Published in http://www.thyroidmanager.org/ © 2016

Chapter 11-DIAGNOSIS AND TREATMENT OF GRAVES' DISEASE

Leslie J De Groot, MD, Research Professor, Univ. of Rhode Island/Providence, 80 Washington St (room 302), Providence, RI 02903 ldegroot@earthlink.net

Paolo Vitti, MD Professor of Medic ine. University of Pisa, Pisa Italy

Revised 2 Nov 2016

ABSTRACT

Diagnosis of the classic form of Graves' disease is easy and depends on the recognition of the cardinal features of the disease and confirmation by tests such as TSH and FTI. The differential diagnosis includes other types of thyrotoxicosis, such as that occurring in a nodular gland, accompanying certain tumors of the thyroid, or thyrotoxicosis factitia, and nontoxic goiter. Types of hypermetabolism that imitate symptoms of thyrotoxicosis must also enter the differential diagnosis. Examples are certain cases of pheochromocytoma, polycythemia, lymphoma, and the leukemias. Pulmonary disease, infection, parkinsonism, pregnancy, or nephritis may stimulate certain features of thyrotoxicosis.

Treatment of Graves' disease cannot yet be aimed at the cause because it is still unknown. One seeks to control thyrotoxicosis when that seems to be the major indication, or the ophthalmopathy when that aspect of the disease appears to be more urgent. The available forms of treatment, including surgery, drugs, and $^{131\text{-}I}$ therapy, are reviewed. There is a difference of opinion as to which of these modalities is best, but to a large degree guidelines governing choice of therapy can be drawn. Antithyroid drugs are widely used for treatment on a long- term basis. About one-third of the patients undergoing long-term antithyroid therapy achieve permanent euthyroidism. Drugs are the preferred initial therapy in children and young adults. Subtotal thyroidectomy is a satisfactory form of therapy, if an excellent surgeon is available, but is less used in 2016. The combined use of antithyroid drugs and iodine makes it possible to prepare patients adequately before surgery, and operative mortality is approaching the vanishing point. Many young adults, are treated by surgery if antithyroid drug treatment fails.

Currently, most endocrinologists consider RAI to be the best treatment for adults, and consider the associated hypothyroidism to be a minor problem. Evidence to date after well over five decades of experience indicates that the risk of late thyroid carcinoma must be near zero. The authors advise this therapy in most patients over age 40, and believe that it is not contraindicated above the age of about 15. Dosage is calculated on the basis of $^{131\text{-}I}$ uptake and gland size. Most patients are cured by one treatment. Hypothyroidism.occurs with a fairly constant frequency for many years after therapy and may be unavoidable if cure of the disease is to be achieved by 131-I.. Many therapists accept this as an anticipated outcome of treatment.

Thyrotoxicosis in children is best handled initially by antithyroid drug therapy. If this therapy does not result in a cure, surgery may be performed. Treatment with $^{131\text{-}I}$ is accepted as an alternative form of treatment by some physicians, especially as age increase toward 15 years. Neonatal thyrotoxicosis is a rarity. Antithyroid drugs, propranolol and iodide may be required for several weeks until maternally-derived antibodies have been metabolized.

The physician applying any of these forms of therapy to the control of thyrotoxicosis

should also pay heed to the patient's emotional needs, as well as to his or her requirements for rest, nutrition, and specific antithyroid medication. Consult our FREE web-book WWW.ENDOTEXT.ORG for complete coverage on this and related topics.

We note that there are currently available 2 very extensive Guidelines on Diagnosis and Treatment of Graves' Disease—The 2016 ATA guideline --- http://online.liebertpub.com/doi/pdfplus/10.1089/thy.2016.0229 (270 pages), and the AACE 2011 version on Hyperthyroidism and other Causes of Thyrotoxicosis (65 pages)--https://www.aace.com/files/hyperguidelinesapril2013.pdf.
Both are well worth reviewing.

CLINICAL DIAGNOSIS

The diagnosis of Graves' disease is usually easily made. The combination of **eye signs**, **goiter**, and any of the characteristic **symptoms and signs of hyperthyroidism** forms a picture that can hardly escape recognition (Fig -1). It is only in the atypical cases, or with coexisting disease, or in mild or early disease, that the diagnosis may be in doubt. The symptoms and signs have been described in detail in the section on manifestations of Graves' disease. For convenience, the classic findings from the history and physical examination are grouped together in Table 1a and 1b.These occur with sufficient regularity that clinical diagnosis can be reasonably accurate. Scoring the presence or absence and severity of particular symptoms and signs can provide a clinical diagnostic index almost as reliable a diagnostic measure as laboratory tests(1).

Figure 1. Graves' disease patient with exophthalmos and vitiligo.

Occasionally diagnosis is not at all obvious.In patients severely ill with other disease, in elderly patients with "apathetic hyperthyroidism", or when the presenting symptom is unusual, such as muscle weakness, or psychosis, the diagnosis depends on clinical alertness and laboratory tests.

The diagnosis of Graves' Disease does not only depend on thyrotoxicosis. Ophthalmopathy, or pretibial myxedema may occasionally occur without goiter and thyrotoxicosis, or even with spontaneous hypothyroidism. While proper classification can be debated, these patients seem to represent one end of the spectrum of Graves' Disease. Thus we are usually making two coincident diagnoses:1)- Is the patient hyperthyroid? and 2)- Is the cause of the problem Graves' disease ?.

Table 1a---Symptoms of Graves' disease

- Preference for cool temperature
- Weight loss with increased appetite
- Prominence of eyes, puffiness of lids
- Pain or irritation of eyes
- Blurred or double vision, decreasing acuity, decreased motility
- Goiter
- Dyspnea
- Palpitations or pounding of the heart
- Ankle edema (without cardiac disease)
- Less frequently, orthopnea, paroxysmal tachycardia, anginal pain, and CHF
- Increased frequency of stools
- Polyuria
- Decrease in menstrual flow; menstrual irregularity or amenorrhea
- Decreased fertility
- Fatigue
- Weakness, Tremor
- Occasional bursitis
- Rarely periodic paralysis
- Nervousness, irritability
- Emotional lability
- Insomnia or decreased sleep requirement
- Thinning of hair, Loss of curl in hair
- Increased perspiration
- Change in texture of skin and nails
- Vitiligo
- Swelling over out surface of shin

Family history of any thyroid disease, especially Graves' disease

TABLE 1B PHYSICAL SIGNS

- Weight loss
- Hyperkinetic behavior, thought, and speech
- Restlessness
- Lymphadenopathy and occasional splenomegaly
- Eyes
- Prominence of eyes, lid lag, globe lag
- Exophthalmos, lid edema, chemosis, extraocular muscle weakness
- Decreased visual acuity, scotomata, papilledema, retinal hemorrhage, and edema
- Goiter
- Sometimes enlarged cervical nodes
- Thyroid thrill and bruit
- Tachypnea on exertion
- Tachycardia, overactive heart, widened pulse pressure, and bounding pulse
- Occasional cardiomegaly, signs of congestive heart failure, and paroxysmal tachycardia or atrial fibrillation
- Tremor
- Objective muscle wasting and weakness
- Quickened and hypermetric reflexes
- Emotional lability
- Fine, warm, moist skin
- Fine and often straight hair
- Oncholysis (Plummer's nails)
- Pretibial myxedema, Acropachy Hyperpigmentation or vitiligo

LABORATORY DIAGNOSIS OF GRAVE'S DISEASE

Serum Hormone Measurements

TSH and FT4 assay-Once the question of thyrotoxicosis has been raised, laboratory data are required to verify the diagnosis, help estimate the severity of the condition, and assist in planning therapy. A single test such as the TSH or estimate of FT4 (free T4) may be enough, but in view of the sources of error in all determinations, most clinicians prefer to assess two more or less independent measures of thyroid function. For this purpose, an assessment of FT4 and sensitive TSH are suitable.

As an initial single test, a sensitive TSH assay may be most cost-effective and specific. **TSH should be 0 - .1 μU/ml in significant thyrotoxicosis**, although values of .1 - .3 are seen in patients with mild illness, especially with smoldering toxic multinodular goiter in older patients(1.1). TSH can be low in some elderly patients without evidence of thyroid disease. TSH can be normal -- or elevated -- only if there are spurious test

results from heterophile antibodies or other cause, or the thyrotoxicosis is TSH-driven, as in a pituitary TSH-secreting adenoma or pituitary resistance to thyroid hormone.

Measurement of **FT4 or FTI** (Free thyroxine index)**is also usually diagnostic**.The degree of elevation of the FT4 above normal provides an estimate of the severity of the disease. During replacement therapy with thyroxine the range of both FTI and fT4 values tend to be about 20% above the normal range, possibly because only T4, rather than T4 and T3 from the thyroid, is providing the initial supply of hormone. Thus many patients will have an fT4 or FTI above normal when appropriately replaced and while TSH is in the normal range. Except for this, elevations of fT4 not due to thyrotoxicosis are unusual, and causes are given in Table 3.

Of course the Total T4 level may normally be as high as 16 or 20 µg/dl in pregnancy, and can be elevated without thyrotoxicosis in patients with familial hyperthyroxinemia due to abnormal albumin, the presence of hereditary excess TBG, the presence of antibodies binding T4 , the thyroid hormone resistance syndrome, and other conditions listed in Table 3. The T4 level may be normal in thyrotoxic patients who have depressed serum levels of T4 -binding protein or because of severe illness, even though they are toxic. Thus, thyrotoxicosis may exist when the total T4 level is in the normal range. However measurement of FT4, FT3 (Free T3), or FTI (Free Thyroxine Index) usually obviates this source of error and is the best test. In the presence of typical symptoms, one measurement of suppressed TSH or elevated fT4 is sufficient to make a definite diagnosis, although it does not identify a cause. If the fT4 is normal, repetition is in order to rule out error, along with a second test such as serum FT3. And it should be noted that in much of Europe FT3 is the preferred test, rather than FT4, and serves very well.

A variety of methods for FT4 determination have become available, including commercial kits. Although these methods are usually reliable, assays using different kits do not always agree among themselves or with the determination of FT4 by dialysis. Usually T4 and T3 levels are both elevated in thyrotoxicosis, as is the FTI (Free Thyroxin Index), or an index constructed using the serum T3 and rT3U levels, and the newer measures of FT3.

Table 3. Conditions Associated with Transient Elevations of the FT4 or FTI

Condition	Explanation
Estrogen withdrawal	Rapid decrease in TBG level
Amphetamine abuse	Possibly induced TSH secretion(2)
Acute psychosis	Unknown
Hyperemesis gravidarum	Associated high hCG can cause thyrotoxicosis
Iodide administration	Thyroid autonomy
Beginning of T4 administration	Delayed T4 metabolism(3)
Severe illness (rarely)	Decreased T4 to T3 conversion (4)
Amiodarone treatment	Decreased T4 to T3 conversion, iodine load
Gallbladder contrast agents	Decreased T4 to T3 conversion, iodine load
Propranolol (large doses)	Inhibition of T4 to T3 conversion

Condition	Explanation
Prednisone (rarely)	Inhibition of T4 to T3 conversion
High altitude exposure	Possibly hypothalamic activation
Selenium deficiency	Decreased T4 to T3 conversion

T3 and FT3 ASSAY-The serumT3 level determined by RIA is almost always elevated in thyrotoxicosis and is a useful but not commonly needed secondary test. Usually the serum T3 test is interpreted directly without use of a correction for protein binding, since alterations of TBG affect T3 to a lesser extent than T4. Any confusion caused by alterations in binding proteins can be avoided by use of a FT3 assay or T3 index calculated as for the FTI. Generally the FT3 assay is as diagnostically effective as the FT4. In patients with severe illness and thyrotoxicosis, especially those with liver disease or malnutrition or who are taking steroids or propranolol, the serum T3 level may not be elevated, since peripheral deiodination of T4 to T3 is suppressed ("T4 toxicosis"). A normal T3 level has also been observed in thyrotoxicosis combined with diabetic ketoacidosis. Whether or not these patients actually have tissue hypermetabolism at the time their serum T3 is normal is not entirely certain. In these patients the rT3 level may be elevated. If the complicating illness subsides, the normal pattern of elevated T4 , FTI, and T3 levels may return(5,6). Elevated T4 levels with normal serum T3 levels are also found in patients with thyrotoxicosis produced by iodine ingestion(7).

T3 Toxicosis Since 1957, when the first patient with T3 thyrotoxicosis was identified, a number of patients have been detected who had clinical thyrotoxicosis, normal serum levels of T4 and TBG, and elevated concentrations of T3 and FT3[8]. Hollander et al [9] found that approximately 4% of patients with thyrotoxicosis in the New York area fit this category. These patients often have mild disease but otherwise have been indistinguishable clinically from others with thyrotoxicosis. Some have had the diffuse thyroid hyperplasia of Graves' disease, others toxic nodular goiter, and still others thyrotoxicosis with hyperfunctioning adenomas. Interestingly, in Chile, a country with generalized iodine deficiency, 12.5% of thyrotoxic subjects fulfilled the criteria for T3 thyrotoxicosis [10]. Asymptomatic hypertriiodothyronemia is an occasional finding several months before the development of thyrotoxicosis with elevated T4 levels [11]. Since T4 is normally metabolized to T3, and the latter hormone is predominantly the hormone bound to nuclear receptors, it makes sense that elevation of T3 alone is already indicative of thyrotoxicosis.

Thyroid Isotope uptake-In patients with thyrotoxicosis the RAIU (Radioactive Iodine Uptake) at 24 hours is characteristically above normal. In the United States, which has had an increasing iodine supply in recent years, the upper limit of normal is now about 25% of the administered dose. This value is higher in areas of iodine deficiency and endemic goiter. The uptake value at a shorter time interval, for example 6 hours, is as valid a test and may be more useful in the infrequent cases having such a rapid isotope turnover that "uptake" has fallen to normal by 24 hours. If there is reason to suspect that thyroid isotope turnover is rapid, it is wise to do both a 6- and a 24-hour RAIU determination during the initial laboratory study. As noted below, rapid turnover of 131-I can seriously reduce the effectiveness of 131-I therapy. Similar studies can be done with 123-I and also technetium. Because of convenience, and since serum assays of thyroid hormones and TSH are reliable and readily available, the RAIU is now infrequently determined unless 131-I therapy is planned.. It is however useful in patients who are mildly thyrotoxic for factitia thyrotoxicosis, subacute thyroiditis and painless thyroiditis in

whom RAIU is low, thus confirming thyrotoxicosis in the absence of elevated RAIU. This may include patients with brief symptom duration, small goiter, or lacking eye signs, absent family history, or negative antibody test result. Obviously other causes of a low RAIU test need to be considered and excluded. Tests measuring suppressibility of RAIU are of historical interest(13-15)

Thyroid IsotopeScanning-Isotope scanning of the thyroid has a limited role in the diagnosis of thyrotoxicosis. It is useful in patients in whom the thyroid is difficult to feel or in whom nodules (single or multiple) are present that require evaluation, or rarely to prove the function of ectopic thyroid tissue. Nodules may be incidental, or may be the source of thyrotoxicosis (toxic adenoma), or may contribute to the thyrotoxicosis that also arises from the rest of the gland. Scanning should usually be done with 123-I in this situation, in order to combine it with an RAIU measurement.

Thyroid Ultrasound- US exam of the thyroid is sometimes of value in diagnosis. For example, if a possible nodule is detected on physical exam. It also may confirm hypoechogenicity or intense vascularity of Graves' disease if a color Doppler flow exam is done.

Antithyroid Antibodies Determination of antibody titers provides supporting evidence for Graves' disease. More than 95% of patients have positive assays for TPO (thyroperoxidase or microsomal antigen), and about 50% have positive anti-thyroglobulin antibody assays. In thyroiditis the prevalence of positive TG antibody assays is higher. Positive assays prove that autoimmunity is present, and patients with causes of thyrotoxicosis other than Graves' disease usually have negative assays. During therapy with antithyroid drugs the titers characteristically go down, and this change persists during remission. Titers tend to become more elevated after RAI treatment.

Antibodies to TSH-Receptor-Thyrotrophin receptor antibody (TRAb) assays have become readily available, and a positive result strongly supports the diagnosis of Graves' disease(15.1). Determination of TRAb is not required for the diagnosis, but the implied specificity of a positive test provides security in diagnosis, and for this reason the assay is now widely used. The assay is valuable as another supporting fact in establishing the cause of exophthalmos, in the absence of thyrotoxicosis. High maternal levels suggest possible fetal or neonatal thyrotoxicosis. TRAb assays measure any antibody that binds to the TSH-R. Assays for Thyroid Stimulating Antibodies (TSAb,TSI) are less available, but are more specific for the diagnosis. Using current tests, both are positive in about 90% of patients with Graves disease who are thyrotoxic. "Second generation" assays becoming available use monoclonal anti-TSH-R antibodies and biosynthetic TSH-R in coated tube assays, are reported to reach 99% specificity and sensitivity(15.2,15.3,3). Although rarely required, serial assays are of interest in following a patient's course during antithyroid drug therapy, and a decrease predicts probable remission(15.4).

Other Assays Rarely Used-General availability of assays that can reliably measure suppressed TSH has made this the gold standard to which other tests must be compared, and has effectively eliminated the need for most previously used ancillary tests. There are only rare causes of confusion in the TSH assay. Severe illness, dopamine and steroids, and hypopituitarism, can cause low TSH, but suppression below 0.1 µ/ml is uncommon and below 0.05 µ/ml is exceptional, except in thyrotoxicosis. Thyrotoxicosis is associated with normal or high TSH in patients with TSH producing

pituitary tumors and selective pituitary resistance to thyroid hormone.
If TSH, FT4, TRAb, and other tests noted above do not establish the diagnosis, it may be wise to do nothing further except to observe the course of events. In patients with significant thyroid hyperfunction, the symptoms and signs will become clearer, and the laboratory measurements will fall into line. Measurement of BMR, T3 suppression of RAIU, TRH testing, and clinical response to KI are of historical interest.

DIFFERENTIAL DIAGNOSIS of THYROTOXICOSIS
Graves' disease must be differentiated from other conditions causing thyrotoxicosis. (Table -4).

T**hyrotoxicosis factitia-**Thyrotoxicosis may be caused by taking T4 or its analogs, most commonly due to administration of excessive replacement hormone by the patient's physician. Hormone may be taken surreptitiously by the patient for weight loss or psychologic reasons. The typical findings are a normal or small thyroid gland, a low131-I uptake, a low serum TG, and, of course, a striking lack of response to antithyroid drug therapy. The problem can easily be confused with "painless thyroiditis", but in thyrotoxicosis factitia, the gland is typically small.

Toxic nodular goiter is usually distinguished by careful physical examination and a history of goiter for many years before symptoms of hyperthyroidism developed. The thyrotoxicosis comes on insidiously, and often, in the older people usually afflicted, symptoms may be mild, or suggest another problem such as heart disease. The thyroid scan may be diagnostic, showing areas of increased and decreased isotope uptake. The results of assays for antithyroid antibodies, including TRAb, are usually negative. TMNG is typically produced by activating somatic mutations in TSH-R in one or more nodules, allowing them to enlarge and become functional even in the absence of TSH stimulation. (Interestingly, cats are well known to develop hyperthyroidism, with thyroid autonomy, often due to TSH-R gene mutations as seen in humans.(16))

Hyperfunctioning solitary adenoma is suggested on the physical finding of a palpable nodule in a otherwise normal gland, and is proved by a scintiscan demonstrating preferential radioisotope accumulation in the nodule. This type of adenoma must be differentiated from congenital absence of one of the lobes of the thyroid. Toxic nodules typically present in adults with gradually developing hyperthyroidism and a nodule > 3 cm in size. These nodules are usually caused by activating somatic mutations in the TSH-R, which endows them with mildly increased function, compared to normal tissue, even in the absence of TSH. These nodules are usually, but not always, monoclonal(17). In adults toxic nodules are very rarely malignant. Rarely, functioning thyroid carcinomas produce thyrotoxicosis. The diagnosis is made by the history, absence of the normal thyroid, and usually widespread functioning metastasis in lung or bones. Invasion of the gland by lymphoma has produced thyrotoxicosis, presumably due to thyroid destruction (18).

Thyrotoxicosis associated with **subacute thyroiditis** is usually mild and transient, and the patient lacks the physical findings of long-standing thyrotoxicosis. If thyrotoxicosis is found in conjunction with a painful goiter and low or absent 131-I uptake, this diagnosis is likely. Usually the erythrocyte sedimentation rate (ESR) and CRP are greatly elevated, and the leukocyte count may also be increased. Occasionally the goiter is non-tender. Antibody titers are low or negative. Many patients have the HLA-B35 antigen, indicating a genetic predisposition to the disease. The rare **TSH secreting pituitary adenoma** will be missed unless one measures the plasma TSH level, or until the enlargement is

sufficient to produce deficiencies in other hormones, pressure symptoms, or expansion of the sella turcica(19). These patients have thyrotoxicosis with inappropriately elevated TSH levels and may/or may not secrete more TSH after TRH stimulation. The characteristic finding is a normal or elevated TSH, and an elevated TSH alpha subunit level in blood, measured by special RIA. TRAbs are not present. Exophthalmos, and antibodies of Graves' disease are absent. Family history is sometimes positive for a similar condition. Demonstration of a suppressed TSH level excludes these rare cases.

The category of patients with **thyrotoxicosis and inappropriately elevated TSH** levels also includes the rare persons with pituitary "T3 resistance" as a part of the Resistance to Thyroid Hormone syndrome caused by TH Receptor mutations. The syndrome of Pituitary Thyroid Hormone Resistance is usually marked by mild thyrotoxicosis, mildly elevated TSH levels, absence of pituitary tumor, a generous response to TRH, no excess TSH alpha subunit secretion [19,20, 21],and by TSH suppression if large doses of T3 are administered. Final diagnosis depends on laboratory demonstration of a mutation in the TR gene, if possible. Hyperthyroidism caused by excess TRH secretion is a theoretical but unproven possibiity.

