced hypothyroidism also can be managed by hormone replacement therapy. Hyperthyroidism secondary to amiodarone takes several months to resolve because of the drug's long half-life. If amiodarone cannot be discontinued, thionamide drugs (methimazole) may be used concurrently to control the symptoms of hyperthyroidism.

Other compounds affecting thyroid function include sulfonamides, anticoagulants, and oxygenated and iodinated aromatic compounds. The hypoglycemic agent carbutamide and the diuretic diamox are examples of sulfonamides. Of the anticoagulants, heparin appears to interfere with the binding of T_4 to plasma transport proteins (see below) but warfarin and dicoumarol are competitive inhibitors of the substrate T_4 or r T_3 in the 5'-D reaction, with a Ki in the micromolar range. Other oxygenated compounds affecting the 5'-D include resorcinol, long known to be a goitrogen, and phloretin, a dihydrochalocone with an I_{50} of 4 M.

A. Pharmacokinetic Interactions with "Conventional Drugs"

Absorption: Bile acid sequestrants (cholestyramine and colestipol) and certain metal preparations including aluminum hydroxide, ferrous sulfate and sucralfate are knoww to bind levothyroxine in the gut forming an insoluble complexes that are not absorbed. The clinical significance of these drug-drug interactions varies among patients. However, patients taking any of these drugs should be educated to take levothyroxine at least 2 hours before or 6 hours after one of these agents. Also, even with dose separation, thyroid hormone levels may still be lowered secondary to enterohepatic circulation of thyroxine.

Metabolism: Several drugs have complex effects on the metabolism of T_4 and T_3. Phenobarbital, phenytoin carbamazepine and rifampin may induce hepatic enzyme activity thereby increasing T_4 and T_3 metabolism and decreasing. The vast majority of people taking these drugs experience alteration in thyroid function tests while remaining clinically euthyroid; however, treated hypothyroid patients taking these drugs may require increased levothyroxine doses. The enzyme thyroxine 5-deiodinase, which converts T_4 to T_3, is also a target for drugs that can disrupt thyroid hormone concentrations. As noted previously, amiodarone inhibits this enzyme. Beta-blockers and corticosteroids can also inhibit thyroxine 5-deiodinase. Most people are able to compensate for these effects and remain clinically euthyroid.

Protein Binding: The binding of thyroid hormones to plasma carrier proteins is affected by endogenous agents or by drugs that can change the concentration of these proteins or compete with thyroid hormones for binding sites (see Table below). Drugs that decrease serum TBG concentrations include corticosteroids, slow-release nicotinic acid, and anabolic steroids; most patients remain clinically euthyroid. Estrogen (endogenous and exogenous), tamoxifen, methadone, mitotane, and fluorouracil increase TBG concentrations. In most cases, the free (biologically active) T_4 and T_3 concentrations are unchanged; however, pregnant women with hypothyroidism may require an increase in levothyroxine dose.

Salicylates, phenytoin, heparin and furosemide are members of the large group competing with

thyroid hormones for binding sites. Alterations in the binding of T_3 and T_4 are of no large physiologic consequence because the steady-state concentrations of free hormone are rapidly restored by homeostatic mechanisms. Knowledge of the presence of agents affecting thyroid hormone binding is, however, important for the interpretation of diagnostic tests assessing the presence of free or total hormone in plasma.

Summary of the effects of physiological states on plasma thyroid binding proteins and T_3 and T_4 levels

Condition	Concentrations of Binding Proteins	Total Plasma T_4, T_3, RT_3	Free Plasma T_4, T_3, RT_3	Plasma TSH	Clinical State
Primary hyperthyroidism	Normal	High	High	Low	Hyperthyroid
Primary hypothyroidism	Normal	Low	Low	High	Hypothyroid
Drugs (estrogens, methadone, heroin, perphenazine, clofibrate), pregnancy, acute and chronic hepatitis, acute intermittent porphyria, estrogen-producing tumors, idiopathic, hereditary	High	High	Normal	Normal	Euthyroid
Drugs (glucocorticoids, androgens, danazol, asparaginase), acromegaly, nephrotic syndrome, hypoproteinemia, chronic liver disease (cirrhosis), testosterone-producing tumors, hereditary	Low	Low	Normal	Normal	Euthyroid

B. Interactions with Alternative/Herbal Medicines and Foods

In view of the role of cysteine residues in the conformation of thyroglobulin, the mode of action of TPO, and the deiodination of T_4, the effect of sulfur-containing compounds on thyroid hormone formation is hardly surprising. Most naturally occurring sulfur compounds are derived from "glucosinolates" (formerly referred to as thioglucosides), present in foods such as cabbage, turnip, mustard seed, salad greens, and radishes (most of these are from the genus brassica of cruciferae) as well as in the milk of cows grazing in areas containing brassica weeds. Chemically, glucosinolates can give rise to many components, including thiocyanate (CNS-), isothiocyanate (SCN-), nitrites (RCN), and thiooxazolidones. Thiocyanate is a large anion that competes with iodide for uptake by the thyroid gland; its goitrogenic effect can be reversed by iodide intake. Goitrin, 5-R-vinyloxazolidine-2-thione, is a potent thyroid peroxidase inhibitor, claimed to be more effective than PTU in humans and held to be the cause of a mild goiter endemia in Finland. In rats, goitrin is actively taken up by the thyroid gland and appears to inhibit the coupling of TG diiodotyrosyl residues. Many workers believe, however, that the goitrogenic effects of brassica are due to the additive effects of all goitrogenic components present.

Approximately 70% of patients using herbal medications do not reveal the use of these products to their physicians. Concomitant use of herbal products can lead to serious and sometimes life-threatening drug-herb interactions. For example, horseradish, used as an antiseptic and promoted for pulmonary and urinary tract infections, may depress thyroid function. Kelp, used for weight loss, heart disease, arthritis, breast cancer, and osteoporosis, contains 0.7 mg of iodine per tablet and can cause hyperthyroidism in people sensitive to iodine. Patients should be informed not to

use kelp products concomitantly with levothyroxine or other thyroid hormone products. Herbal medicines containing ma huang or stimulants similar to amphetamines or methylphenidate could also cause serious adverse consequences in patients with thyroid disorders.

Some herbal medicine advocates promote desiccated thyroid hormone as "natural" and more effective than synthetic levothyroxine. Pharmacists and physicians should keep in mind that desiccated thyroid products prepared from animal thyroid glands are more rapidly absorbed than T4 and T3. Because T3 is more rapidly absorbed than T4, supraphysiologic concentrations of T3 can occur (resulting in symptoms of hyperthyroidism) and cause adverse cardiovascular effects. Allergic reactions to the protein component of desiccated thyroid may also occur. Therefore, preparations containing desiccated thyroid are not recommended.