Administration of **large amounts of iodide** in medicines, for roentgenographic examinations, or in foods can occasionally precipitate thyrotoxicosis in patients with multinodular goiter or functioning adenomas. This history is important to consider since the illness may be self-limiting. Induction of thyrotoxicosis has also been observed in apparently normal individuals following prolonged exposure to organic iodide containing compounds such as antiseptic soaps and amiodarone. **Amiodarone** is of special importance since the clinical problem often is the presentation of thyrotoxicosis in a patient with serious cardiac disease including dysrythmia. Amodarone can induce thyrotoxicosis in patients without known prior thyroid disease, or with multinodular goiter. The illness appears to come in two forms. In one the RAIU may be low or normal. In the second variety , which appears to be more of a thyroiditis-like syndrome, the RAIU is very suppressed, and IL-6 may be elevated. In either case TSH is suppressed, FTI may be normal or elevated, but T3 is elevated if the patient is toxic. Antibodies are usually negative.

An increasingly recognized form of thyrotoxicosis is the syndrome described variously as **painless thyroiditis, transient thyrotoxicosis, or "hyperthyroiditis**". Its hallmarks are self-limited thyrotoxicosis, small painless goiter, and low or zero RAIU(22,23). The patients usually have no eye signs, a negative family history, and often positive antibody titers. This condition is due to autoimmune thyroid disease, and is considered a variant of Hashimoto's Thyroiditis. It occurs sporadically, usually in young adults. It frequently occurs 3 - 12 weeks after delivery, sometimes representing the effects of immunologic rebound from the immunosuppressive effects of pregnancy in patients with Hashimoto's thyroiditis or prior Graves' Disease, and is called **Post Partum Thyroiditis**(22-25). The course typically includes development of a painless goiter, mild to moderate thyrotoxicosis, no eye signs, remission of symptoms in 3 -20 weeks, and often a period of hypothyroidism before return to euthyroid function. The cycle may be repeated several times. Histologic examination shows chronic thyroiditis, but it is not typical of Hashimoto's disease or subacute thyroiditis and may revert to normal after the attack(26). In most patients, the thyrotoxic episode occurs in the absence of circulating TSAb. This finding suggests that the pathogenesis is quite distinct from that in Graves' disease. The thyrotoxicosis is caused by an inflammation-induced discharge of preformed hormone due to the thyroiditis. The T4/T3 ratio is higher than in typical Graves' disease,and thyroid iodine stores are depleted. Since the thyrotoxicosis is due

to an inflammatory process, therapy with antithyroid drugs or potassium iodide is usually to no avail, and RAI treatment of course cannot be given when RAIU is suppressed. Propranolol is usually helpful for symptoms. Glucocorticoids may be of help if the process -- often transient and mild -- requires some form of therapy. Propylthiouracil and/or ipodate can be used to decrease T4 to T3 conversion and will ameliorate the illness. Repeated episodes may be handled by surgery or by RAI therapy during a remission. Occasionally painless post-partum thyroiditis is followed by typical Graves' Disease(27-29.1).

Hyperemisis gravidarum is frequently associated with elevated serum T4 , FTI, and variably elevated T3, and suppressed TSH. The abnormalities in thyroid function are caused by high levels of hCG. This molecule, or a closely related form, share enough homology with TSH so that it has about 1/1000 the thyroid stimulating activity of TSH, and can produce thyroid stimulation or thyrotoxicosis(29.12-29.14). It is typically self limited without specific treatment, disappears with termination of pregnancy, but may occasionally require anti-thyroid treatment temporarily or throughout pregnancy(29.3). Patients with minimal signs and symptoms, small or no goiter, and elevation of FTI up to 50 % above normal probably do not require treatment. Rarely those with goiter, moderate or severe clinical evidence of thyrotoxicosis, highly elevated T4 and T3 and suppressed TSH are best treated with antithyroid drugs. If antibodies are positive or eye signs are present, the picture is usually interpreted as a form of Graves' disease. Familial severe hyperemesis gravidarum with fetal loss has been reported with an activating germline mutation in the TSH-R, which made it specifically more sensitive to activation by hCG(.29.2,29.3). Hyperthyroidism can be induced by "hyperplacentosis", which is characterized by increased placental weight and circulating hCG levels higher than those in normal pregnancy(29.4). After hysterotomy, hCG levels declined in the one case reported and hyperthyroidism was corrected.

Congenital hyperthyroidism caused by a germ-line activating mutation in the TSH-R has recently been recognized . The mutations are usually single aminoacid transitions in the extracellular loops or transmembrane segments of the receptor trans-membrane domain. The diagnosis may be difficult to recognize in the absence of a family history. However the patients lack eye signs, and have negative assays for antibodies(29.2, 29.3)

Hydatidiform moles, choriocarcinomas, and rarely seminomas secrete vast amounts of hCG. hCG, with an alpha subunit identical to TSH , and beta subunit related to TSH , that binds to and activates the thyroid TSH receptor with about 1/1,000th the efficiency of TSH itself (Fig.-3)(30-33). Current evidence indicates that very elevated levels of native hCG or perhaps desialated hCG, cause the thyroid stimulation. Many patients have goiter or elevated thyroid hormone levels or both, but little evidence of thyrotoxicosis, whereas others are clearly thyrotoxic. Diagnosis rests on recognizing the tumor (typically during or after pregnancy) and measurement of hCG. Therapy is directed at the tumor.

Hyperthyroidism also is seen as one manifestation of **autoimmune thyroid disease** induced by interferon-alpha treatment of chronic hepatitis C. It can be self limiting, or severe enough to require cessation of IFN, or in some cases continue on after INF is stopped(33.1).

Hyperthyroidism also occurs during **immune reconstitution** seen after effective anti-viral therapy of patients with HIV(33.2), has occurred during recovery of low lymphocyte levels induced by therapy with CAMPATH in patients with Multiple sclerosis, has occurred after cessation of immune-suppressive treatment in patients with T1DM.

Table 4. Causes of Thyrotoxicosis

Disease	Course of disease	Physical finding	Diagnostic finding	Treatment/Comment
Graves' disease	Familial, prolonged	Goiter	+ Ab, + RAIU, eye signs	Antithyroids, RAI, Surgery
Transient thyrotoxicosis	Brief	Small goiter	Low Ab, no eye signs, RAIU=0	Time, beta blocker, steroids
Subacute thyroiditis	Brief	Tender goiter	RAIU=0, elevated ESR, recent URI	Nothing, NSAID, steroids
Toxic multinodular goiter	Prolonged, mild	Nodular goiter	Typical scan	Antithyroids, RAI, surgery
Iodide induced	Recent, mild	Nodular goiter, occ.normal	Low RAIU, abnormal scan	Antithyroids, KClO4, time, stop I source
Toxic adenoma	Prolonged, mild	One nodule	"Hot" nodule on scan	Surgery, RAI
Thyroid carcinoma	Recent	Variable, metastases	Functioning metastases	Surgery + RAI
Exogenous hormone	Variable	Small thyroid	RAIU and TG low, psychiatric illness	Withdrawal, counseling
Hydatiform mole	Recent, mild	Goiter	Pregnancy, bleeding,HCG	Surgery, chemotherapy
Choriocarcinoma	Recent, mild	Goiter	Increased HCG	Surgery, chemotherapy
TSH-oma	Prolonged	Goiter	Excess alpha, TSH, adenoma	Op, somatostatin, thyroid ablation
Pituitary T3 resistance	Prolonged	Goiter	Elevated or normal TSH, no tumor, mod. thyrotox, no excess alpha	Triac, somatostatin, thyroid ablation, beta blocker
Struma ovarii	Variable	+ / - goiter	Positive scan or US	Surgery
Thyroid destruction	Variable	Variable	Variable	Steroids
Hamburger toxicosis	Recent, self-limited	Small gland, no eye signs	Suppressed TSH and TG and RAIU	Avoid neck meat trimmings

Disease	Course of disease	Physical finding	Diagnostic finding	Treatment/Comment
Hyperemesis	Onset first trimester	Pregnancy, variably toxic	UP FTI, Low TSH, High HCG	ATD if severe, pregnancy termination
TSH-R mutation	Congenital	Typical thyrotoxicosis	+ FH, germline mutation	Thyroid ablation
Familial gestational hyperthyroidism	Onset first trimester	Severe hyperthyroidism	+ FH, TSH-R mutation sensitizing to hCG	ATD, Surgery
Amiodarone	Prolonged	Thyroid usually enlarged. Often heart disease.	Suppressed RAIU, nl or increased FTI, elevated T3	ATD + KClO4,Prednisone, Surgery,iopanoic acid
Interferon-alpha induced	Induced by INF treatment of hepatitis C	Clinically significant		Often remits if IFN stopped.
Treatment of HIV	During T cell recovery	Clinically significant	With or without prior thyroid autoimmunity	May need treatment
Administration of CAMPATH	During recovery of T cells	Clinically significant	With or without prior thyroid autoimmunity	May need treatment
Sunitinib therapy	During tyrosine kinase therapy for cancer	Clinically significant	Usually induces hypothyroidism, rarely hyper	May need treatment

Subclinical hyperthyroidism

It should be remembered that thyrotoxicosis is today not only a clinical but also a laboratory diagnosis. Consistent elevation of the fT4 , and the T3 level, and suppressed TSH, or only suppression of TSH, can indicate that thyrotoxicosis is present even in the absence of clear-cut signs or symptoms These elevations themselves are a sufficient indication for therapy, especially in elderly patients with coincident cardiac disease(33a,b). Antithyroid drug treatment of patients with subclinical hyperthyroidism was found to result in a decrease in heart rate, decrease in number of atrial and ventricular premature beats, a reduction of the left ventricular mass index, and left ventricular posterior wall thickness, as well as a reduction in diastolic peak flow velocity. These changes are considered an argument for early treatment of subclinical hyperthyroidism. Subclinical hyperthyroidism may disappear or evolve into Graves hyperthyroidism, or when caused by MNG, persist for long periods unchanged.

Individuals of any age with consistent suppression of TSH should be fully evaluated to determine if evidence of hyperthyroidism is present, or there is coincident disease that might be aggrevated by hyperthyroidism. SCH with TSH of 0.2-0.3.5 may not need treatment. Individuals with TSH at or below 0.1uU/ml most likely will require treatment by one of the methods described below.

Apathetic hyperthyroidism designates a thyrotoxic condition characterized by fatigue, apathy, listlessness, dull eyes, extreme weakness, often congestive heart failure, and low-grade fever.[34, 35] Often such patients have small goiters, modest tachycardia, occasionally cool and even dry skin, and few eye signs. The syndrome may, in some patients, represent an extreme degree of fatigue induced by long-standing thyrotoxicosis. Once the diagnosis is considered, standard laboratory tests should confirm or deny the presence of thyrotoxicosis even in the absence of classical symptoms and signs.

Other diagnostic problems Two common diagnostic problems involve (1) the question of hyperthyroidism in patients with **goiter** of another cause, and (2) mild **neuroses** such as anxiety, fatigue states, and neurasthenia. Most patients with goiter receive a battery of examinations to survey their thyroid function at some time. Usually these tests are done more for routine assessment than because there is serious concern over the possibility of thyrotoxicosis. In the absence of significant symptoms or signs of hyperthyroidism and ophthalmologic problems, a normal FTI or TSH determination is sufficiently reassuring to the physician and the patient. Of course, the most satisfactory conclusion of such a study is the identification of an alternate cause for enlargement of the thyroid.
Some patients complain of fatigue and palpitations, weight loss, nervousness, irritability, and insomnia. These patients may demonstrate brisk reflex activity, tachycardia (especially during examinations), perspiration, and tremulousness. In the abscence of thyrotoxicosis, the hands are more often cool and damp rather than warm and erythematous. Serum TSH assay should be diagnostic.

Mild and temporary elevation of the FTI may occur if there is a transient **depression of TBG** production -- for example, when estrogen administration is omitted. This problem is occasionally seen in hospital practice, usually involving a middle-aged woman receiving estrogen medication that is discontinued when the patient is hospitalized. Estrogen withdrawal leads to decreased TBG levels and a transiently elevated FTI. After two to three weeks, both the T4 level and the FTI return to normal (Table -3).
In the differential diagnosis of **heart disease**, the possibility of thyrotoxicosis must always be considered. Some cases of thyrotoxicosis are missed because the symptoms are so conspicuously cardiac that the thyroid background is not perceived. This is especially true in patients with atrial fibrillation.
Many disorders may on occasion show some of the features of hyperthyroidism or Graves' disease. In **malignant disease**, especially lymphoma, weight loss, low grade fever, and weakness are often present. Parkinsonism in its milder forms may initially suggest thyroid disease. So also do the flushed countenance, bounding pulse, thyroid hypertrophy, and dyspnea of **pregnancy**. Patients with chronic pulmonary disease may have prominent eyes, tremor, tachycardia, weakness, and even goiter from therapeutic use of iodine. One should remember the weakness, fatigue, and jaundice of hepatitis and the puffy eyes of trichinosis and nephritis. **Cirrhotic patients** frequently have prominent eyes and lid lag, and the alcoholic patient with tremor, prominent eyes, and flushed face may be initially suspected of having thyrotoxicosis. Distinguishing between Graves' disease with extreme myopathy and **myopathies** of other origin can be clinically difficult. The term chronic thyrotoxic myopathy is used to designate a condition characterized by weakness, fatigability, muscular atrophy, and weight loss usually associated with severe thyrotoxicosis. Occasionally fasciculations are seen. The electromyogram result may be abnormal. If the condition is truly of hyperthyroid origin, the thyroid function tests are abnormal and the muscular disorder is reversed when the thyrotoxicosis is relieved. Usually a consideration of the total clinical picture and

assessment of TSH and FTI are sufficient to distinguish thyrotoxicosis from polymyositis, myasthenia gravis, or progressive muscular atrophy. True myasthenia gravis may coexist with Graves' disease, in which case the myasthenia responds to neostigmine therapy. (The muscle weakness of hyperthyroidism may be slightly improved by neostigmine, but never relieved.) Occasionally electromyograms, muscle biopsy, neostigmine tests, and ACH-receptor antibody assays must be used to settle the problem.

TREATMENT OF THYROTOXICOSIS–
SELECTION OF PRIMARY THERAPY

No treatment is ideal and thus indicated in all patients (35.1).Three forms of primary therapy for Graves' disease are in common use today: (1) **destruction of the thyroid by 131-I**; (2) **blocking of hormone synthesis by antithyroid drugs;** and (3) **partial or total surgical ablation of the thyroid**. Iodine alone as a form of treatment was widely used in the past, but is not used today because its benefits may be transient or incomplete and because more dependable methods became available. Iodine is primarily used now in conjunction with antithyroid drugs to prepare patients for surgical thyroidectomy when that plan of therapy has been chosen. There is, however, some revival of interest in use of iodine treatment as described subsequently. Roentgen irradiation was also used in the past, but is not currently [36]. Suppression of the autoimmune response is being attempted, and currently new treatments blocking the action of Thyroid Stimulating Immunoglobulins are being investigated.

Selection of therapy depends on a multiplicity of considerations [36.1]. Availability of a competent surgeon, for example, undue emotional concern about the hazards of 131-I irradiation, or the probability of adherence to a strict medical regimen might govern one's decision regarding one program of treatment as opposed to another. More than 90% of patients are satistactorly treated cumulating the effects of these treatment.(36.2) Fig. 2

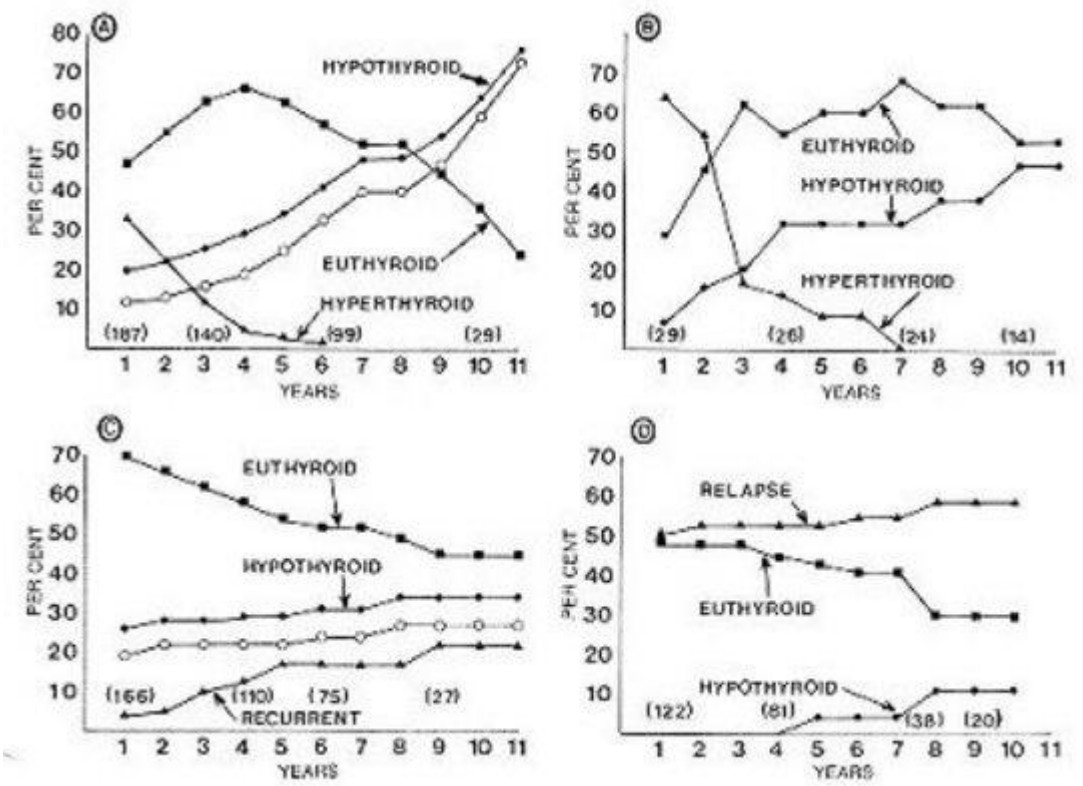

Figure 2. Comparison of outcome of treatment of Graves' disease in adults by 131-I (left upper panel); 131-I plus ATD + KI (right upper panel); surgery (left lower panel); and ATD (right lower panel); over ten years follow-up at the University of Chicago. Surgery produced the highest final percentage of euthyroidism without therapy, followed by ATD and 131-I. 131-I treatment caused the highest incidence of permanent hypothyroidism requiring replacement treatment.

Antithyroid drug therapy offers the opportunity to avoid induced damage to the thyroid (and parathyroids or recurrent nerves), as well as exposure to radiation and operation. In recent studies patients with thyroids under 40 gm weight, with low TRAb levels, and age over 40, were most likely to enter remission (in up to 80%) (36.3, 36.31). The difficulties are the requirement of adhering to a medical schedule for many months or years, frequent visits to the physician, occasional adverse reactions, and, most importantly, a disappointingly low permanent remission rate. Therapy with antithyroid drugs is used as the initial modality in most patients under age 18, in many adults through age 40, and in most pregnant women(36.31). Remission is most likely in young patients, with small thyroids, and mild disease. ATDs may be preferred in elderly patients, those with serious co-morbidities and who have been previously operated upon.

Iodine-131 therapy is quick, easy, moderatly expensive, avoids surgery, and is without significant risk in adults and probably teenagers. The larger doses required to give prompt and certain control generally induce hypothyroidism, and low doses are associated with a frequent requirement for retreatment or ancillary medical management over one to two years. 131-I is used as the primary therapy in most persons over age 40 and in most adults above age 21 if antithyroid drugs fail to control the disease.

Treatment of children with 131-I is less common, as discussed later. It can be used in the elderly and those with co-morbidities with precautions.

Surgery, which was the main therapy until 1950, has been to a large extent replaced by 131-I treatment. As the high frequency of 131-I induced hypothyroidism became apparent, some revival of interest in thyroidectomy occurred. The major advantage of surgery is that definitive management is often obtained over an 8- to 12-week period, including preoperative medical control, and many patients are euthyroid after operation. Its well-known disadvantages include expense, surgery itself, and the risks of recurrent nerve and parathyroid damage, hypothyroidism, and recurrence. Nevertheless, if a skillful surgeon is available, surgical management may be used as the primary or secondary therapy in many young adults, as the secondary therapy in children poorly controlled on antithyroid drugs, in pregnant women requiring excessive doses of antithyroid drugs, in patients with significant exophthalmos, and in patients with coincident suspicious thyroid nodules. Early total thyroidectomy has been recommended for treating older, chronically ill patients with thyrotoxic storm if high-dose thionamide treatment, iopanoic acid, and glucocorticoids fail to improve the patient's condition within 12 – 24 hours (36.4).

Two recent surveys reporting trends in therapeutic choices made by thyroidologists have been published [37]. In Europe, most physicians tended to treat children and adults first with antithyroid drugs, and adults secondarily with 131-I or less frequently surgery. Surgery was selected as primary therapy for patients with large goiters. 131-I was selected as the primary treatment in older patients. Most therapists attempted to restore euthyroidism by use of 131-I or surgery. In the United States, 131-I is the initial modality of therapy selected by members of the American Thyroid Association for management of uncomplicated Graves' disease in an adult woman [38]. Two-thirds of these clinicians attempt to give 131-I in a dosage calculated to produce euthyroidism, and one-third plan for thyroid ablation.

131-I THERAPY FOR THYROTOXICOSIS OF GRAVES' DISEASE

Introduction-In many thyroid clinics 131-I therapy is now used for most patients with Graves' disease who are beyond the adolescent years. It is used in most patients who have had prior thyroid surgery, because the incidence of complications, such as hypoparathyroidism and recurrent nerve palsy, is especially high in this group if a second thyroidectomy is performed. Likewise, it is the therapy of choice for any patient who is a poor risk for surgery because of complicating disease. Surgery may be preferred in patients with significant ophthalmopathy, often combined with prednisone prophylaxis.

Treatment of children-The question of an age limit below which RAI should not be used frequently arises. With lengthening experience these limits have been lowered. Several studies with average follow-up periods of 12 - 15 years attest to the safety of 131-I therapy in adults [39- 41]. In two excellent studies treated persons showed no tendency to develop thyroid cancer, leukemia, or reproductive abnormalities, and their children had no increase in congenital defects or evidence of thyroid damage [42- 44]. Franklyn and co workers recently reported on a population based study of 7417 patients treated with 131-I for thyrotoxicosis in England [44.1]. They found an overall decrease in incidence of cancer mortality, but a specific increase in mortality from cancer of the small bowel (7 fold) and of the thyroid (3.25) fold. The absolute risk remains very low, and it is not possible to determine whether the association is related to the basic disease, or to

radioiodine treatment. Although there is much less data on long term results in children, there is a increased use of this treatment in teenagers age 15-18, as discussed below. The epidemic of thyroid cancer apparently induced by radioactive iodine isotopes in infants and children living around Chernobyl suggests caution in use of 131-I in younger children.

Since the possibility of a general induction of cancer by 131-I is of central concern, it is interesting to calculate the risk in children using the data presented by Rivkees et al (44.2) who are proponents of use of RAI for therapy in young children..The risk of death from any cancer due specifically to radiation exposure is noted by these authors to be 0.16%/rem for children, and the whole body radiation exposure from RAI treatment at age 10 to be 1.45 rem/mCi administered. Rivkees et al advise treatment with doses of RAI greater then 160 uCi/gram thyroid, to achieve a thyroidal radiation dose of at least 150Gy (about 15000 rads). Assuming a reasonable RAIU of 50% and gland size of 40 gm, the administered dose would thus be 40(gm) x 160uCi/gm x 2 (to account for 50% uptake) =12.8 mCi. Thus the long term cancer death risk would be 12.8 (mCi) x 1.45 rem (per mCi) x 0.16% (per rem) = 3%. For a dose of 15mCi the theoretical incremental risk of a later radiation-induced cancer mortality would be 4% at age 5, 2% at age 10, and 1% at age 15.
Whether or not accepting a specific 2-4% risk of death from any cancer because of this treatment is of course a matter of judgment by the physician and family. However, this would seem to many persons to constitute a significant risk that might be avoided. We note that this is a thoretical risk, based on known effects of ioniing radiation to induce malignancies, but not so far proven in this setting.

Low 131-I uptake-Certain other findings may dictate the choice of therapy. Occasionally, the 131-I uptake is significantly blocked by prior iodine administration. The effect of iodide dissipates in a few days after stopping exposure, but it may take 3-12 weeks for the effect of amiodarone or IV contrast dyes to be lost. One may either wait for a few days to weeks until another 131-I tracer indicates that the uptake is in a treatable range or use an alternative therapeutic approach such as antithyroid drugs.

Coincident nodule(s)-Sometimes a patient with thyrotoxicosis harbors a thyroid gland with a configuration suggesting the presence of a malignant neoplasm. These patients probably should have surgical exploration. While FNA may exclude malignancy, the safety of leaving a highly irradiated nodule in place for many years is not established. Currently few patients who will have RAI therapy are subjected to ultrasonagraphy or scintiscaning. However Stocker et al. found that 12% of Graves' patients had cold defects on scan, and among these half were referred for surgery. Six of 22, representing 2% of all Graves' patients, 15% of patients with cold nodules, 25% of patients with palpable nodules, and 27% of those going to surgery, had papillary cancer in the location corresponding to the cold defect. Of these patients, one had metastasis to bone and two required multiple treatments with radioiodine. They argue for evaluating patients with a thyroid scintigram and further diagnostic evaluation of cold defects(44.3). Certainly any patient with GD in whom a thyroid nodule is detected, deserves consideration for surgical treatment

Ophthalmopathy-131-I therapy causes an increase in titers of TSH-R Abs, and anti-TG or TPO antibodies, which reflects an activation of autoimmunity. It probably is due to release of thyroid antigens by cell damage, and possibly destruction of intrathyroidal T cells. Many thyroidologists are convinced that 131-I therapy can lead to exacerbation of

infiltrative ophthalmopathy, perhaps because of this immunologic response. Tallstedt and associates published data indicating that 131-I therapy causes exacerbation of ophthalmopathy in nearly 25% of patients, while surgery is followed by this response in about half as many.The same group conducted a second randomized trial (44.3) with a follow-up of 4 yr. Patients with a recent diagnosis of Graves' hyperthyroidism were randomized to treatment with iodine-131 (163 patients) or 18 months of medical treatment (150 patients). Early substitution with L-T4 was given in both groups.: Worsening or development of eye problems was significantly more common in the iodine-131 treatment group (63 patients; 38.7%) compared with the medical treatment group (32 patients; 21.3%) ($P < 0.001$). This adverse effect of RAI therapy has since been confirmed in multiple meta-analyses of randomized studies (44.4-44.7) Thus, as described below, patients with significant ophthalmopathy may receive corticosteroids along with131-I, or may be selected for surgical management. The indications and contraindications for 131-I therapy are given in Table 5.

Table 5-Indications and Contraindication for RAI Therapy

Indications
• Any patients above a preselected age limit (possibly 15-18 yrs) • Patients who fail to respond to antithyroid drugs • Prior thyroid or other neck surgery Contraindications to surgery, such as severe heart, lung,or renal disease Women intending to become pregnant (more than 6 months later)
General Contraindications
• Pregnancy or lactation • Insufficient $^{131\text{-}I}$ uptake due to prior medication or disease • Question of malignant thyroid tumor • Age below a preselected age limit, such as (possibly) age 15-18 Patient concerns regarding radiation exposure
Other Possible Contraindications
• Unusually large glands • Active exophthalmos

SELECTION OF 131-I Dosage

There are two basically different goals in 131-I dose selection. The traditional approach has been to attempt to give the thyroid 1) sufficient radiation to return the patient to euthyroidism, but not induce hypothyroidism. An alternative approach is to intend to 2) induce hypothyroidism, or euthyroidism and avoid any possible return of hyperthyroidism.

Background-The dosage initially was worked out by a trial-and-error method and by successive approximations. By 1950, the standard dose was 160 uCi 131-I per gram of estimated thyroid weight. Of course, estimating the weight of the thyroid gland by examination of the neck is an inexact procedure, but can now be made more accurate by use of ultrasound. Also, marked variation in radiation sensitivity no doubt exists and cannot be estimated at all. It was gratifying that in practice this dosage scheme worked

well enough**.** In the early 1960s, it was recognized that a complication of RAI therapy was a high incidence of hypothyroidism. This reached 20 - 40% in the first year after therapy and increased about 2.5% per year, so that by 10 years 50 - 80% of patients had low function [45,46]. In an effort to reduce the incidence of late hypothyroidism, Hagen and colleagues reduced the quantity of 131-I to 0.08 mCi per gram of estimated gland weight [48]. No increase was reported in the number of patients requiring retreatment, and there was a substantial reduction in the incidence of hypothyroidism. Most of these patients were maintained on potassium iodide for several months after therapy, in order to ameliorate the thyrotoxicosis while the radioiodine had its effect [49, 50]. Patients previously treated with 131-I are sensitive to and generally easily controlled by KI. However KI often precipitates hypothyroidism in these patients, which may revert to hyperthyroidism when the KI is discontinued.

Over the years some effort was made to refine the calculation. Account was taken of uptake, half-life of the radioisotope in the thyroid, concentration per gram, and so on, but it is evident that the result in a given instance depends on factors that cannot be estimated precisely [47,]. One factor must be the tendency of the thyroid to return to normal if a dose of radiation is given that is large enough to make the gland approach, for a time, a normal functional state. In many patients, "cure" is associated with partial or total thyroid ablation. Although we, and many endocrinologists, attempt to scale the dose to the particular patient, some therapists believe it is futile, advocate giving up this attempt, and provide a standard dose giving up to 10000 rads to the thyroid(47.1). Leslie et al reported a comparison of fixed dose treatment and treatment adjusted for 24 hour RAIU, using low or high doses, and found no difference in outcome in either rate of control or induction of hypothyroidism on comparison of the methods. They favor the use of a fixed dose treatment with a single high or low dose (47.2).

Many attempts have been made to improve the therapeutic program by giving the RAI in smaller doses. Reinwein et al [51]. studied 334 patients several years after they had been treated with serial doses of less than 50 uCi 131-I per gram of estimated thyroid weight. One-third of these patients had increased levels of TSH, although they were clinically euthyroid. Only 3% were reported to be clinically hypothyroid.

Dosage adjustmentsmade to induce euthyroidism usually include a factor inc reassing with gland size, a standard dose in microCuries per gram, and a correction to account for 131-I uptake [52]. A**"Low Dose Protocol**" was designed to compensate for the apparent radiosensitivity of small glands and resistance of larger glands [53]. Using this approach, after one year, 10% of patients were hypothyroid, 60% are euthyroid, and 30% remained intrinsically toxic [53], although euthyroid by virtue of antithyroid drug treatment. At ten year follow-up, 40% were euthyroid and 60% hypothyroid. A problem with low-dose therapy is that about 25% of patients require a second treatment and 5% require a third. Although this approach reduces early hypothyroidism, it does so at a cost in time, money and patient convenience (Fig. 2). To answer these problems, patients can be re-treated, if need be, within six months, and propranolol and antithyroid drugs can be given between 131-I doses if needed. Unfortunately, experience shows that even low-dose $^{131\text{-}I}$therapy is followed by a progressive development of hypothyroidism in up to 40 - 50% of patients ten years after therapy[54- 57].

Table 6. LOW Dosage Schedule for 131-I Therapy

Thyroid wt. in gms.	uCi retained/gm thyroid at 24h	Thyroid rads, avg.
10-20	40	3310
21-30	45	3720
31-40	50	4135
41-50	60	4960
51-60	70	5790
61-70	75	6200
71-80	80	6620
81-90	85	7030
91-100	90	7440
100 +	100	8270

Impressed by the need to retreat nearly a third of patients, a "**Moderate Dose Protoco**l" was developed Table -6). This is a fairly conventional program with a mean dose of about 9 mCi. The $^{131\text{-}I}$ dosage is related to gland weight and RAIU, and is increased as gland weight increases. The calculation used is as follows:

uCi given = (estimated thyroid weight in grams) X (uCi/g for appropriate weight from Table 6) / (fractional RAIU at 24 hours) (For readers who may find difficult the conversion of older units in Curies, rads, and rems to newer units of measurement, see Table -7.)

Table 6. MODERATE Dosage Schedule for 131-I Therapy

Thyroid wt. in gms.	Planned uCi retained/gm thyroid at 24h	Thyroid rads, avg.
10-20	**80**	6620
21-30	90	7440
31-40	100	8270
41-50	120	9920
51-60	140	11580
61-70	150	12400
71-80	160	13240
81-90	170	14060
91-100	180	14880
100 +	200	16540

Table 7. Conversion of International Units of Measurement

International Units	Conversion Factors
Becquerel (Bq)	2.7 x 10^{-11}Curies (1mCi=37MBq, 100mCi= 3.7GBq)
Gray (Gy)	100 rads (1 rad= 0.01Gy)
Sievert (Sv)	100 rems (1 rem = 0.01 Sv)

Probably it is wise to do uptakes and treatment using either capsules or liquid isotope for both events. Rini et al have reported that RAIU done with isotope in a capsule appears to give significantly lower values (25 – 30% lower) than when the isotope is administered in liquid form, and this can significantly influence the determination of the dosage given for therapy(57.1). Berg et al report using a relatively similar protocol (absorbed doses of 100-120 Gy) and that 93% of their patients required replacement therapy after 1-5 years [57.2]. Many studies have presented methods for more accurately delivering a specific radiation dose to the thyroid, and report curing up to 90% of patients, with low incidence of recurrence or hypothyroidism(57.3, 57.4). Franklyn and co-workers analyzed their data on treatment of 813 hyperthyroid patients with radioactive iodide and corroborate many of the previously recognized factors involved in response. Lower dose (in this case 5 mCi), male gender, goiters of medium or large size and severe hyperthyroidism were factors that were associated with failure to cure after one treatment. They suggest using higher fixed initial doses of radioiodine for treating such patients (58.2), as do Leslie et al(58.4). Santos et al (58.4) compared fixed doses of 10 and 15mCi and found no difference in outcome at 12 months post treatment. These authors suggest a standard 10mCi dose, with the larger dose reserved for larger glands.

Planned thyroid partial or complete ablation-All attempts to induce euthyroidism by a calculated moderate dose protocol end up with some patients hypothyroid, and others with persistent hyperthyroidism requiring further treatment. At this time many physicians giving 131-I therapy make no attempt to achieve euthyroidism, and instead use a dose sufficient to largely destroy the thyroid, followed by L- T4 replacement therapy [58]. For example, a dose is given that will result in 7-20 mCi retained at 24 hrs, which is intended to induce hypothyroidism, accepting that in some (or many) patients this will ablate the thyroid completely. A dose of 30 Mci was found to offer a slightly higher cure rate, not surprisingly, at one year than 15 Mci (95 vs 74% (58.1), They argue that this is realistic and preferable since it offers 1) near certainty of prompt control, 2) avoids any chance of persistent or recurrent disease, 3)there is no benefit in having residual thyroid tissue, and 4) hypothyroidism is inevitable in most patients given RAI. Probably many patients given this treatment do in fact have some residual thyroid tissue that is either heavily damaged or reduced in amount so that it can not produce normal amounts of hormone.

So far there is no evidence, in adults, that this residual radiated tissue will develop malignant change. There is no certainty at this time that one approach is better than the other. It may be worth remembering that over 50% of patients given calculated moderate dose therapy remain euthyroid after ten years and can easily be surveyed at yearly intervals for hypothyroidism.

When giving large doses of 131-I it is prudent to calculate the rads delivered to the gland (as above), which can reach 40-50,000rads. Such large doses of radiation can cause clinically significant radiation thyroiditis, and occasionally damage surrounding structures.

And lastly, a speculation. Practitioners comment that the incidence of serious ophthalmopathy seems to be less that in former decades. Prompt diagnosis and therapy might contribute to such a change. Another factor could be the more common ablation of the thyroid during therapy for Graves disease, since this should over time reduce exposure of patient's immune system to thyroid antigens.

Lithium with RAI therapy- Although rarely used, RAI combined with lithium is safe and more effective than RAI alone in the cure of hyperthyroidism due to Graves' disease, probably because it it causes greater retention of RAI within the thyroid gland.. Bogazzi et al (58.5)reported a study combining lithium with RAI therapy. MMI treatment was withdrawn 5 days prior to treatment, Two hundred ninety-eight patients were treated with RAI plus lithium (900 mg/d for 12 d starting 5 days prior to 131-I treatment) and 353 with RAI alone. RAI dosage was 260mCi/g estimated thyroid weight, corrected for RAIU (done on lithium).. All patients receive prednisone 0.5mg/kg/day, beginning on day 7 after RAI, tapering over 2 months. Patients treated with RAI plus lithium had a higher cure rate (91.0%) than those treated with RAI alone (85.0%, P = 0.030). In addition, patients treated with RAI plus lithium were cured more rapidly (median 60 d) than those treated with RAI alone (median 90 d, P = 0.000). Treatment with lithium inhibited the serum FT4 increase seen after methimazole withdrawal and RAI therapy.

Pretreatment with antithyroid drugs--Patients are often treated directly after diagnosis, without prior therapy with antithyroid drugs. This is safe and common in patients with mild hyperthyroidsm and especially those without eye problems. However often physicians give antithyroid drugs before 131-I treatment in order to deplete the gland of stored hormone and to restore the FTI to normal before $^{131\text{-}I}$ therapy. This offers several benefits. The possibility of 131-I induced exacerbation of thyrotoxicosis is reduced, the patient recovers toward normal health, and there is time to reflect on the desired therapy and review any concerns about the use of radioisotope for therapy. If the patient has been on antithyroid drug, it is discontinued two days before RAIU and therapy. Patients can be treated while on antithyroid drug, but this reduces the dose retained, reduces the post-therapy increment in hormone levels, and reduces the cure rate, so seems illogical(58.6) . When antithyroid drugs are discontinued the patient's disease may exacerbate, and this must be carefully followed. Beta blockers can be given in this interim, but there is no reason for a prolonged interval between stopping antithyroid drug, and 131-I therapy, unless there is uncertainty about the need for the treatment. Pretreatment with antithyroid drug does not appear in most studies to reduce the efficacy of 131-I treatment. [59] but the debate about the effect of antithyroid drug pretreatment on the efficacy of radioactive iodine therapy continues. In recent studies in which patients were on or off antithyroid therapy, which was discontinued four days, or 1-2 days before treatment, there was no effect on the efficacy of treatment at a one year endpoint (59.1,59.2, 59,3). In another study Bonnema et al found that PTU pretreatment , stopped 4 days prior to 131-I, reduced the efficacy of 131-I(59.6).

Pretreatment is usually optional but is logical in patients with large glands and severe hyperthyroidism. Antithyroid drug therapy does reduce the pretreatment levels of hormone and reduces the rise in thyroid hormone level that may occur after radioactive iodide treatment. This certainly could have a protective effect in individuals who have coincident serious illness such as coronary artery disease, or perhaps individuals who have very large thyroid glands (59.3). It is indicated in two circumstances. In patients with severe heart disease, an 131-I- induced exacerbation of thyrotoxicosis could be serious or fatal. Pretreatment may reduce exacerbation of eye disease (see below), and it does reduce the post-RAI increase in antibody titers(59.1,59.31). The treatment dose of 131-I is best given as soon as possible after the diagnostic RAIU in order to reduce the period in which thyrotoxicosis may exacerbate without treatment, and since any intake of iodine (from diet or medicines or tests) would alter uptake of the treatment dose (59.4), and 2 days seems sufficient.

Post 131-I treatment management--Many patients remain on beta-blockers but require no other treatment after 131-I therapy. Antithyroid drugs can be reinstituted after 5 (or preferably 7) days, with minimal effect on retention of the treatment dose of 131-I.

Alternatively, one may prescribe antithyroid drug (typically 10 mg methimazole q8h) beginning one day after administration of 131-I and add KI (2 drops q8h) after the second dose of methimazole. KI is continued for two weeks, and antithyroid drug as needed. This promotes a rapid return to euthyroidism, but by preventing recirculation of 131-I it can lower the effectiveness of the treatment. This method has been employed in a large number of patients, and is especially useful in patients requiring rapid control- for example, with CHF. A typical response is shown in Fig -3. It also has provided the largest proportion of patients remaining euthyroid at 10 years after therapy, in comparison to other treatment protocols. Glinoer and Verelst also report successful use of this strategy [59.1]. As noted, antithyroid drugs may be given starting 7-10 days after RAI without significantly lowering the radiation dose delivered to the gland.

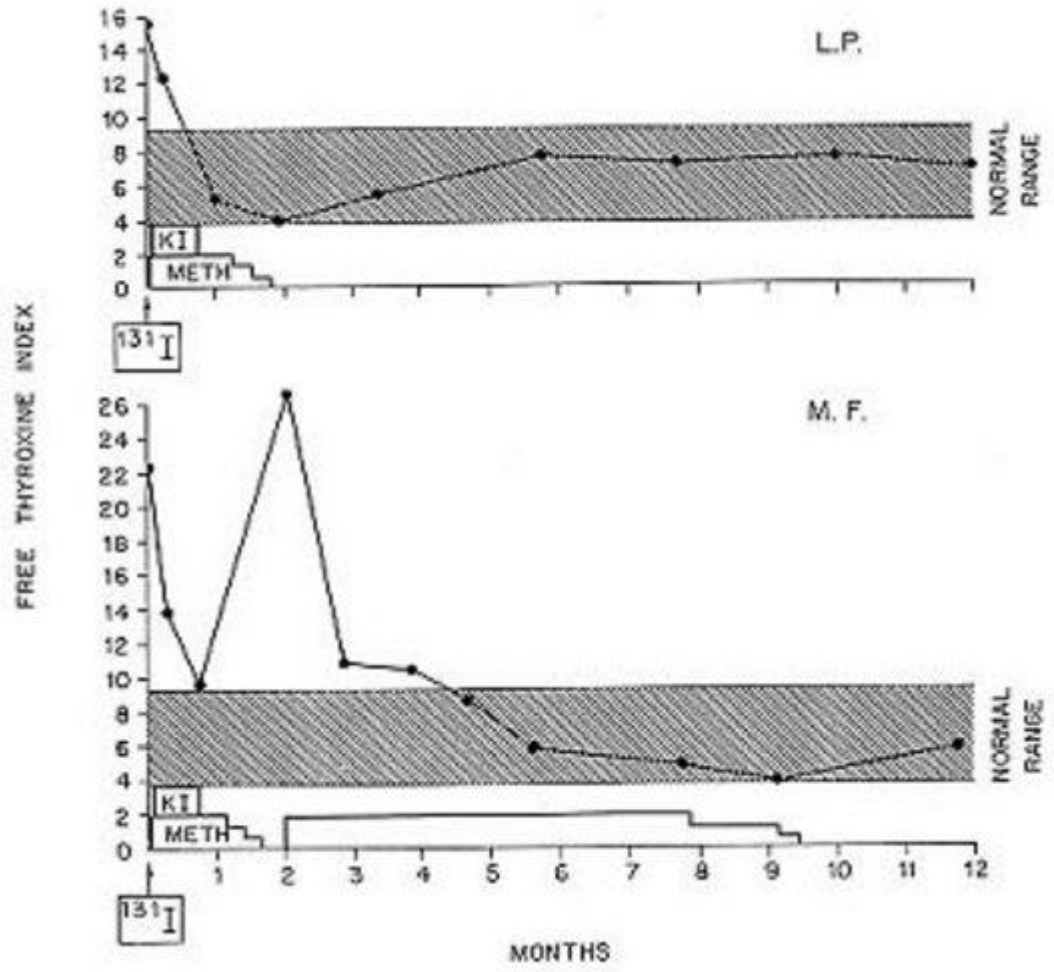

Figure 3. 131-I-ATD-KI protocol. Twenty-four hours after 131-I therapy, methimazole is instituted (5-10mg q8h), followed by KI) two drops Lugol's solution or similar q8h) at the time of each subsequent dose of ATD. KI is stopped at two weeks, and ATD continued or tapered as appropriate.

Treatment using 125-I was tried as an alternative to 131-I, because it might offer certain advantages [60]. 125-I is primarily a gamma ray emitter, but secondary low-energy electrons are produced that penetrate only a few microns, in contrast to the high-energy beta rays of 131-I. Thus, it might theoretically be possible to treat the cytoplasm of the thyroid cell with relatively little damage to the nucleus. Appropriate calculations indicated that the radiation dose to the nucleus could be perhaps one-third that to the cytoplasm, whereas this difference would not exist for 131-I. Extensive therapeutic trials have nonetheless failed to disclose any advantage thus far for ^{125}I. Larger doses -- 10-20 mCi -- are required, increasing whole body radiation considerably [61, 62].

SAFETY PRECAUTIONS AFTER 131-I THERAPY

Doses of 131-I up to 33 mCi can be given to an outpatient basis, and this level is rarely exceeded in treatment of Graves' disease. However patients must be given advice (written if possible) on precautions to be followed to prevent unneccessary or excessive exposure of other individuals by radiaactivity administered to the patient.

For maximum safety, patients who have received 20 mCi should avoid extended time in public places for 1 day, maximize distance (6 feet) from children and pregnant women for 2 days, may return to work after 1 day, sleep in a separate (6-feet separation) bed from adults for 8 days, sleep in a separate bed from pregnant partners, infant, or child for 20 days, and avoid contact with body fluids (saliva, urine) for at least one week. Lower therapeutic doses require proportionally more moderate precautions. The basic NRC rule is that patients may be released from hospital when (1) the ^{131}I measured dose rate is ≤7 mrem/hr at 1 m, or (2) when the expected total dose another person would receive is unlikely to exceed 500 mrem (5 mSv). Written precaution instructions are required If 100 mrem (1 mSv) may be exceeded in any person. This topic is well covered in articles by Sisson et al (http://www.ncbi.nlm.nih.gov/pubmed/21417738) andLiu et al (62.1).

Course After Treatment-

If adequate treatment has been given, the T4 level falls progressively, beginning in one to three weeks.. Labeled thyroid hormones, iodotyrosines, and iodoproteins appear in the circulation [63,63.1]. TG is released, starting immediately after therapy. Another iodoprotein, which seems to be an iodinated albumin, is also found in plasma. This compound is similar or identical to a quantitatively insignificant secretion product of the normal gland. It comprises up to 15% or more of the circulating serum 131-I in thyrotoxic patients [64]. It is heavily labeled after 131-I therapy, and its proportional secretion is probably increased by the radiation. Iodotyrosine present in the serum may represent leakage from the thyroid gland, or may be derived from peripheral metabolism of TG or iodoalbumin released from the thyroid.

The return to the euthyroid state usually requires at least two months, and often the declining function of the gland proceeds gradually over six months to a year. For this reason, it is logical to avoid retreating a patient before six months have elapsed unless there is no evidence of control of the disease. While awaiting the response to131-I the symptoms may be controlled by propranolol, antithyroid drugs, or iodide. Hypothyroidism develops transiently in 10 - 20% of patients, but thyroid function returns to normal in most of these patients in a period ranging from three to six months. These patients rarely become toxic again. Others develop permanent hypothyroidism and require replacement therapy. It is advantageous to give the thyroid adequate time to recover function spontaneously before starting permanent replacement therapy. This can be difficult for the patient unless partial T4 replacement is given. Unfortunately, one of the common side effects of treating hyperthyroidism is weight gain, averaging about 20 lbs through four years after treatment (64.1).

Patients may develop transient increases in FTI and T3 at 2-4 months after treatment [63.1], sometimes associated with enlargement of the thyroid. This may represent an inflammatory or immune response to the irradiationinduced thyroid damage, and the course may change rapidly with a dramatic drop to hypothyroidism in the 4-5th month.

Hypothyroidism may ultimately be inescapable after any amount of radiation that is sufficient to reduce the function of the hyperplastic thyroid to normal [65]. Many apparently euthyroid patients (as many as half) have elevated serum levels of TSH long after $^{131-I}$ therapy, with "normal" plasma hormone levels [66]. An elevated TSH level with a low normal T4level is an indicator of changes progressing toward hypothyroidism [67]. The hypothyroidism is doubtless also related to the continued autoimmune attack on

thyroid cells. Hypofunction is a common end stage of Graves' disease independent of $^{131\text{-}I}$ use; it occurs spontaneously as first noted in 1895(!) [68] and in patients treated only with antithyroid drugs [69]. Just as after surgery, the development of hypothyroidism is correlated positively with the presence of antithyroid antibodies.

During the rapid development of postradiation hypothyroidism, the typical symptoms of depressed metabolism are evident, but two rather unusual features also occur. The patients may have marked aching and stiffness of joints and muscles. They may also develop severe centrally located and persistent headache. The headache responds rapidly to thyroid hormone therapy. Hair loss can also be dramatic at this time.

In patients developing hypothyroidism rapidly, the plasma T4 level and FTI accurately reflect the metabolic state. However, it should be noted that the TSH response may be suppressed for weeks or months by prior thyrotoxicosis; thus, the TSH level may not accurately reflect hypothyroidism in these persons and should not be used in preference to the FTI or FT4.

If permanent hypothyroidism develops, the patient is given replacement hormone therapy and is impressed with the necessity of taking the medication for the remainder of his or her life. Thyroid hormone replacement is not obligatory for those who develop only temporary hypothyroidism, although it is possible that patients in this group should receive replacement hormone, for their glands have been severely damaged and they are likely to develop hypothyroidism at a later date. Perhaps these thyroids, under prolonged TSH stimulation, may tend to develop adenomatous or malignant changes, but this has not been observed. Many middle-aged women gain weight excessively after radioactive iodide treatment of hyperthyroidism. Usually such patients are on what is presumed to be appropriate T4 replacement therapy. Tigas et al note that such weight gain is less common after ablative therapy for thyroid cancer, in which case larger doses of thyroxine are generally prescribed. Thus they question whether the excessive weight gain after radioactive iodide treatment of Graves' disease is due to the fact that insufficient thyroid hormone is being provided, even though TSH is within the "normal" range. They suggest that restoration of serum TSH to the reference range by T4 alone may not constitute adequate hormone replacement [69a}. We noted above that the correct reference range for TT4 and FT4, when the patient is on replacement T4, should be 20% higher than normal.

Permanent replacement therapy (regardless of the degree of thyroid destruction) for children who receive 131-I has a better theoretical basis. In these cases, it is advisable to prevent TSH stimulation of the thyroid and so mitigate any possible tendency toward carcinoma formation.

Exacerbation of thyrotoxicosis-During the period immediately after therapy, there may be a transient elevation of the T4 or T3 level [70], but usually the T4 level falls progressively toward normal. Among treated hyperthyroid patients with Graves' disease, only rare exacerbations of the disease are seen. These patients may have cardiac problems such as worsening angina pectoris, congestive heart failure, or disturbances of rhythm such as atrial fibrillation or even ventricular tachycardia. Radiation-induced thyroid storm and even death have unfortunately been reported [71- 73]. These untoward events argue for pretreatment of selected patients who have other serious illness, especially cardiac disease, with antithyroid drugs prior to 131-I therapy.

Other Problems Associate With 131-I Therapy

The immediate side effects of $^{131-I}$ therapy are typically minimal. As noted above, transient exacerbation of thyrotoxicosis can occur, and apparent thyroid storm has been induced within a day (or days) after 131-I therapy. A few patients develop mild pain and tenderness over the thyroid and, rarely, dysphagia. Some patients develop temporary hair loss, but this condition occurs two to three months after therapy rather than at two to three weeks, as occurs after ordinary radiation epilation. Hair loss also occurs after surgical therapy, so that it is a metabolic rather than a radiation effect. If the loss of hair is due to the change in metabolic status, it generally recovers in a few weeks or months. However hair thinning, patchy alopecia, and total alopecia, are all associated with Graves' Disease, probably as another auto-immune processes. In this situation the prognosis for recovery is less certain, and occasionally some other therapy for the hair loss (such as steroids) is indicated. Permanent hypoparathyroidism has been reported very rarely as a complication of RAI therapy for heart disease and thyrotoxicosis[74-76]. Patients treated for hyperthyroidism with 131-I received approximately 39 microGy/MBq administered (about 0.144rad/mCi) of combined beta and gamma radiation to the testes. This is reported to cause no significant changes in FSH. Nevertheless, testosterone declines transiently for several months, but there is no variation in sperm motility or % abnormal forms (76.1). Long term studies of patients after RAI treatment by Franklyn et al (76.2) show a slight increase in mortality which appears to be related to cardiovascular disease, possibly related to periods of hypothyroidism.

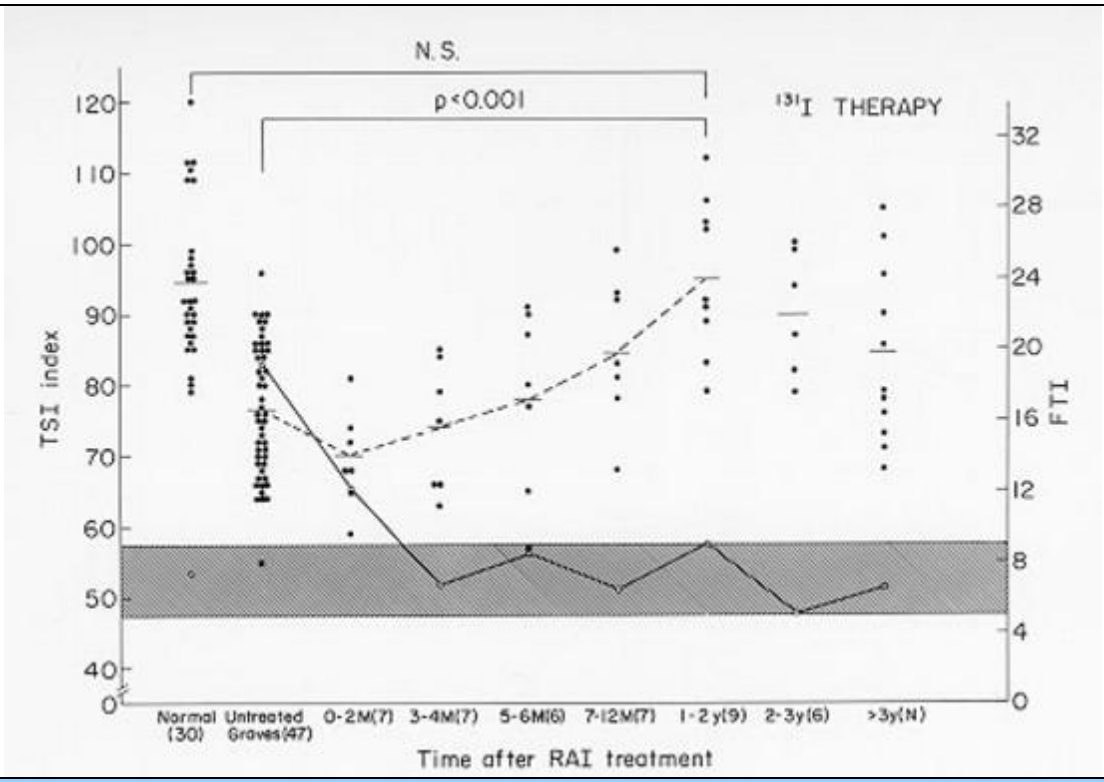

Figure 4. Transient increase in TBAb, followed years later by a decrease, in patients treated with 131-I. Note that in this study the "TSI Index" is a measure of TSH Receptor Blocking antibodies.

Worsening of ophthalmopathy after RAI---In contrast to the experience with antithyroid drugs or surgery, antithyroid antibodies including TSAb levels increase after RAI [77, 78]. (Fig. 11-4, above). Coincident with this condition, exophthalmos may be worsened [79].(Fig. 11-5, below). This change is most likely an immunologic reaction to discharged thyroid antigens.The relationship of radiation therapy to exacerbation of exophthalmos has beem questioned], but much recent data indicates that there is a definite correlation[79, 80, 80.1, 80.2, 80.3]. Many therapists consider "bad eyes" to be a relative contraindication to RAI. Induction of hypothyroidism, with elevation of TSH, may contribute to worsening of ophthalmopathy. This offers support for early induction of T4 replacement (80.3).
Pretreatment with antithyroid drugs has been used empirically in an attempt to prevent this complication. Its benefit, if any, may be related to an immunosuppressive effect of PTU, described below. Treatment with methimazole before and for three months after I-131 therapy has been shown to help prevent the treatment-induced rise in TSH-R antibodies which is otherwise seen[81].

Prophylaxis with prednisone after 131-I helps prevent exacerbation of exophthalmos, and this approach is now the standard approach in patients who have significant exophthalmos at the time of treatment [82, 82.1]. (Fig. 6, below) The recommended dose is 30 mg/day for one month, tapering then over 2-3 months. Of course prednisone or other measures can be instituted at the time of any worsening of ophthalmopathy. In this instance doses of 30-60 mg/day are employed, and usually are required over several months. While treatment with prednisone helps prevent eye problems, it does not appear to reduce the effectiveness of RAI in controlling the hyperthyroidism(82.2).

Thyroidectomy, with total removal of the gland, should be considered for patients with serious active eye disease. Operative removal of the thyroid is followed by gradual diminution is TSH-R antibodies.(82.3), and as shown by Tallstedt is associated with a lower incidence of worsening eye problems than is initial RAI treatment. Several studies document better outcomes of ophthalmopathy in patients with GD who have total thyroidectomy vs those treated by other means(82.4, 82.5, 82.6).

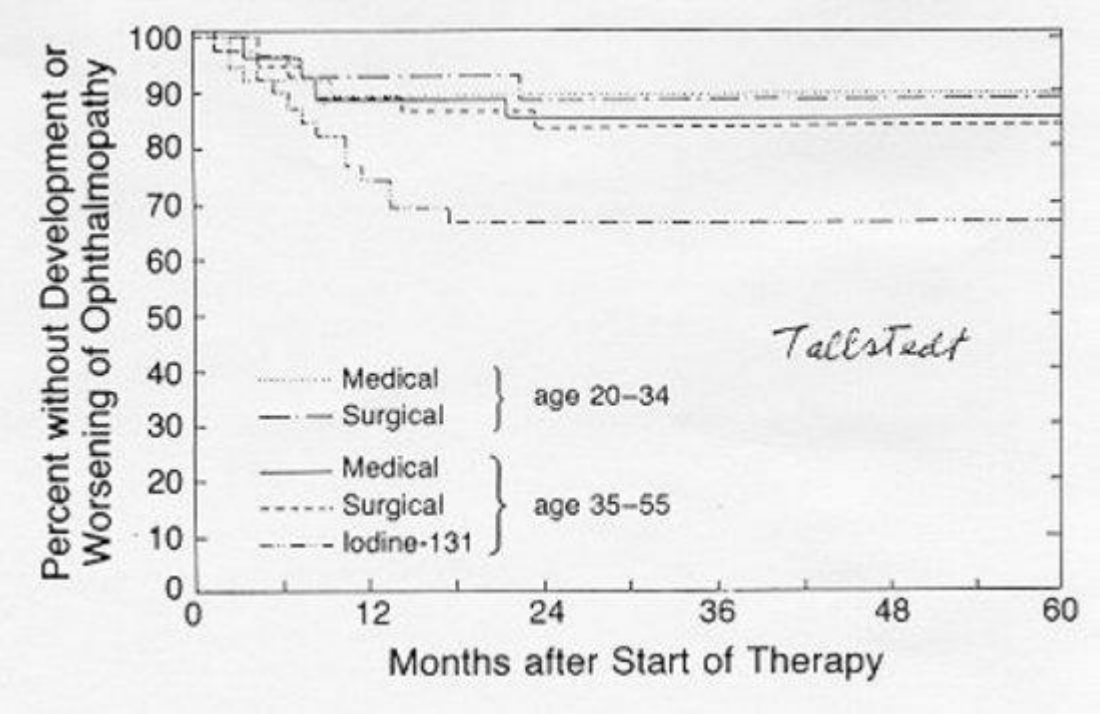

Figure 5. More patients experienced worsening of exophthalmos following 131-I therapy than after surgery or ATD treatment.

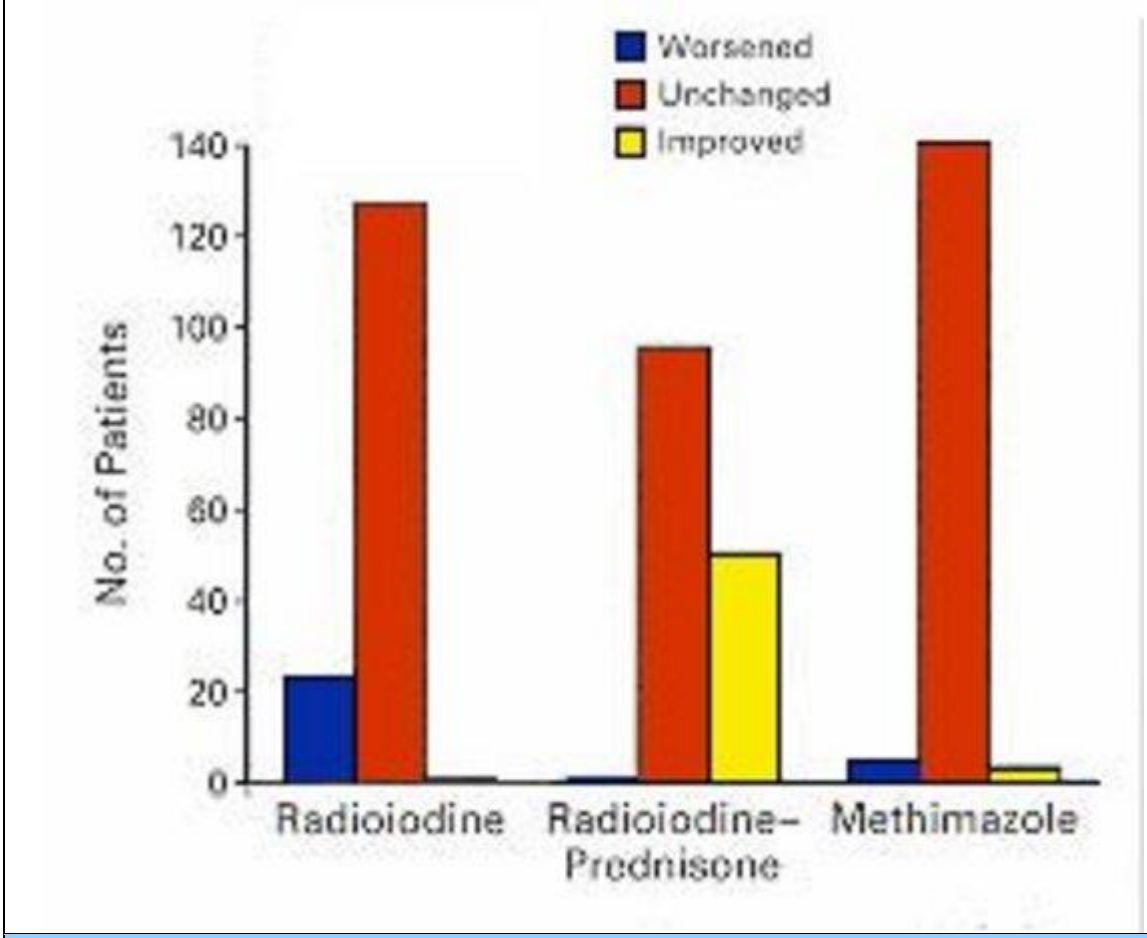

Figure 6. Redrawn from Bartelena et al, New England J. of Medicine, 338:73-78,1998.Patients with Graves' Disease were followed on methimazole, or given 131-I, or 131-I with prednisone 0.4-0.5mg/kg starting 2 or 3 days after 131-I treartment, and continuing for one month, after which the dose was tapered. Patients are grouped according to those who worsened, were unchanged, or improved during each treatment during 12 months.

Failure of 131-I to cure thyrotoxicosis occurs occasionally even after 2 or 3 treatments, and rarely 4 or 5 therapies are given. The reason for this failure is usually not clear. The radiation effect may occur slowly. A large store of hormone in a large gland may be one cause of a slow response. Occasional glands having an extremely rapid turnover of 131-I requiring such high doses of the isotope that surgery is preferable to continued 131-I therapy and its attendant whole body radiation. If a patient fails to respond to one or two doses of 131-I, it is important to consider that rapid turnover may reduce the effective radiation dose. Turnover can easily be estimated by measuring RAIU at 4, 12, 24, and 48 hours, or longer. The usual combined physical and biological half-time of 131-I retention is about 6 days. This may be reduced to 1 or 2 days in some cases, especially in patients who have had prior therapy or subtotal thyroidectomy. If this rapid release of 131-I is found, and 131-I therapy is desired, the total dose given must be increased to compensate for rapid release. A rough guide to this increment is as follows:

Increased dose = usual dose X ((usual half time of 6 days) / (observed half time of "X" days))

Most successfully treated glands return to a normal or cosmetically satisfactory size. Some large glands remain large, and in that sense may constitute a treatment failure. In such a situation secondary thyroidectomy could be done, but it is rarely required in practice.

Long term care- Patients who have been treated with RAI should continue under the care of a physician who is interested in their thyroid problem for the remainder of their lives. The first follow-up visit should be made six to eight weeks after therapy. By this time, it will often be found that the patient has already experienced considerable improvement and has begun to gain weight. The frequency of subsequent visits will depend on the progress of the patient. Symptoms of hypothyroidism, if they develop, are usually not encountered until after two to four months, but one of the unfortunate facts of RAI therapy is that hypothyroidism may occur almost any time after the initial response.

HAZARDS OF 131-I TREATMENT

In the early days of RAI treatment for Graves' disease, only patients over 45 years of age were selected for treatment because of the fear of ill effects of radiation. This age limit was gradually lowered, and some clinics, after experience extending over nearly 40 years, have now abandoned most age limitation. The major fear has been concern for induction of neoplasia, as well as the possibility that 131-I might induce undesirable mutations in the germ cells that would appear in later generations.

Table 8. Gonadal Radiation Dose (in Rads) From Diagnostic Procedures and 131-I Therapy

Proceedure	Males-median	Females-median
Barium meal	0.03	0.34
IV pyelogram	0.43	0.59
Retrograde pyelogram	0.58	0.52
Barium enema	0.3	0.87
Femur xray	0.92	0.24
131-I-therapy, 5mCi	usually <1.6	usually <1.6
Adapted from Robertson and Gorman [95]		

Carcinogenesis

Radiation is known to induce tumor formation in many kinds of tissues and to potentiate the carcinogenic properties of many chemical substances. Radiation therapy to the thymus or nasopharyngeal structures plays an etiologic role in thyroid carcinoma both in children and in adults[83- 85]. 131-I radiation to the animal thyroid can produce tumors, especially if followed by PTU therapy [86]. Cancer of the thyroid has appeared more frequently in survivors of the atomic explosions at Hiroshima and Nagasaki than in control populations [87]. Thyroid nodules, some malignant, have appeared in the natives

of Rongelap Island as the result of fallout after a nuclear test explosion in which the radiation cloud unexpectedly passed over the island [88].

Thyroid cancer following 131-I treatment?
The experience at 26 medical centers with thyroid carcinoma after **131-I** therapy was collected in a comprehensive study of the problem. A total of 34,684 patients treated in various ways were included. Beginning more than one year after **131-I** therapy, 19 malignant neoplasms were found; this result did not differ significantly from the frequency after subtotal thyroidectomy. Thyroid adenomas occurred with increased frequency in the 131-I treated group, and the frequency was greatest when the patients were treated in the first two decades of life [39]. Holm et al [41] have thoroughly examined the history of a large cohort of 131-I-treated patients in Sweden and similarly found no evidence for an increased incidence of thyroid carcinoma or other tumors. For reasons that are not clear, the injury caused by 131-I therapy for Graves' disease seems to induce malignant changes infrequently.. This may be because the treatment has largely been given to adults with glands less sensitive to radiation, because damage from 131-Itherapy is so severe that the irradiated cells are unable to undergo malignant transformations, or because all cells are destroyed, or possibly because of the slow rate at which the dose is delivered [89]. In up to one-half of patients followed for 5-10 years, there may be no viable thyroid cells remaining. We note that two studies reported above extend through an average follow-up period of 15 years. As described above [44.1], a recent report by Franklyn and coworkers indicated that there is an increased (3.25 fold) risk of mortality from cancer of the thyroid (and also bowel) after RAI, detected in along term follow up of a very large patient cohort. However it remains uncertain that this is related to hyperthyroidism per se, or radioiodine therapy.

While these data are reassuring in regard to 131-I use in adults, Chernoby made it clear that its use in children can not be considered safe. Children in the area surrounding Chernobyl have developed a hugely increased incidence of thyroid carcinoma predominately due to ingestion of iodine-131 [89.]. The latency has been about 5 years, and younger children are most affected. Risk is probably linearly related to dose. It is apparent that low doses, possibly down to 20 rads, produce malignant change in children(89.2).Risk of carcinogenesis decreases with increasing age at exposure, and is much less common after age 12. However some data indicates that an increased incidence of thyroid carcinoma is seen even among adults exposed at Chernobyl.

Leukemia
The incidence of leukemia among patients treated with RAI for Graves' disease has not exceeded that calculated from a control group [90]. This problem was also studied by the consortium of 26 hospitals [91]. The incidence of leukemia in this group was slightly lower than in a control group treated surgically, but slightly higher in the latter surgical group than in the general population.

Genetic Damage

In the group of RAI-treated patients, there has been no evidence of genetic damage, although, as will shortly be seen, this problem cannot be disregarded. In the United States, about 100×10^6 children will be born to a population of over 200×10^6 persons. Approximately 4% of these children will have some recognizable defect at birth. Of these, about one-half will be genetically determined or ultimately mutational, and

represent the effects of the baseline mutation rate in the human species. These mutations are attributed in part to naturally occurring radiation.

All penetrating radiation, from whatever sources, produces mutations. The effects may vary with rate of application, age of the subject, and no doubt many other factors, and are partially cumulative. Nearly all of these mutations behave as recessive genetic factors; perhaps 1% are dominant. Almost all are minor changes, and those produced by experimental radiation are the same as those produced by natural radiation.

Whether or not mutations are bad is in essence a philosophic question. Most of us would agree that the cumulative effect of mutations over past eras brought the human race to its present stage of development. However, most mutations, at least those that are observable, are detrimental to individual human adaptation to the present environment. In terms of the human population as a whole, detrimental mutant genes must be eliminated by the death of the carrier. We can agree that an increase in mutation rate is not desirable. It is hardly worth considering the pros and cons of the already considerable spontaneous mutation rate.

In mice, the occurrence of visible genetic mutations in any population group is probably doubled by acute exposure of each member of the group over many generations to about 30 - 40 rads, or by chronic exposure to 100 - 200 rads [92]. This radiation dosage is referred to as the doubling dose. Ten percent of this increase in mutations might be expressed in the first-generation offspring of radiated parents, the remainder gradually appearing over succeeding generations. The change in mutation rate in Drosophila is in proportion to the dosage in the range above 5 rads. Data from studies of mice indicate that at low exposures (from 0.8 down to 0.0007 rads/min), the dose causing a doubling in the spontaneous rate of identifiable mutations is 110 rads [92,93]. Linearity, although surmised, has not been demonstrated at lower doses.

At present, residents of the United States receive about 300 mrad/year, or 9 rad before age 30, the median parental age. Roughly half of this dose is from natural sources and half from medical and, to a lesser extent, industrial exposure. The National Research Council has recommended a maximum exposure rate for the general population of less than 10 rad above background before age 30. (The present level may therefore approach this limit.)

The radiation received by the thyroid and gonads during $^{131\text{-}I}$ therapy of thyrotoxicosis can be estimated from the following formula:

Total beta radiation dose = 73.8 x concentration of 131-I in the tissue (µCi/g) x average beta ray energy (0.19 meV) x effective isotope half-life

For illustration, we can assume a gland weight of 50 g, an uptake of 50% at 24 hours, a peak level of circulating protein-bound iodide (PB $^{131\text{-}I}$) of 1% dose/liter, an administered dose of 10 mCi, a thyroidal iodide biologic half-life of 6 days, and a gamma dose of about 10% of that from beta rays. On this basis, the thyroid receives almost 8200 rads, or roughly 1,600 rads/mCi retained. The gonadal dose, being about one-half the body dose, would approximate 4 rads, or roughly 0.4 rads/mCi administered.

If the radiation data derived from Drosophila and lower vertebrates are applied to human radiation exposure (a tenuous but not illogical assumption), the increased risk of visible

mutational defects in the progeny can be calculated. On the basis of administration to the entire population of sufficient $^{131\text{-}I}$ to deliver to the gonads 2 rads or 2% of the doubling dose (assumed to be the same as in the mouse), the increase in the rate of mutational defects would ultimately be about 0.04%, although only one-tenth would be seen in the first generation. Obviously only a minute fraction of the population will ever receive therapeutic 131-I. The incidence of thyrotoxicosis is perhaps 0.03% per year, or 1.4% for the normal life span. At least one-half of these persons will have their disease after the childbearing age has passed. Although most of them will be women, this fact does not affect the calculations after a lapse of a few generations. Assuming that the entire exposed population receives 131-I therapy in an average amount of 5 mCi, the increase in congenital genetic damage would be on the order of 0.02 (present congenital defect rate) x 0.04 (131-I radiation to the gonads as a fraction of the doubling dose) x 0.014 (the fraction of the population ever at risk) x 0.5 (the fraction of patients of childbearing age) = 0.0000056.

This crude estimate, developed from several sources, also implies that, if all patients with thyrotoxicosis were treated with $^{131\text{-}I}$, the number of birth defects might ultimately increase from 4 to 4.0006%. This increase may seem startlingly small or large, depending on one's point of view, but it is a change that would be essentially impossible to confirm from clinical experience.

Unfortunately, it is more difficult to provide a reliable estimate of the increased risk of genetic damage in the offspring of any given treated patient. Calculations such as the above simply state the problem for the whole population. Since most of the mutations are recessive, they appear in the children only when paired with another recessive gene derived from the normal complement carried by all persons. Assuming that only one parent received radiation from $^{131\text{-}I}$ therapy amounting to 2% of the doubling dose, the risk of apparent birth defects in the patient's children might increase from the present 4.0% to 4.008%.

0.02 (present genetic defect rate) x 0.04 (fraction of the doubling dose) x 0.1 (fraction of defects appearing in the first generation) = 0.00008, or an increase from 4.0% to 4.008%.

Similar estimates can be derived by considering the number of visible mutations derived from experimental radiation in lower species.[92, 93]

6 x 10-8 (mutations produced per genetic locus per rad of exposure) x 10^4 (an estimate of the number of genetic loci in humans) x 2 (gonadal radiation in rads as estimated above) x 0.1 (fraction of mutations appearing in the first generation) = 0.00012 or 0.012%

On this basis, the increase in the birth defect rate would be from 4.0% to 4.012%. One important observation stemming from these calculations is that large numbers of children born to irradiated parents must be surveyed if evidence of genetic damage is ever to be found. Reports of "no problems" among 30 to 100 such children are essentially irrelevant when one is seeking an increase in the defect rate of about 4.0% to about 4.008%.

These statistics are presented in an attempt to give some quantitation to the genetic risk involved in 131-I therapy, and should not be interpreted as in any sense exact or final. The point we wish to stress is that radiation delivered to future parents probably will

result in an increased incidence of genetic damage, but an increase so slight that it is difficult to measure. Nonetheless, the use of 131-I for large numbers of women who subsequently become pregnant will inevitably introduce change in the gene pool.

In considering the significance of these risks, one must remember that the radiation exposure to the gonads from the usual therapeutic dose of 131-I may be only one or two times that produced during a procedure such as a barium enema [94, 95] and similar to the 10 rads received from a CAT scan. These examinations are ordered by most physicians without fear of radiation effect (Table 11-8).

When assessing the risks of 131-I therapy, one must, of course, consider the risks of any alternative choice of procedure. Surgery carries a small but finite mortality, as well as a risk of permanent hypoparathyroidism, hypothyroidism, and vocal cord paralysis. Some of these risks are especially high in children, the group in which radiation damage is most feared. Some physicians have held that 131-I therapy should not be given to patients who intend subsequently to have children. In fact, there is at present no evidence to support this contention, as discussed above. Chapman [44] studied 110 women treated with 131-I who subsequently became pregnant and were delivered of 150 children. There was no evidence of any increase in congenital defects or of accidents of pregnancy. Sarkar et al [96] also found no evidence of excess abnormalities among children who received 131-I therapy for cancer. Other studies have confirmed the apparent lack of risk[42, 43]. It should be noted that no increase in congenital abnormalities has been detected among the offspring of persons who received much larger radiation doses during atomic bomb explosions [97].

Often the patient wishes to know about the possibility of carcinogenesis or genetic damage. These questions must be fully but delicately handled. It is not logical to treat a patient of childbearing age with 131-I and have the patient subsequently live in great fear of bearing children. These problems and considerations must be faced each time a patient is considered for RAI therapy.

Pregnancy and 131-I Pregnancy is an absolute contraindication to $^{131\text{-}I}$ therapy. The fetus is exposed to considerable radiation from transplacental migration of $^{131\text{-}I}$, as well as from the isotope in the maternal circulatory and excretory systems. In addition, the fetal thyroid collects $^{131\text{-}I}$ after the 12th week of gestation and may be destroyed. The increased sensitivity of fetal structures to radiation damage has already been described. Physicians treating women of childbearing age with $^{131\text{-}I}$ should be certain that the patients are not pregnant when given the isotope. Therapy during or immediately after a normal menstrual period or performance of a pregnancy test are appropriate precautions if pregnancy is possible. Women should be advised to avoid pregnancy for at least six months after treatment with RAI, since it usually takes this long to be certain that retreatment will not be needed.

TREATMENT OF THYROTOXICOSIS WITH DRUGS

Drug therapy for thyrotoxicosis was introduced by Plummer when he observed that the administration of iodide ameliorated the symptoms of this disease [98]. (Fig 7) Administration of iodide has since been used occasionally as the complete therapeutic program for thyrotoxicosis, and widely as an adjunct in preparing patients for subtotal thyroidectomy. In 1941 the pioneering observations of MacKenzie and MacKenzie [99] and Astwood [100] led to the development of the thiocarbamide drugs, which reliably

block the formation of thyroid hormones. It soon became apparent that, in a certain proportion of patients with Graves' disease, use of these drugs could induce a prolonged or permanent remission of the disease even after the medication was discontinued. It is not yet understood why a temporary reduction in the formation of thyroid hormone should result in reduction of TSHR antibodies, and permanent amelioration of the disease.

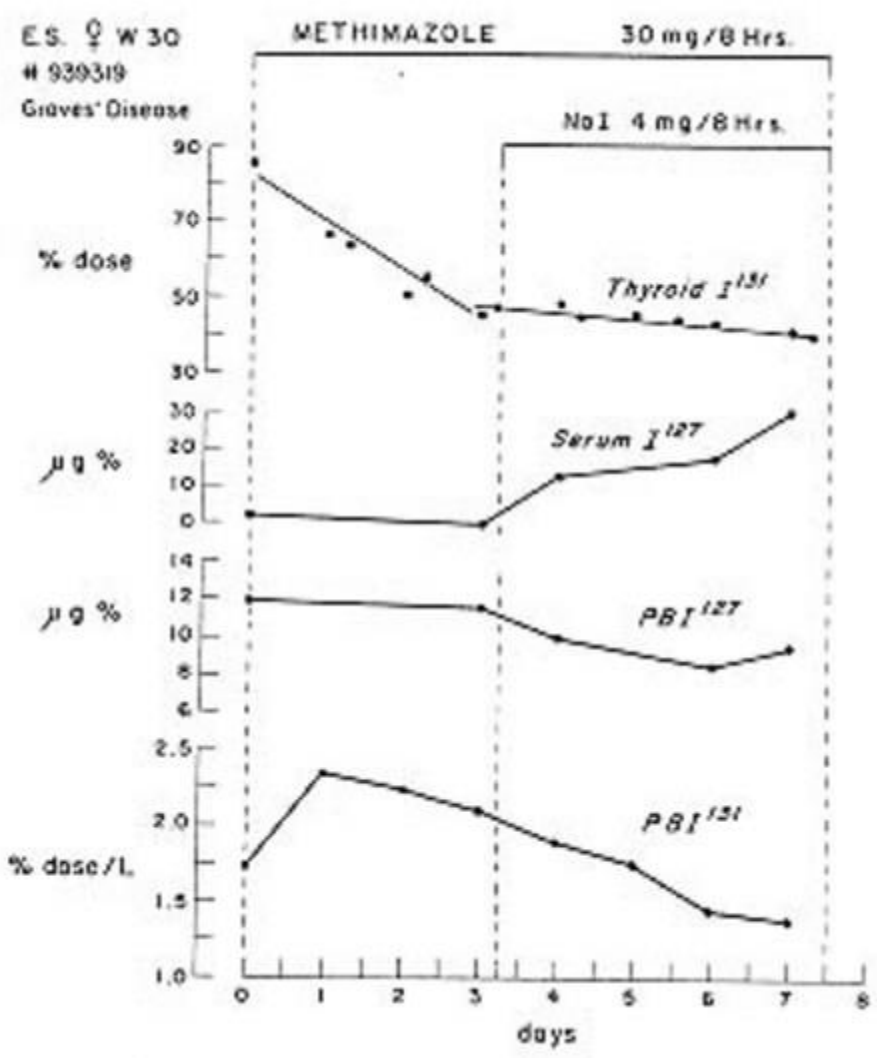

Figure 7. KI in doses over 6 mg/day dramatically inhibits release of hormone from the Graves' thyroid, as shown after treatment in this study starting during day 4. Serum hormone levels (PBI) consequently fall.

The antithyroid drug initially introduced for treatment of Graves' disease was thiourea, but this drug proved to have a large number of undesirable toxic effects. Subsequently a number of derivatives and related compounds were introduced that have potent antithyroid activity without the same degree of toxicity. Among these substances are propyl- and methylthiouracil, methimazole, and carbimazole. In addition to this class of compounds, potassium perchlorate has been used in the treatment of thyrotoxicosis, but is infrequently employed for this purpose because of occasional bone marrow

depression. This drug prevents the concentration of iodide by the thyroid. Beta adrenergic blockers such as propranolol have a place in the treatment of thyrotoxicosis. These drugs alleviate some of the signs and symptoms of the disease but have little or no direct effect on the metabolic abnormality itself. They do not uniformly induce a remission of the disease and can be regarded as adjuncts, not as a substitute for more definitive therapy.

Mechanism of Action- Antithyroid drugs inhibit thyroid peroxidase, and PTU (not methimazole) has the further beneficial action of inhibiting T4 to T3 conversion in peripheral tissues. Antithyroid therapy is associated with a reduction in circulating antithyroid antibody titers [101], and anti-receptor antibodies [77, 78, 102]. Studies by MacGregor and colleagues [103] indicate that antibody reduction also occurs during antithyroid therapy in patients with thyroiditis maintained in a euthyroid state, thus indicating that the effect is not due only to lowering of the FT4 in Graves' disease. These authors also found a direct inhibitory effect of PTU and carbimazole on antithyroid antibody synthesis in vitro and postulate that this is the mechanism for diminished antibody levels [104]. Other data argue against this hypothesis [105, 105.1].

Antithyroid drug therapy is also associated with a prompt reduction in the abnormally high levels of activated T lymphocytes in the circulation [106], although Totterman and co-workers found that this therapy caused a prompt and transient elevation of activated T suppressor lymphocytes in blood [107]. During antithyroid drug treatment the reduced numbers of T suppressor cells reported to be present in thyrotoxic patients return to normal [106, 108]. Antithyroid drugs do not directly inhibit T cell function [109]. All of these data argue that antithyroid drugs exert a powerful beneficial immunosuppressive effect on patients with Graves' disease. While much has been learned about this process, the exact mechanism remains uncertain. Evidence that antithyroid drugs exert their immunosuppressive effect by a direct inhibition of thyroid cell production of hormones has been reviewed by Volpe [109].

Long-Term Antithyroid Drug Therapy with Thiocarbamides
Propylthiouracil warning-**Propylthiouracil and methimazole have for years been considered effectively interchangeable, and liver damage was considered a very rare problem. Recently a commission appointed by the FDA reevaluated this problem, and concluded that the rare but severe complications of liver failure needing transplantation, and death, were sufficient to contraindicate the use of PTU as the normal first-line drug (109.1).** The **Endocrine Society and other advisory groups have suggested that methimazole be used for treatment except in circumstances of inavailability of the drug, patient allergy, or pregnancy. Because of the association of scalp defects and probably a severe choanal syndrome with administration of methimazole during the first 12 weeks of pregnancy, current advice is to avoid use of methimazole during the first trimester, for instance giving PTU during the first trimester, and then switching to methimazole.**

Selection of patients-Many patients with Graves' disease under age 40 - 45 are given a trial of therapy with one of the thiocarbamide drugs. Younger patients, and those with recent onset of disease, small goiters [110], and mild disease, are especially favorable candidates, since they tend to enter remission most frequently (110.1). It is generally found that one-fourth to one-third of these patients who satisfactorily complete a one year course have a long term or permanent remission. The remainder need repeated courses of drug therapy, must be maintained on the drug for years or indefinitely [111,

112], or must be given some other treatment. It appears that the percentage of patients responding has progressively fallen over the past years from about 50% to at present 25 - 30%[113, 114]. This change was thought to reflect an alteration in iodide in our diet [115], which increased from about 150 µg/day in 1955 to 300 - 600 µg/day. However other factors including greater precision in diagnosis and more complete data probably play major roles in establishing the response rate recognized at present. Some physicians do not consider antithyroid drug therapy to be the most efficacious means of treating thyrotoxic patients because of the high recurrence rate.

Therapeutic program-Patients are initially given 100 - 150 mg PTU **(if used)** every 8 hours or 10 - 15 mg methimazole (Tapazole) every 12 hours. The initial dosage is varied depending on the severity of the disease, size of the gland, and medical urgency. Antithyroid drugs must usually be given frequently and taken with regularity since the half-time in blood is brief -- 1.65 hours or less for PTU [116]. Frequent dosage is especially needed when instituting therapy in a severely ill patient. Methimazole has the advantage of a longer therapeutic half-life, and appears to produce fewer reactions when given in low dosage. Propylthiouracil is preferred in patients with very severe hyperthyroidism since it inhibits T4>T3 conversion, and in early pregnancy[117, 118]

In most thyrotoxic patients, the euthyroid state, as assessed by clinical parameters, and FT4, can be reached within 4 - 6 weeks. If the patient fails to respond, the dosage may be increased. Iodine-131 studies may be performed to determine whether a sufficiently large dose of medication is being employed [119], but these studies are rarely needed. In general, it is assumed that iodide uptake should be nearly completely blocked, but the 24-hour 131-I thyroid uptake in the patient under therapy may range from O% to 40%. This iodide is partly unbound and is usually released rapidly from the gland by administration of 1 g potassium thiocyanate or 400 mg potassium 131-I perchlorate. If perchlorate or thiocyanate does not discharge the iodide, it is obvious that iodide organification is occurring despite the thiocarbamide therapy. The quantity of drug administered may then be increased. In experimental animals, the thiocarbamides block synthesis of iodothyronines more readily than they block formation of MIT and DIT. This observation suggests that a complete block in organification of iodide may not be necessary to produce euthyroidism. The patient's thyroid might accumulate and organify iodide and form iodotyrosines, but be unable to synthesize the iodothyronines. Clinical observations to prove this point are not available.

An RIA for PTU has been developed but has not proven useful in monitoring therapy [120]. Doses of 300 mg PTU produced serum levels of about 7.1 µg/ml, and serum levels of PTU correlated directly with decreases in serum T_3 levels.

It is theoretically possible to give therapeutic doses of methimazole by rectal administration in a saline enema or by suppository if the oral route is unavailable [121]. Propylthiouracil has also been administered in suppositories or in enemas and found to be effective in treating hyperthyroidism. In a recent study PTU tablets were mixed in mineral oil, and then with cocoa butter, and frozen, to produce 1 gm suppositories each containing 400mg PTU. Suppositories given 4 times daily maintained a therapeutic blood level(121.1). Jongjaroenprasert et al compared the effectiveness of a 400 mg dose of PTU in 90 ml of water vs. 400 mg of PTU given in polyethylene glycol suppositories. Both methods were effective treatments, but the enema appeared to provide greater bioavailability (121.2).

Long Term Therapeutic Program After the initial period of high-dose therapy, the amount of drug administered daily is gradually reduced to a level that maintains the patient in a euthyroid condition, as assessed by clinical evaluation and serial observations of serum T4 , FT4, or T3 . These tests should appropriately reflect the metabolic status of the patient. Measurement of TSH level is useful when the FT4 falls, to make sure that the patient has not been overtreated, but, as noted previously, TSH may remain suppressed for many weeks after thyrotoxicosis is alleviated. Serum T3 levels can also be monitored and are occasionally still elevated when the T4 level is in the normal range. During the course of treatment, the thyroid gland usually remains the same in size or becomes smaller. If the gland enlarges, the patient has probably become hypothyroid with TSH elevation; this condition should be ascertained by careful clinical and laboratory evaluation. If the patient does become hypothyroid, the dose of antithyroid drug should be reduced. Decrease in size of the thyroid under therapy is a favorable prognostic sign, and more often than not means that the patient will remain euthyroid after the antithyroid drugs have been discontinued. The dose is gradually reduced as the patient reaches euthyroidism, and often one-half or one-third of the initial dose is sufficient to maintain control. The interval between doses -- typically 8-12 hours initially -- can be extended, and patients can often be maintained on twice- or once-a-day therapy with methimazole [122]. Alternatively, antithyroid drugs can be maintained at a higher dose, and thyroxine can be added to produce euthyroidism. Occasionally ingestion of large amounts of iodide interferes with antithyroid drug therapy.

Duration of Treatment- The appropriate duration of antithyroid drug therapy is uncertain, but usually it is maintained for one year. Treatment for six months has been effective in some clinics but is not general practice [123]. Longer treatment -- such as one to three years -- does gradually increase the percentage of responders [124], but this increase must be balanced against the added inconvenience to the patient [125, 126]. Azizi and coworkers have reported treatment of a group of 26 patients for ten years, during which time no serious problems occurred, and the cost approximated that of RAI therapy(126.1). At least one study suggests that treatment with large doses of antithyroid drugs may increase the remission rate, perhaps because of an immunosuppressive action [125]. Body mass, muscle mass, and bone mineral content gradually recover, although bone mass remains below normal [126.2]. Risedronate treatment has been demonstrated to help restore bone mass in osteopenia/osteoporosis associated with Graves' disease (126.3).

After the patient has taken the antithyroid drugs for a year, the medication is gradually withdrawn over one to two months, and the patient is observed at intervals thereafter. Elevated TRAbs at the time ATDs are to be withdrawn strongly (but imperfectly) suggest relapse will occur (110.1). Most of those who will ultimately have an exacerbation of the disease do so within three to six months; others may not develop recurrent hyperthyroidism for several years [127]. Some patients may have a recurrence after discontinuing the drug that lasts for a short time, and then a remission without further therapy [128]. Addition of iodide therapy is also a useful possibility, as noted below. A report that administration of iodide increases the relapse rate after drug therapy is withdrawn has not been confirmed [129].

Hashizume and co-workers reported that administration of T4 to suppress TSH for a year after stopping antithyroid drugs produced a very high remission rate [130]. Similar results were found when T4 treatment was given after a course of antithyroid drugs during pregnancy. [131]. These studies engendered much interest because of the uniquely high remission rate obtained by the continuation of thyroxine treatment to

suppress TSH for a year or more after the usual course of antithyroid drug therapy. Possibly such treatment is beneficial since it inhibits the release of thyroid antigens. However subsequent studies have not found a beneficial effect of added T4 therapy [131.1,131.2]. It appears that the results are, for some reason, peculiar to this study group.

The probability of prolonged remission correlates with reduction in gland size, disappearance of thyroid-stimulating antibodies from serum[132, 133], (Fig.11-8) return of T3 suppressibility, decrease in serum TG, and a haplotype other than HLA-DR3 [130 - 136]. However, none of these markers predict recovery or continued disease with an accuracy rate above 60-70% [136.1]. Long after apparent clinical remission, many patients show continued abnormal thyroid function, including partial failure of T3 suppression, or absent or excessive TRH responses [127-140]. These findings probably indicate the tenuous balance controlling immune responses in these patients.

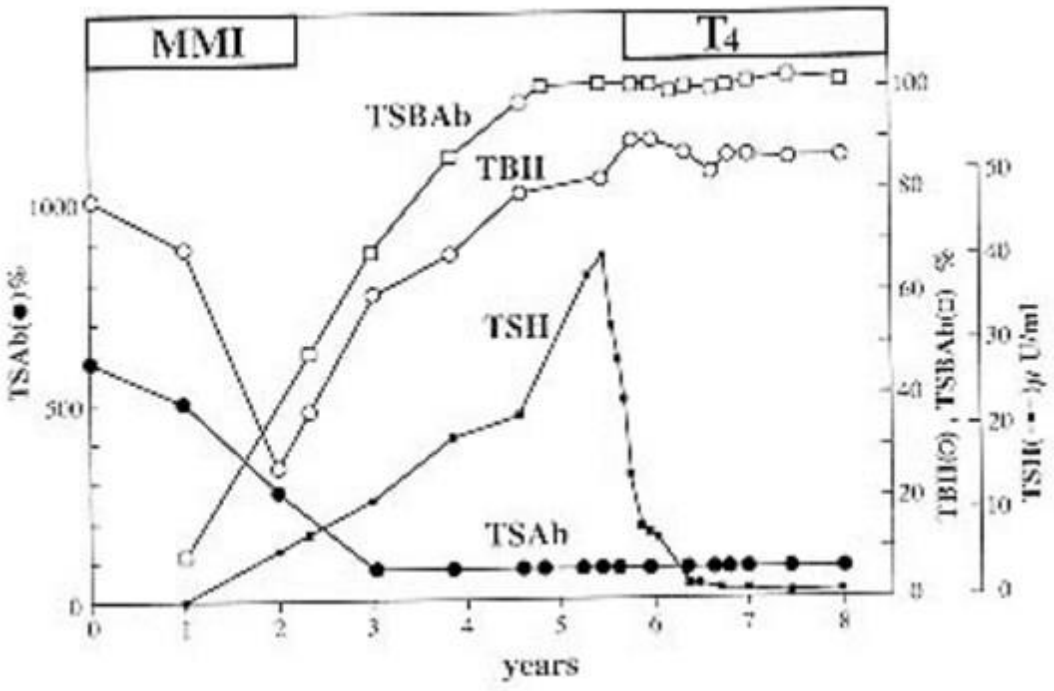

Figure 8. In this patient with Graves' Disease, the mixture of antibodies shifted during antithyroid therapy from dominance by TSAb, to a dominant effect by TSBAb and TBII, leading to spontaneous development of hypothyroidism. From Takasu et al, J. Endocrinol. Invest. 20:452-461, 1997.

Breast feeding- Lactating women taking PTU have PTU levels of up to 7.7 µg/ml in blood, but in milk the level is much lower, about 0.7 µg/ml [141]. Only 1-2 mg PTU could be transferred to the baby daily through nursing; this amount is inconsequential except for the possibility of reactions to the drug. Azizi et al. studied intellectual development of children whose mothers took methimazole during lactation, and found that there was no evident effect on physical and intellectual development, at least in children whose mothers took up to 20 mg of MMI daily [141a].

Hypothyroidism- It has long been known that some patients with Graves' disease eventually develop spontaneous hypothyroidism [68]. Reports have shown that most patients who become euthyroid after antithyroid drug therapy, if followed long enough, also develop evidence of diminished thyroid function [69]. In a prospective study, Lamberg et al [139]found that the annual incidence in these patients of subclinical hypothyroidism was 2.5%, and of overt hypothyroidism 0.6%.

TOXIC REACTIONS TO ANTITHYROID DRUGS

The use of antithyroid drugs may be accompanied by toxic reactions, depending on the drug and dose, in 3 - 12% of patients[117, 118, 142- 146]. Most of these reactions probably represent drug allergies[147- 148]. Chevalley et al., in a study of 180 patients given methimazole[143], found an incidence of toxicity of 4.3%, broken down as follows: Total reactions 4.3%; Pruritus 2.2%; Granulocytopenia 1.6%; Urticaria 0.5%.Methimazole may be the drug least likely to cause a toxic reaction, but there is little difference between it and PTU. When the antithyroid drugs are prescribed, the patient should be apprised of the possibility of reactions, and should be told to report phenomena such as a sore throat, fever, or rash to the physician and to discontinue the drug until the cause of the symptoms has been evaluated. These symptoms may herald a serious reaction.

Allergic rash-If a patient taking a thiocarbamide develops a mild rash, it is permissible to provide an antihistamine and continue using the drug to see whether the reaction subsides spontaneously, as it commonly does. If the reaction is more severe or if neutropenia occurs, another drug should be tried or the medication withdrawn altogether. Usually a switch is made to another thiocarbamide, because cross-reactions do not necessarily occur between members of this drug family. Alternatively, the program of therapy may be changed to the use of RAI, which may be given after the patient has stopped taking the antithyroid drug for 48 hours, or the patient may be prepared for surgery by the administration of iodides and propranolol.

The incidence of **agranulocytosis** in a large series of patients was 0.4% [149]. It occurs most frequently in older patients and those given large amounts of the drug (20-30 mg methimazole every eight hours) [117].Reactions tend to be most frequent in the first few months of therapy but can occur at any time, with small doses of drug, and in patients of all ages [117]. The most common reactions are fever and a morbilliform or erythematous rash with pruritus. Reactions similar to those of serum sickness, with migratory arthralgias, jaundice, lymphadenopathy, polyserositis, and episodes resembling systemic lupus erythematosus have also been observed [147]. Pyoderma gangrenosum can occur (147.1). Neutropenia and agranulocytosis are the most serious complications. These reactions appear to be due to sensitization to the drugs, as determined by lymphocyte reactivity in vitro to the drugs [148]. Occasionally agranulocytosis can develop even though the total WBC remains within normal ranges- a hazard to be remembered and differential counts should be done. Fortunately, even these problems almost always subside when the drug is withdrawn. **Aplastic anemia** with marrow hypoplasia has been reported (perhaps 10 cases), again with spontaneous recovery in 2-5 weeks in 70%, but fatal outcome in 3 patients [149]. Thrombocytopenia and/or anemia may accompany the neutropenia. **Vasculitis** is a fortunately rare complication during treatment with antithyroid drugs.

Neutropenia-It is probably wise to see patients receiving the thiocarbamides at least monthly during the initiation of therapy and every two to three months during the entire program. Neutropenia can develop gradually but often comes on so suddenly that a routine white cell count offers only partial protection. A white cell count must be taken

whenever there is any suggestion of a reaction, and especially if the patient reports malaise or a sore throat. A white cell count taken at each visit will detect the gradually developing neutropenia that may occur. While many physicians do not routinely monitor these levels, the value of monitoring is suggested by the study of Tajiri et al [144]. Fifty-five of 15398 patients treated with antithyroid drugs developed agranulocytosis, and 4/5 of these were detected by routine WBC at office visits. Low total leukocyte counts are common in Graves' disease because of relative neutropenia, and for this reason a baseline WBC and differential should be performed before starting anti-thyroid drugs. However, total polymorphonuclear counts below 2,000 cells/mm3 should be carefully monitored; below 1,200 cells/mm3 it is unsafe to continue using the drugs.

In the event of severe neutropenia or agranulocytosis, the patient should be monitored closely, given antibiotics if infection develops, and possibly adrenal steroids. There is no consensus on the use of glucocorticoids, since they have not been shown to definitely shorten the period to recovery. Administration of recombinant human granulocyte colony stimulating factor (75 µg/day given IM) appears to hasten neutrophile recovery in most patients who start with neutrophile counts > 0.1 X 10^9/L [150-151]. Antithymocyte globulin and cyclosporin have also been used [151]. Care must be taken to ensure against exposure to infectious agents, and some physicians prefer not to hospitalize their patients for this reason. If the patient is hospitalized, he or she should be placed in a special-care room with full bacteriologic precautions.

ANCA antibodies- Patients may develop antineutrophil cytoplasmic antibodies, either pericytoplasmic or cytoplasmic, during treatment, with or without vasculitis. Most cases appear to be associated with the use of propylthiouracil, and therapy includes cessation of the drug, sometimes treatment with steroids or cyclophosphamide for renal involvement, and rarely plasmapheresis. The commonest cutaneous lesion associated is leukocytoclastic vasculitis associated with purpuric lesions. Symptoms may include fever, myalgia, arthralgia, and lesions in the kidneys and lungs. Prognosis is usually good if the medication is discontinued, although death has occurred. ANCA positivity (pericytoplasmic, cytoplasmic, directed to myeloperoxidase, proteinase3, or human leukocyte elastase) can occur in patients on antithyroid drugs associated with vasculitis. It is also found without clinical evidence of vasculitis, and the significance of this finding is unclear [151.1]. Guma et al recently reported that, in a series of patients with Graves' disease, 67% were found to be ANCA positive before medical treatment, and that 19% remained positive after one year of antithyroid treatment. This data suggests that ANCA antibodies reflect in some way the autoimmunity associated with Graves' hyperthyroidism, rather than simply being a manifestation due to the treatment with antithyroid drugs (151.2). In addition to suppression of hematopoiesis and agranulocytosis, methimazole has been associated in one patient with massive plasmocytosis, in which 98% of the cells in the bone marrow were plasma cells. After discontinuation of the drug, and treatment with dexamethasone and G-CSF, the patient's marrow recovered to normal (151.3).

Liver damage-Thiocarbamides can also cause liver damage ranging from elevation of enzymes, through jaundice, to fatal hepatic necrosis. **Toxic hepatitis** (primarily with propylthiouracil) and cholestatic jaundice (primarily with methimazole) are fortunately uncommon [150].Toxic hepatitis can be severe or fatal, but the incidence of serious liver complications is so low that routine monitoring of function tests has not been advised[1514, 152]. Liver transplantation has been used with success in several patients [152.1]. As noted above, any sign of liver damage must be carefully monitored, and progress of abnormalities in liver function tests demand cessation of the drug[147, 152].

Diffuse interstitial pneumonitis has also been produced by propylthiouracil [153].

Pregnancy-(Please also see chapter on Thyroid Regulation and Dysfunction in the Pregnant Patient). **Methimazole** should be avoided in early pregnancy as disc ussed above. Very rare cases of esophageal atresia, omphalocele, and choanal atresia occurred in Sweden almost only in infants whose mothers took methimazole during early pregnancy.This is thought to be a true, although fortunately very infrequent, complication of methimazole use. Their observations obviously suggest that methimazole should best not be given during early months of pregnancy (153.1). As noted elsewhere in this web-book, various options are available, including 1) arranging definitive treatment before pregnancy, 2) switching to propylthiouracil as soon as possible and use of that drug during the first trimester, and leaving mild hyperthyroidism untreated (wich associated risks). iodide treatment can be tried instead of ATD, and is reported to be significantly more safe, although experience with this approach is inadequate for recommendation (154)

Potassium Perchlorate, Lithium,and Cholestyramine

Potassium perchlorate was introduced into clinical use after it was demonstrated that several monovalent anions, including nitrates, have an antithyroid action. Perchlorate was the only member of the group that appeared to have sufficient potency to be useful. This drug, in doses of 200 - 400 mg every six hours, competitively blocks iodide transport by the thyroid. Accordingly, therapeutic doses of potassium iodide will overcome its effect. Institution and control of therapy with perchlorate are similar to those discussed for the thiocarbamides. Toxic reactions to this agent occur in about 4% of cases [155] and usually consist of gastric distress, skin rash, fever, lymphadenopathy, or neutropenia; they usually disappear when the drug is discontinued. The reaction rate is higher when doses of more than 1 g/day are given [155]. Nonfatal cases of neutropenia or agranulocytosis have been reported, and four cases of fatal aplastic anemia have been associated with the use of this drug [156]. Because of toxic reactions, perchlorate is not used at present for routine therapy. It has found a role in therapy of thyrotoxicosis induced by amiodarone [157]. Apparently blocking of iodide uptake is an effective antithyroid therapy in the presence of large body stores of iodide, while in this situation, methimazole and propylthiouracil are not effective alone.

Lithium ion inhibits release of T4 and T3 from the thyroid and has been used in the treatment of thyrotoxicosis, but is most effective when used with a thiocarbamide drug. It does not have a well-established place in the treatment of Graves' disease[157, 158]. It has possible value in augmenting the retention of $^{131-I}$ [159] and in preparing patients allergic to the usual antithyroid drugs or iodide for surgery, although propranolol is generally used for the latter problem.

Cholestyramine (4gm, q8h) for a month has been shown to hasten return of T4 to normal [159.1] by binding hormone in the gut. It can be used as an adjunct to help speed return of hormone levels to normal, and may be especially beneficial in thyroid storm.

Iodine treatment- Plummer originally observed that the administration of iodide to thyrotoxic patients resulted in an amelioration of their symptoms. This reaction is associated with a decreased rate of release of thyroid hormone from the gland and with a gradual increase in the quantity of stored hormone. The effect of iodide on thyroid hormone release and concentration in blood is apparent in Figure 7. The mechanism of action may be by inhibition of generation of cAMP, and involves inhibition of TG

proteolysis, but is not fully understood. Therapeutic quantities of iodide also have an effect on hormone synthesis through inhibition of organification of iodide. Iodide has similar but less intense effects on the normal thyroid gland, apparently because of adaptive mechanisms.

Administration of large amounts of iodide to laboratory animals or humans blocks the synthesis of thyroid hormone and results in an accumulation of trapped inorganic iodide in the thyroid gland (the Wolff-Chaikoff effect, see Ch 2). The thyrotoxic gland is especially sensitive to this action of iodide. Raising the plasma iodide concentration to a level above 5 µg/dl results in a complete temporary inhibition of iodide organification by the thyrotoxic gland. In normal persons elevation of the inorganic 127-I level results, up to a point, in a progressive increase of accumulation of iodide in the gland. When the plasma concentration is above 20 µg/dl, organification is also inhibited in the normal gland [160]. The sensitivity of the thyrotoxic gland, in comparison with that of the euthyroid gland, may be due to an increased ability to concentrate iodide in the thyroid, and its failure to "adapt" by decreasing the iodide concentrating mechanism.

When iodine is to be used therapeutically in Graves' disease, one usually prescribes a saturated solution of potassium iodide (which contains about 50 mg iodide per drop) or Lugol's solution (which contains about 8.3 mg iodide per drop). Thompson and co-workers [161] found that 6 mg of I- or KI produces a maximum response. This fact was reemphasized by Friend, who pointed out that the habit of prescribing the 5 drops of Lugol's or SSKI three times daily is unnecessary [162]. Two drops of Lugol's solution or 1 drop of a saturated solution of potassium iodide two times daily is more than sufficient.

The therapeutic response to iodide begins within two to seven days and is faster than can be obtained by any other methods of medical treatment. Only 3% of patients so treated fail to respond. Men, older persons, and those with nodular goiter are in the group less likely to have a response to iodide. Although almost all patients initially respond to iodide, about one-third respond partially and remain toxic, and another one-third initially respond but relapse after about six weeks [163].

Because of the partial responses and relapse rate, use of iodide as definitive therapy for thyrotoxicosis has been replaced by the modalities described above. Currently Iodides are given sometimes after 131-I therapy to control hyperthyroidism, and are usually given as part of treatment before thyroidectomy. However some recent reports suggest iodide might have a larger role to play. Addition of iodine (38 mg/day) to methimazole (15mg/d) accelerated response over methimazole alone (154), and long term iodine treatment induced remission in 38% of patients who were given this treatment because of adverse reactions to ATD (164). In a study of 30 drug-naïve patients with "mild" GD, all but 3 were controlled on iodine alone (165.). Use of iodides instead of methimazole during the first trimester of pregnancy reduced major anomalies from 4.1% to 1.5% in one study (165.1). Iodine treatment is not currentty considered standard, but this may change soon.

Adjunctive Therapy for Graves' Disease
Propranolol, metopranol, atenolol
Beta-adrenergic blocking agents have won a prominent position in the treatment of thyrotoxicosis. Although they alleviate many of the signs and symptoms, they have little effect on the fundamental disease process[166, 167]. Palpitations, excessive sweating, and nervousness improve, and tremor and tachycardia are controlled. Many patients feel

much improved, but others are psychologically depressed by the drug and prefer not to take it. Improvement in myocardial efficiency and reduction in the exaggerated myocardial oxygen consumption have been demonstrated [168]. Propranolol lowers oxygen consumption [169, 170] and reverses the nitrogen wasting of thyrotoxicosis, although it does not inhibit excess urinary calcium and hydroxyproline loss. Propranolol is useful in symptomatic treatment while physician and patient are awaiting the improvement from antithyroid drug or 131-I therapy [171]. Some patients appear to enter remission after using this drug alone for six months or so of therapy[169, 172]. It has been useful in neonatal thyrotoxicosis [173] and in thyroid storm [174]. The drug must be used cautiously when there is evidence of severe thyrotoxicosis, or heart failure, but often control of tachycardia permits improved circulation. Beta blockade can induce cardiovascular collapse in patients with or without heart failure, and asystolic arrest (174.1,174.2). Administration of beta blocker was shown by Ikram to reduce CO by 13% in patients with uncontrolled CHF, and apparently this reduction in CO can be near fatal in rare patients.
Some surgical groups routinely prepare patients for **thyroidectomy with propranolol** for 20 - 40 days and add potassium iodide during the last week [175]. The BMR and thyroid hormone level remain elevated at the time of operation, but the patient experiences no problems. We prefer conventional preoperative preparation with thiocarbamides, with or without iodide, and would use propranolol as an adjunct, or if the patient is allergic to the usual drugs.

Propranolol is usually given orally as 20 - 40 mg every four to six hours, but up to 200 mg every six hours may be needed. In emergency management of thyroid storm (see also Chapter 12) or tachycardia, it may be given intravenously (1 - 3 mg, rarely up to 6 mg) over 3 - 10 minutes and repeated every four to six hours under electrocardiographic control. Atropine (0.5 - 1.0 mg) is the appropriate antidote if severe brachycardia is seen.

Reserpine and Guanethidine Drugs such as reserpine [177] and guanethidine [178] that deplete tissue catecholamines were used extensively in the past as adjuncts in the therapy for thyrotoxicosis, but fell into disuse as the value of beta -sympathetic blockade with propranolol became recognized.

Glucocorticoids, Ipodate, and Other Treatments As described elsewhere, potassium iodide acts promptly to inhibit thyroid hormone secretion from the Graves' disease thyroid gland. PTU, propranolol, glucocorticoids [181], amiodarone, and sodium ipodate (Oragrafin Sodium) inhibit peripheral T4 to T3 conversion, and glucocorticoids may have a more prolonged suppressive effect on thyrotoxicosis [182]. Orally administered resins bind T4 in the intestine and prevent recirculation [183]. All of these agents have been used for control of thyrotoxicosis [184, 185]. Combined dexamethasone, potassium iodide, and PTU can lower the serum T3 level to normal in 24 hours, which is useful in severe thyrotoxicosis. Prednisone has been reported to induce remission of Graves' disease, but at the expense of causing Cushing's syndrome [187]. **Ipodate** (0.5 - 1 g orally per day) acts to inhibit hormone release because of its iodine content, in addition to its action to inhibit T4 to T3 conversion. This dose of ipodate given to patients with Graves' disease reduced the serum T3 level by 58% and the T4 level by 20% within 24 hours, and the effect persisted for three weeks[188, 189]. This dose of ipodate was more effective than 600 mg of PTU, which decreased the T3 level by only 23% during the first 24 hours, whereas the T4 level did not drop. Ipodate may prove to be a useful adjunct in the early therapy of hyperthyroidism, but will increase total body and thyroidal iodine. However, when the drug is stopped, the RAIU in Graves' patients usually returns to pre-

treatment levels within a week [189]. Because it is the most effective agent available in preventing conversion of T4 to T3, it has a useful role in managing thyroid storm.

Immunosuppressive Therapy- Development of new targeted and relatively safe immune suppressive treatments has allowed their extension to Graves' disease. Rituximab, an anti CD20 B cell lymphocyte depleting monoclonal antibody, was initially found to induce remission in Graves' ophthalmopathy. It also mediates decreases in anti thyroid antibodies, and is currently employed in a Phase II trial for therapy of mild, relapsing Graves' disease (189.1, 189.2). Significant adverse events during therapy with rituximab ("serum sickness", mild colitis, iridocyclitis, polyarthritis) have been reported, and will probably limit its usefulness (189.3) Use of agents of this type, that work by increasing function of regulatory T cells, will probably become common in the next few years. Another approach has been pioneered by Gershengorn and colleagues, who devised a small molecule that is an "allosteric inverse agonist" of TSHR, and inhibits stimulation of TSH receptor activation by TSAbs (189.4). Such agents are used in current clinical trials, and should offer entirely new treatment stategies in the future.

SURGICAL THERAPY

Subtotal thyroidectomy is an established and effective form of therapy for Graves' disease, providing the patient has been suitably prepared for surgery. In competent hands, the risk of hypoparathyroidism or recurrent nerve damage is under 1%, and the discomfort and transient disability attendant upon surgery may be a reasonable price to pay for the rapid relief from this unpleasant disease. In some clinics it is the therapy of choice for most young male adults, especially if a trial of antithyroid drugs has failed. Total thyroidectomy may be preferred in patients with serious eye disease or high TRAb levels, in order to help the eye disease and to keep down the incidence of recurrence [190-194].

As with other effective methods available, it is necessary for the physician and the patient to decide on the form of therapy most suitable for the case at hand. Because of the potential but unproved risks of 131-I therapy, it is not always possible to make an entirely rational choice; the fears and prejudices of the physician and the patient will often enter into the decision. Surgery is clearly indicated in certain patients. Among these are (1) patients who have not responded to prolonged antithyroid drug therapy, or who develop toxic reactions to the drug and for whatever reason are unsuitable for 131-I therapy; (2) patients with huge glands, which frequently do not regress adequately after 131-I therapy; and (3) patients with thyroid nodules that raise a suspicion of carcinoma. Stocker et al have reviewed the problem of nodules in Graves' glands (195). They found that 12% of Graves' patients had cold defects on scan, and among these half were referred for surgery. Six of 22, representing 2% of all Graves' patients, 15% of patients with cold nodules, 25% of patients with palpable nodules, and 27% of those going to surgery, had papillary cancer in the location corresponding to the cold defect. Of these patients, one had metastasis to bone and two required multiple treatments with radioiodine. These authors argue for evaluating patients with a thyroid scintigram and further diagnostic evaluation of cold defects. Subtotal or near total thyroidectomy is often the treatment of choice for patients with amiodarone induced thyrotoxicosis, since response to ATDs is typically poor, and RAIU can not be given (196). Surgery may also have a place in therapy of older patients with thyroid storm and/or cardio-respiratory failure, who do not respond rapidly to intensive medical therapy(197).

Surgery in patients with ophthalmopathy

Contemporary data indicate that exophthalmos may be exacerbated by RAI therapy [80],although in some studies appearance of progressive ophthalmopathy was about the

same after treatment with 131-I as with surgery [79]. Thus, in the presence of serious eye signs, treatment with antithyroid drugs followed by surgery is an important alternative to consider, and total thyroidectomy is preferred [80-82]. The preferential use of surgery rather than radioactive iodide in the management of patients with severe Graves' ophthalmopathy, and the greater, more frequent exacerbation of eye disease after RAI therapy, has been supported in a number of studies including those by Torring et al [36.2], Moleti et al [44.4], and De Bellis et al [44.5] and others documented above. Marcocci et al, in contrast, report that near-total thyroidectomy had no efffect on the course of ophthalmopathy in a group of patients who had absent or non-severe preexisting ophthalmopathy. The relevance of this to patients with more severe ocular disease is uncertain, since it is logical to expect that in these patients there would be no effect of removing antigens, if the patients lacked any tendency to develop ophthalmopathy [44.6]. Moleti et al recently reported on 55 patients with Graves' disease and mild to moderate Graves' ophthalmopathy, who underwent near-total thyroidectomy, and of whom 16 had standard ablative doses of radioactive iodide. They found that the course of ophthalmopathy, both short and long term after treatment, was significantly better in the group of patients who underwent thyroidectomy and $^{131\text{-}I}$ ablation, and suggest that this is a more effective means of inducing and maintaining ophthalmopathic inactivity (44.7). In a randomized, prospective study, total thyroidectomy, rather than partial thyroidectomy, was followed by a better outcome of GO in patients given iv glucocorticoids. Radioiodine uptake test and thyroglobulin assay showed complete ablation in the majority of total, but not of partial thyroidectomy patients(44.6) .

The rate of patient rehabilitation is probably quickest with surgery. Although the source of hormone is directly and immediately removed by surgery, the patient usually must undergo one to three months of preparation before operation. The total time from diagnosis through operative convalescence is thus three to four months. Antithyroid drugs, in contrast, provide at best only 30 - 40% permanent control after one year of therapy. Iodine-131 can assuredly induce prompt remission, but low dose protocols, as noted, are plagued by a need for medical management and retreatment over one to three years before all patients are euthyroid. Treatment with higher doses provides more certain remission at the expense of more certain hypothyroidism.

There are several strong contraindications to surgery, including previous thyroid surgery, severe coincident heart or lung disease, the lack of a well-qualified surgeon, and pregnancy in the third trimester, since anesthesia and surgery may induce premature labor.

More enthusiastic surgeons have in the past recommended surgery for all children as the initial approach, claiming that there is less interference with normal growth and development than with prolonged antithyroid drug treatment [191]. Therapy for childhood thyrotoxicosis is discussed further below.

Preparation for Surgery

Antithyroid drugs of the thiocarbamide group are employed to induce a euthyroid state before subtotal thyroidectomy when surgery is the desired form of treatment. Two approaches are used. Mmethimazole (or PTU if used) may be administered until the patient becomes euthyroid. After this state has been reached, and while the patient is maintained on full doses of thiocarbamides, Lugol's solution or a saturated solution of potassium iodide is administered for 7 - 10 days. This therapy induces an involution of the gland and decreases its vascularity, a factor surgeons find helpful in the subsequent

thyroidectomy. In one study Lugol solution treatment resulted in a 9.3-fold decreased rate of intraoperative blood loss. Preoperative Lugol solution treatment decreased the rate of blood flow, thyroid vascularity measured by histomorphometry , and intraoperative blood loss during thyroidectomy(198).

The iodide should be given only while the patient is under the effect of full doses of the antithyroid drug; otherwise, the iodide may permit an exacerbation of the thyrotoxicosis. Alternatively patients may be prepared by combined treatment with antithyroid drugs and thyroxine. It is not obvious that one method is superior to the other. Severely ill patients can be prepared for surgery rapidly by combining several treatments-iopanoic acid 500mg bid, dexamethasone 1mg bid, antithyroid drugs, and beta-blockers(199).

Pre-treatment should have the patient in optimal condition for surgical thyroidectomy. By this time the patient has gained weight, the nutritional status has been improved, and the cardiovascular manifestations of the disease are under control. At the time of surgery, the anesthesia is well tolerated without the risk of hypersensitivity to sympathoadrenal discharge characteristic of the thyrotoxic subject. The surgeon finds that the gland is relatively avascular. Convalescence is customarily smooth. The stormy febrile course characteristic of the poorly prepared patient in past years is rarely seen.

Reactions to the thiocarbamide drugs occasionally occur during preparation for surgery. If the problem is a minor rash or low-grade fever, the drug is continued, or a change is made to a different thiocarbamide. More severe reactions (severe fever or rash, leukopenia, jaundice, or serum sickness) necessitate a change to another form of therapy, but no entirely satisfactory alternative is available. One course is to administer iodide and propranolol and proceed to surgery. In some patients, it is best to proceed directly to 131-I therapy if difficulties arise in the preparation with antithyroid drugs.

Propranolol has been used alone or in combination with potassium iodide [199] in preparation for surgery, and favorable results have generally been reported[200-201]. This procedure is doubtless safe in the hands of a medical team familiar and experienced with this protocol and willing to monitor the patient carefully to ensure adequate dosage. It is safe to use in young patients with mild disease, but is not advised as a standard protocol. Propranolol is used as an adjunct, or combined with potassium iodide as the sole therapy only when complications with antithyroid drugs preclude their use and surgery is strongly preferred to treatment with 131-I.

Amiodarone induced hyperthyroidism is typically difficult to manage, as described in Chapter 13. Administration of iopanoic acid, 1 gm daily for 13 days, has been shown to provide successful pre-operative therapy, reducing T3 levels to normal (196). Propranolol is the usual drug used for preparation of patients with amiodarone induced hyperthyroidism going to surgery.

Surgical Techniques and Complications

The standard operation is a one-stage subtotal thyroidectomy. General anesthesia is standard, but cervical plexus block and out-patient surgery is employed by some surgeons [202]. The amount of tissue left behind is about 4-10 grams, but this amount is variable. Taylor and Painter [203] found that the average volume of this remnant in 43 patients achieving a remission was about 8 ml, and Sugino et al recommended leaving 6 grams of tissue [204]. The toxic state recurred in only two patients in their series, and in these twice the amount of tissue mentioned above was left. Ozaki also noted the

importance of the amount of thyroid remaining as the principal predictor of eu- or hypo-thyroidism [205].There seems however to be no relation between the original size of the thyroid and the size of the remnant necessary to maintain normal metabolism.

Motivated in part by economic considerations, there has been in recent years a reevaluation of **thyroidectomy done under local anesthesia** as a day-surgery proceedure. Pros and cons have recently been discussed. In proper hands local anesthesia and prompt discharge seem acceptable, but most surgeons opt for the standard in hospital approach since it offers a more controlled operative setting and an element of safety the night after surgery. Some clinicians argue for total-thyroidectomy in an effort to reduce recurrence rates (206, 207), and point out that this operation seems to reduce anti-thyroid autoimmunity and reduces the chance of exacerbation of ophthalmopathy. Permanent cure of the hyperthyroidism is produced in 90 - 98% of patients treated this way.

Complications of Surgery

Although surgery of the thyroid has reached a high degree of perfection, it is not without problems even in excellent hands. The complication rates at present are low [208]. Among 254 patients operated on at three Nashville hospitals in the decade before 1970, there was no mortality, only minor wound problems, a 1.9% incidence of permanent hypoparathyroidism, and a 4.2% recurrence rate [209]. Hypo-parathyroidism is the major undesirable chronic complication. Surgical therapy at the Mayo Clinic has [210] been associated with a 75% rate of hypothyroidism but only a 1% recurrence rate, as an effort was made to remove more tissue and prevent recurrences. There is typically an inverse relationship between these two results of surgery. In the recent experience of the University of Chicago Clinics, the euthyroid state has been achieved by surgery in 82%; 6% became hypothyroid, and the recurrence rate was 12% [200]. Palit et al. published a meta analysis of collected series of patients treated for Graves' disease, either by total thyroidectomy or subtotal thyroidectomy. Overall, the surgery controlled hyperthyroidism in 92% of patients. There was no difference in complication rates between the two kinds of operations, with permanent laryngeal nerve injury occurring in 0.7 - 0.9% of patients, and permanent hypoparathyroidism in 1 – 1.6% of patients. Since many surgeons have become more familiar with and capable of total thyroidectomy, and this avoids the possible recurrence of disease, although possibly slightly increasing the risk of nerve or parathyroid damage, total thyroidectomy has become a common or even preferred alternative to subtotal thyroidectomy for managing hyperthyroidism. Recurrence rates are higher in patients with progressive exophthalmos or strongly positive assays for TRAb, suggesting that total thyroidectomy may be preferred in these cases [207]. Geographic differences in iodine ingestion have been related to the outcome.

Death rates are now approaching the vanishing point [206-210] Of the nonfatal complications, **permanent hypoparathyroidism** is the most serious, and requires lifelong medical supervision and treatment. Experienced surgeons have an incidence under 1%. Unfortunately, the general experience is near 3%. More patients, perhaps 10%, develop transient post-operative hypocalcemia but soon recover apparently normal function. Perhaps these patients have borderline function that may fail in later years.

Unilateral vocal cord paralysis rarely causes more than some hoarseness and a weakened voice, but bilateral injury leads to permanent voice damage even after corrective surgery. **Bilateral recurrent nerve injury** may be associated with severe respiratory impairment when an acute inflammatory process supervenes and may be

life-threatening. Fortunately, it is now extremely rare after subtotal thyroidectomy. Damage to the superior external laryngeal nerve during surgery may alter the quality of the voice and the ability to shout without causing hoarseness. One may speculate whether declining skills in the techniques of subtotal thyroidectomy, attendant upon a dramatic fall in the use of this procedure, may lead to an increase in the hazards of the procedure.

Hypothyroidism, whether occurring after surgery or 131-I therapy, can be readily controlled. Transient hypothyroidism is common, with recovery in one to six months. The presence of autoimmunity to thyroid antigens predisposes to the development of hypothyroidism after subtotal thyroidectomy for thyrotoxicosis. A positive test for antibodies to the microsomal/TPO antigen was found years ago by Buchanan et al [211] to correlate with an increased incidence of postoperative hypothyroidism. The incidence of hypothyroidism is certainly of importance in weighing the virtues of 131-I and surgical therapy. The ability of surgical therapy to produce a euthyroid state in many patients over long-term follow-up gives it one advantage over RAI therapy, but this must be weighed against the risk of hypoparathyroidism and recurrent nerve damage.

Course After Surgery --
In the immediate postoperative period, patients should be followed closely. They should ideally have a special duty nurse or family member providing watch during the first 24 hours, and a tracheotomy set and calcium chloride or gluconate for infusion should be at the bedside. During this period, **undetected hemorrhage** can lead to asphyxiation. Current use of drains with constant suction helps protect against this problem.
Transient hypocalcemia is common, resulting from trauma to the parathyroid glands and their blood supply and also possibly to rapid uptake of calcium by the bones, which have been depleted of calcium by the thyrotoxicosis [212,213]. Oral or intra- venous calcium supplementation suffices in most instances to control the symptoms. The calcium may be given slowly intravenously as calcium gluconate or calcium chloride in a dose ranging from 0.5 to 1.0 g every 4-8 hours, as indicated by clinical observation and determination of Ca2+.

Replacement thyroid hormone-
If sub-total throidectomy has been performed, thyroid hormeone replacement may not be needed. In 50-70% of patients, the residual gland is able to form enough hormone to prevent even transient clinical hypothyroidism. Serum hormone levels should be determined every two to four months until it is clear that the patient does not need replacement. Some surgeons give their patients thyroxine for an indefinite period after the operation in an attempt to avoid transient hypothyroidism and to remove any stimulus to regeneration of the gland.
If total thyroidectomy has been performed, as is increasingly the case, full replacement doses of thyroxine (1.7 ug/kg BW, or about 1ug/pound of lean body mass) should be instituted immediately, and T4 levels checked in about 2 weeks for adjustment. Patients should be informed that they will need this treatment for life, and that they should re regularly checked, and consistent in their daily dosage.

Long Term Follow-Up
Probably the thyroid remnant is not normal. It has a rapid $^{131\text{-}I}$ turnover rate and a small pool of stored organic iodine. Suppressibility by T3 administration returns within a few months of operation in some patients. TSAb tend to disappear from the blood in the ensuing 3 - 12 months [214-2156]. After subtotal thyroidectomy, thyrotoxicosis recurs in 5 - 10% of patients, often many years after the original episode. The long term outcome

of thyroid surgery for hyperthyroidism was reviewed by the Department of Surgery at Karolinska Institute. Of 380 patients observed and treated by surgery for thyrotoxicosis, primarily by subtotal thyroidectomy, 1% developed permanent hypoparathyroidism. Recurrent disease occurred in 2%. The operators intended to leave less than two grams of thyroid tissue, which presumably accounts for the low recurrence rate (216).

Finally, adequate follow-up must be carried out after any kind of treatment of Graves' disease. Recurrence is always possible, either early or late, and there is always the threat that the ophthalmopathic problems may worsen when all else in the progress of the patient seems favorable. A surprisingly large proportion of patients who have had subtotal thyroidectomy for Graves' disease and who are clinically euthyroid can be shown to have an abnormal TRH response (excessive or depressed), and up to a third have elevated serum TSH levels [217, 218]. Some of them are undoubtedly mildly hypothyroid, whereas others are close to euthyroid but require the stimulation of TSH to maintain this state. These patients should have replacement T_4 therapy if the elevated TSH persists. Over subsequent years the residual thyroid fails in more patients, due either to reduced blood supply, fibrosis from trauma, or continuing autoimmune thyroiditis. After 10 years, and depending on the extent of the original surgery, 20 - 40% are hypothyroid. This continuing thyroid failure is also seen after antithyroid drug therapy with ^{131}-I and represents the natural evolution of Graves' disease.

SPECIAL CONSIDERATIONS IN THE TREATMENT OF THYROTOXICOSIS IN CHILDREN Thyrotoxicosis may occur in any age group but is unusual in the first five years of life. The same remarkable preponderance of the disease in females over males is observed in children as in the adult population, and the signs and symptoms of the disease are similar in most respects. Behavioral symptoms frequently predominate in children and produce difficulty in school or problems in relationships within the family. Thyrotoxic children are tall for their age, probably as an effect of the disease. These children are restored to a normal height/age ratio after successful therapy for the thyrotoxicosis. Permanent brain damage and craniosynostosis are reported as complications of early childhood thyrotoxicosis (219). Bone age is also often advanced [220].

No more is known about the cause of the disease in children than in adults. Diagnosis rests upon eliciting a typical history and signs and upon the standard laboratory test results. Normal values for children are not the same as for adults during the first weeks of life, and these differencesshould be taken into account.

Therapy of Childhood Graves' Disease

131-I Treatment- In some clinics, RAI is used in the treatment of thyrotoxicosis in children. In an early report, 73 children and adolescents were so treated. Hypothyroidism developed in 43. Subsequent growth and development were normal [221]. In another group of 23 treated with 131-I, there were 4 recurrences, at least 5 became hypothyroid, and one was found to have a papillary thyroid cancer 20 months after the second dose [222]. Safa et al. [40] reviewed 87 children treated over 24 years and found no adverse effects except the well-known occurrence of hypothyroidism. Hamburger has examined therapy in 262 children ages 3 - 18 and concluded ^{131}-I therapy to be the best initial treatment [42]. Read et al (223) reviewed experience with 131-I over a 36 year period, including six children under age 6, and 11 between 6 and 11 years. No adverse effects on the patients or their offsprings were found, and they advocate 131-I as a safe and effective treatment.

Nevertheless, most physicians remain concerned about the risks of carcinogenesis, and the experience of Chernobyl has accentuated this concern. This problem was more fully discussed earlier in this chapter. Others believe that the risks of surgery and problems with antithyroid drug administration outweigh the potential risk of $^{131\text{-}I}$ therapy. This problem was critically reviewed by Rivkees et al [224]. They point out the significant risks of reaction to antithyroid drugs, and of surgery. Surgery may have a mortality rate in hospital in children of about one per thousand operations, although this may have decreased in recent years. Among problems with radioactive iodide therapy, they note the whole body radiation, possibly worsening of eye disease, and the apparent lack of significant thyroid cancer risk so far reported among children treated with I-131 for Graves' disease. They assumed that risk would be lower in children after age five, and especially after age ten, and if all thyroid cells were destroyed. They advise using higher doses of radioiodine to minimize residual thyroid tissue, and avoiding treatment of children under age five, but they believe that RAI is a convenient, effective, and useful therapy in children with Graves' disease. However, as noted above in the section on risks related to use od 131-i, Rivkees own data indicate that treatnment of children with conventional doses of RAI may induce a lifetime risk of any fatal cancer of over 2%, a very serious consideration (44.2) .Concern about the potential long term induction of cancer by RAI given to children is discussed above. Many physicians remain reluctant to use 131-I in children under age 15-18 as a first line therapy.

Surgery in children- Although $^{131\text{-}I}$ therapy may gain acceptance, the most common choice for therapy is between antithyroid drugs and subtotal thyroidectomy [225-227]. Proponents of antithyroid drug therapy believe that there is a greater tendency for remission of thyrotoxicosis in children compared to adults and that antithyroid drug therapy avoids the psychic and physical problems caused by surgery in this age group. With drugs the need for surgery (or 131-I) can be delayed almost indefinitely until conditions become favorable.

As arguments against surgery, one must consider the morbidity and possible, although rare, mortality. Surgery means a permanent scar, and the recurrence rate is much higher (up to 15%) than that observed in adults. If the recurrence rate is kept acceptably low by performing near-total thyroidectomies, there is always an attendant rise in the incidence of permanent hypothyroidism, and greater potential for damage to the recurrent laryngeal nerves and parathyroid glands. Damage to the parathyroids necessitates a complicated medical program that may be permanent, and is one of the major reasons for opposing routine surgical therapy in this disease. However Rudberg et al [228] reported that, in a series of 24 children treated surgically, only one had permanent hypoparathyroidism, and two recurred within 12 years. Soreide et al [229] operated on 82 children and had no post-op nerve palsy, no tetany, nor mortality, and point out that surgery can provide a prompt, safe, and effective treatment. Childhood Graves' disease was managed by near-total thyroidectomy in 78 patients of average age 13.8 years as reported by Sherman et al. Transient hypoparathyroidism and RCN damage were seen. Only three patients required subsequent 131-I treatment. Eighty-five % of those with ophthalmopathy were improved after surgery. The authors conclude that the treatment is safe and effective when performed by experienced surgeons (230).Others have pointed out the high relapse rate with all forms of therapy in the pediatric age group.

The main argument favoring surgery is that it may correct the thyrotoxicosis with surety and speed, and result in less disruption of normal life and development than is associated with long-term administration of antithyroid drugs and the attendant constant

medical supervision. Often children are unable to maintain the careful dosage schedule needed for control of the disease.

If surgery is elected, the patient should be prepared with an antithyroid drug such as methimazole in a dosage and duration sufficient to produce a euthyroid state, and then should be given iodide for seven days before surgery. Lugol's solution, or a saturated solution of potassium iodide, 1 or 2 drops twice daily, is sufficient to induce involution of the gland.

Anti-thyroid drug therapy in children- Antithyroid drug therapy is the usual preferable initial therapy in children. Favorable indications for its use are mild thyrotoxicosis, a small goiter, recent onset of disease, and especially the presence of some obvious emotional problem that seems to be related to precipitation of the disease. Antithyroid drug administration necessitates much supervision by the physician and the parents, the permanent remission rate will be 50% or less, and there is always the possibility of a reaction to the medication.

There is no consensus on **secondary treatment** if antithyroid drugs fail.. Some physicians favor surgery if the patient and parents seem incapable of following a regimen requiring frequent administration of medicine for a prolonged period or drug reactions occur. A factor that must be remembered in selecting the appropriate course of therapy is the experience of the available surgeon. Lack of experience contributes to a high rate of recurrence, permanent hypothyroidism, or permanent hypoparathyroidism. Other physicians believe the possible but unproven risks of 131-I are more than outweighed by the known risks of operation, and 131-I treatment is increasingly accepted for patients over age 15.

If antithyroid drugs are chosen as primary therapy, the patient is initially given a course of treatment for one or two years, according to the dosage schedule shown in Table 11-9. The dosage of PTU (**if used**) needed is usually 120 - 175 mg/m^2 body surface area daily divided into three equal doses every eight hours. Methimazole can be used in place of PTU; approximately one-tenth as much, in milligrams, is required. **Methimazole is now the preferred drug.** During therapy the dosage can usually be gradually reduced. Many patients will be satisfactorily controlled by once-a-day treatment. Although the plasma half-life of methimazole in children is only 3-6 hours, the drug is concentrated in the thyroid and maintains higher levels there for up to 24 hours after a dose [231].

The program is similar to that employed in adult thyrotoxicosis. It is sensible to see the child once each month, and at that time to make sure that the program is being followed and progress made. Any evidence of depression of the bone marrow should prompt a change to an alternative drug or a different form of treatment, as discussed below.

At the end of one or two years the medication is withdrawn. If thyrotoxicosis recurs, a second course of treatment lasting for one year or more may be given. A decrease in the size of the goiter during therapy is good evidence that a remission has been achieved. Progressive enlargement of the gland during therapy implies that hypothyroidism has been produced. This enlargement can be controlled by reduction in the dose of antithyroid drug or by administration of replacement thyroid hormone. There is no adequate rule for deciding when medical therapy has failed. After courses of antithyroid drug therapy totaling two to six years and attainment of age 15, if the patient still has not entered a permanent remission it is probably best to proceed with surgical or ^{131}-I

treatment. Barrio et al (225) reported on truly long term antithyroid drug therapy, which achieved 40% remissions in pediatric patients, with average time to remission of 5.4 years. Non-remitters were cured by RAI or surgery. Leger reported a similar program with 50% of children appearing to enter a permanent remission (232). In an other study 72% of children treated for 2 years relapsed. Occasionally a drug reaction develops while the condition is being controlled with an antithyroid drug. A change to another thiocarbamide may be satisfactory, but patients should be followed carefully. If a reaction is seen again, or if severe neutropenia occurs, it is usually best to stop antithyroid drug therapy and (1) give potassium iodide and an agent such as propranolol and to proceed with surgery, or (2) to give ^{131}-I. RAI therapy will be necessary if surgery is contraindicated by uncontrollable thyrotoxicosis,for whatever reason, or with prior thyroidectomy.

Table 9

Surface area-M^2	Weight (lbs)	Approximate daily dose of MMI (mg)
0.1	5	2-3
0.2	10	2-5
0.5	30	5-10
0.75	60	10
1.0	90	10-15
1.25	110	15-20
1.5	140	20
2.0	200	20-25

INTRAUTERINE AND NEONATAL THYROTOXICOSIS

Thyrotoxicosis in utero is a rare but recognized syndrome occurring in pregnant women with very high TSH-R stimulating Ab in serum, due to transplacental passage of antibodies. It can also develop in the neonate. It is possible to screen for this risk by assaying TSAb in serum of pregnant women with known current or prior Graves' Disease. Intra-uterine thyrotoxicosis causes fetal tachycardia, failure to grow, acceleration of bone age, premature closure of sutures, and occasionally fetal death. Multiple sequential pregnancies with this problem have been recorded. Clinical diagnosis is obviously inexact. Antithyroid drugs can be given, but control of the dosage is uncertain [233]. Propylthiouracil is considered to be the safest drug to use in the first trimester, because of fetal anomalies attributed to methimazole exposure in early pregnancy(234), with switching to MMI in the second and third trimesters..

Luton et al (233) provided their extensive experience in managing these difficult cases. Measurement of TSAb is important. Mothers with negative TSAb assay, and not on ATD, rarely have any fetal problem. Mothers with positive TSAb or on ATD must be monitored by following maternal hormone and TSH levels, fetal growth, heart rate, and by ultrasound for evidence of goiter or other signs of fetal hyper- or hypothyroidism. If maternal hormone levels are low and TSH elevated, with fetal goiter and evidence of hypothyroidism, ATD therapy is reduced and intra-amniotic T4 may be given. If maternal

T4 levels are high and TSH low, with fetal goiter and signs of fetal hyperthyroidism, increased doses of ATD are suggested. If the probable metabolic status of the fetus is not clear, fetal blood sampling is feasible although carrying significant risk to the fetus. Plasmapheresis to reduce maternal TRAb has been recommended, but few facts are available.

Thyrotoxicosis is rare in the newborn infant and is usually associated with past or present maternal hyperthyroidism [235,236]. Neonatal hypermetabolism usually arises from transplacental passage of TSAb. Frequently the infant is not recognized as thyrotoxic at birth, but develops symptoms of restlessness, tachycardia, poor feeding, occasionally excessive hunger, excessive weight loss, and possibly fever and diarrhea a few days after birth. The fetus converts T4 to T3 poorly in utero, but switches to normal T4 to T3 deiodination at birth. This phenomenon may normally provide a measure of protection in utero that is lost at birth, allowing the development of thyrotoxicosis in a few days. The syndrome may persist for two to five weeks, until the effects of the maternal antibodies have disappeared. The patient may be treated with propranolol, antithyroid drugs given according to the schedule above, and iodide. The antithyroid drug can be given parenterally if necessary in saline solution after sterilization by filtration through a Millipore filter. Newborn infants with thyrotoxicosis are frequently extremely ill, and ancillary therapy, including sedation, cooling, fluids in large amounts, electrolyte replacement, and oxygen, are probably as important in management as specific therapy for the thyrotoxicosis. Propranolol is used to control the tachycardia (236). Because of the increased metabolism of such infants, attention to fluid balance and adequacy of nutrition are important.

The patient usually survives the thyrotoxicosis, and the disease is typically self-limiting, with the euthyroid state being established in one or two months. Antithyroid medication can be gradually withdrawn at this time.

Graves' disease can also occur in the newborn because the same disturbance that is causing the disorder in the mother is also occurring independently in the child. Hollingsworth et al [2379] described their experience in such patients. The mothers did not necessarily have active disease during pregnancy. Graves' disease persisted in these patients from birth far beyond the time during which TSAb of maternal origin could persist. Advanced bone age was one feature of the disorder. Behavioral disturbances were later found in some of these children at a time when they were euthyroid.

General Therapeutic Relationship of the Patient and Physician

The foregoing discussion explains several methods for specifically decreasing thyroid hormone formation. They are, in a sense, both unphysiologic and traumatic to the patient. As a good physician realizes in any problem, but especially in Graves' disease, attention to the whole patient is mandatory.

During the initial and subsequent interviews, the physician caring for a patient with Graves' disease should recognize any psychological and physical stresses. Frequently major emotional problems come to light after the patient recognizes the sincere interest of the physician. Typically the problem involves interpersonal relationships and often is one of matrimonial friction. The upset may be deep-seated and may involve very difficult adjustments by the patient, but characteristically it is related to identifiable factors in the environment. To put it another way, the problem is not an endogenous emotional

reaction but a difficult adjustment to real external problems. On the other hand, one must be aware that the emotional lability of the thyrotoxic patient may be a trial for those with whom he or she must live, as well as for the patient. Thus thyrotoxicosis itself may create interpersonal problems. From whatever cause they arise, these problems are dealt with insofar as possible by the wise physician.

We have been unimpressed by the benefits of formal psychiatric care for the average thyrotoxic patient, but are certain that sympathetic discussion by the physician, possibly together with assistance in environmental manipulation, is an important part of the general attack on Graves' disease. In other cases, personal problems may play a less important etiologic role but may still strongly affect therapy by interfering with rest or by causing economic hardship.

In addition to providing assistance in solving personal problems, two other general therapeutic measures are important. The first is rest. The patient with Graves' disease should have time away from normal duties to help in reestablishing his or her psychic and physiologic equilibria. Patients can and do recover with appropriate therapy while continuing to work, but more rapid and certain progress is made if a period away from the usual occupation can be provided. Often a mild sedative or tranquilizer is helpful.

Another important general measure is attention to nutrition. Patients with Graves' disease are nutritionally depleted in proportion to the duration and severity of their illness. Until metabolism is restored to normal, and for some time afterward, the caloric and protein requirements of the patient may be well above normal. Specific vitamin deficiences may exist, and multivitamin supplementation is indicated. The intake of calcium should be above normal.

REFERENCES

1. Wayne EJ: The diagnosis of thyrotoxicosis. Br Med J 1:411, 1954.

1.1.Sawin CT, Geller A, Kaplan MM, Bacharach P, Wilson PWF, Hershman JM. Low serum thyrotropin (thyroid stimulating hormone) in older persons without hyperthyroidism. Arch Intern Med 151:165-168, 1991.

2. Morley JE, Shafer RB, Elson MK, Slag MF, Raleigh MJ, Brammer GL, Yuwiler A, Hershman JM: Amphetamine-induced hyperthyroxinemia. Ann Intern Med 93:707, 1980.

3. Brown ME, Refetoff S: Transient elevation of serum thyroid hormone concentration after initiation of replacement therapy in myxedema. Ann Intern Med 92:491, 1980.

4. Kaptein EM, Macintyre SS, Weiner JM, Spencer CA, Nicoloff JT: Free thyroxine estimates in nonthyroidal illness: Comparison of eight methods. J Clin Endocrinol Metab 52:1073, 1981.

5. Engler D, Donaldson EB, Stockigt JR, Taft P: Hyperthyroidism without triiodothyronine excess: An effect of severe nonthyroidal illness. J Clin Endocrinol Metab 46:77, 1978.

6. Mayfield RK, Sagel J, Colwell JA: Thyrotoxicosis without elevated serum triiodothyronine levels during diabetic ketoacidosis. Arch Intern Med 140:408, 1980.

7. Sobrinho LG, Limbert ES, Santos MA: Thyroxine toxicosis in patients with iodine induced thyrotoxicosis. J Clin Endocrinol Metab 45:25, 1977.

8. Sterling K, Refetoff S, Selenkow HA: T3 thyrotoxicosis due to elevated serum triiodothyronine levels. J Amer Med Assn 213:571, 1970.

9. Hollander CS, Nihei N, Burday SZ, Mitsuma T, Shenkman L, Blum M: Clinical and laboratory observations in cases of triiodothyronine toxicosis confirmed by radioimmunoassay. Lancet 1:609, 1972.

10. Hollander CS, Mitsuma T, Shenkman L, Stevenson C, Pineda G, Silva E: T3 toxicosis in an iodine-deficient area. Lancet 2:1276, 1972.

11. Hollander CS, Mitsuma T, Kastin AJ, Shenkman L, Blum M, Anderson DG: Hypertriiodothyroninemia as a premonitory manifestation of thyrotoxicosis. Lancet 2:731, 1971.

13. Ormston BJ, Alexander L, Evered DC, Clark F, Bird T, Appleton D, Hall R: Thyrotropin response to thyrotropin-releasing hormone in ophthalmic Graves' disease: Correlation with other aspects of thyroid function, thyroid suppressibility and activity of eye signs. Clin Endocrinol 2:369, 1973.

14. Franco PS, Hershman JM, Haigler ED, Pittman JA: Response to thyrotropin-releasing hormone compared with thyroid suppression tests in euthyroid Graves' disease. Metabolism 22:1357, 1973.

15. Clifton-Bligh P, Silverstein GE, Burke G: Unresponsiveness to thyrotropin-releasing hormone (TRH) in treated Graves' hyperthyroidism and in euthyroid Graves' disease. J Clin Endocrinol Metab 38:531, 1974.

15.1. Murakami M, Miyashita K, Kakizaki S, Saito S, Yamada M, Iriuchijima T, Takeuchi T, Mori M. Clinical usefulness of thyroid-stimulating antibody measurement using Chinese hamster ovary cells expressing human thyrotropin receptors. Eur J Endocrinol 1995:80-86, 1995.

15.2 Costagliola S, Morgenthaler NG, Hoermann R, Badenhoop K, Struck J, Freitag D, Poertl S, Weglohner W, Hollidt JM, Quadbeck B, Dumont JE, Schumm-Draeger PM, Bergmann A, Mann K, Vassart G, Usadel KH. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease.J Clin Endocrinol Metab. 1999 Jan;84(1):90-7.

15.3. Takasu N, Oshiro C, Akamine H, Komiya I, Nagata A, Sato Y, Yoshimura H, Ito K. Thyroid-stimulating antibody and TSH-binding inhibitor immunoglobulin in 277 Graves patients and in 686 normal subjects. J Endocrinol Invest 20:452-461, 1997.

15.4. Feldt-Rasmussen U, Schleusener H, Carayon P. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long-term remission after medical therapy of Graves disease. J Clin Endocrinol Metab 78:98-102, 1994.

16. Watson SG, Radford AD, Kipar A, Ibarrola P, Blackwood L Somatic mutations of the thyroid-stimulating hormone receptor gene in feline hyperthyroidism: parallels with human hyperthyroidism.J Endocrinol. 2005 Sep;186(3):523-37.

17. Namba H, Ross JL, Goodman D, Fagin JA: Solitary polyclonal autonomous thyroid nodule: A rare cause of childhood hyperthyroidism. J Clin Endocrinol Metab 72:1108-1112, 1991.

18. Shimaoka K, Van Herle AJ, Dindogru A: Thyrotoxicosis secondary to involvement of the thyroid with malignant lymphoma. J Clin Endocrinol Metab 43:64, 1976.

19. Emerson CH, Utiger RD: Hyperthyroidism and excessive thyrotropin secretion. N Engl J Med 287:328, 1972

20. Spanheimer RG, Bar RS, Hayford JC: Hyperthyroidism caused by inappropriate thyrotropin hypersecretion. Studies in patients with selective pituitary resistance to thyroid hormone. Arch Intern Med 142:1283-1286, 1982.

21. Gershengorn ML: Thytropin-induced hyperthyroidism caused by selective pituitary resistance to thyroid hormone. A new syndrome of "inappropriate secretion of TSH". J Clin Invest 56:271, 1975.

22. Woolf PD, Daly R: Thyrotoxicosis with painless thyroiditis. Am J Med 60:73, 1976.

23. Gluck FB, Nusynowitz ML, Plymate S: Chronic lymphocytic thyroiditis, thyrotoxicosis, and low radioactive iodine uptake. N Engl J Med 293:624, 1975.

24. Ginsberg J, Walfish PG: Post-partum transient thyrotoxicosis with painless thyroiditis. Lancet 1:1125, 1977.

25. Amino N, Yabu Y, Miyai K, Fujie T, Azukizawa M, Onishi T, Kumahara Y: Differentiation of thyrotoxicosis induced by thyroid destruction from Graves' disease. Lancet 1:344, 1978.

26. Inada M, Nishikawa M, Naito K, Ishii H, Tanaka K, Imura H: Reversible changes of the histological abnormalities of the thyroid in patients with painless thyroiditis. J Clin Endocrinol Metab 52:431, 1981.

27. Yabu Y, Amino N, Mori H, Miyai K, Tanizawa O, Takai S-I, Kumahara Y, Matsusuka F, Kuma K: Postpartum recurrence of hyperthyroidism and changes of thyroid-stimulating immunoglobulins in Graves' disease. J Clin Endocrinol Metab 51:1454, 1980.

28. Amino N, Miyai K, Azukizawa M, Yabu Y, Fujie T, Onishi T, Kumahara Y: Differentiation of thyrotoxicosis induced by thyroid destruction from Graves' disease. Lancet 2:344, 1978.

29. Shigemasa C, Ueta Y, Mitani Y, Taniguchi S, Urabe K, Tanaka T, Yoshida A, Mashiba H: Chronic thyroiditis with painful tender thyroid enlargement and transient thyrotoxicosis. J Clin Endocrinol Metab 70:385, 1990.

29.1. Sarlis NJ, Brucker-Davis F, Swift JP, Tahara K, Kohn LD. Graves' disease following thyrotoxic painless thyroiditis. Analysis of antibody activities against the thyrotropin receptor in two cases. Thyroid 7:829, 1997

29.12. Yoshimura M, Hershman JM. Thyrotropic action of human chorionic gonadotropin. Thyroid 5:425-434, 1995.

29.13 Hershman JM. 1999 Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. Thyroid 9:653.

29.14. Goodwin TM, Hershman JM. Hyperthyroidism due to inappropriate production of human chorionic gonadotropin. Clin Obstet Gynecol 40:32-44, 1997.

29.2. Rodien P. Bremont C. Sanson ML. Parma J. Van Sande J. Costagliola S. Luton JP. Vassart G. Duprez L. Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. New England Journal of Medicine. 339(25):1823-6, 1998 .

29.3. Fuhrer D, Wonerow P, Willgerodt H, Paschke R. Identification of a new thyrotropin receptor germline mutation (Leu629 Phe) in a family with neonatal onset of autosomal dominant nonautoimmune hyperthyroidism. J Clin Endocrinol Metab 82:4234-4238,

29.4. Ginsberg J, Lewanczuk RZ, Honore LH. Hyperplacentosis: a novel cause of hyperthyroidism. Thyroid 11:393-396, 20011997.

30. Cave WT Jr, Dunn JT: Choriocarcinoma with hyperthyroidism: Probable identity of the thyrotropin with human chorionic gonadotropin. Ann Intern Med 85:60, 1976.

31. Nagataki S, Mizuno M, Sakamoto S, Irie M, Shizume K, Nakao K, Galton VA, Arky RA, Ingbar SH: Thyroid function in molar pregnancy. J Clin Endocrinol Metab 44:254, 1977.

32. Tsuruta E, Tada H, Tamaki H, Kashiwai T, Asahi K, Takeoka K, Mitsuda N, Amino N. Pathogenic role of asialo human chorionic gonadotropin in gestational thyrotoxicosis. J Clin Endocrinol Metab 80:350-355, 1995.

33. Miyai K, Tanizawa O, Yamamoto T, Azukizawa M, Kawai Y, Noguchi M, Ishibas K, Kumahara Y: Pituitary-thyroid function in trophoblastic disease. J Clin Endocrinol Metab 42:254, 1976.

33.1 Doi F, Kakizaki S, Takagi H, Murakami M, Sohara N, Otsuka T, Abe T, Mori M .Long-term outcome of interferon-alpha-induced autoimmune thyroid disorders in chronic hepatitis C.Liver Int. 2005 Apr;25(2):242-6

33.2 Chen F, Day SL, Metcalfe RA, Sethi G, Kapembwa MS, Brook MG, Churchill D, de Ruiter A, Robinson S, Lacey CJ, Weetman AP.Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease.Medicine (Baltimore). 2005 Mar;84(2):98-106.

33a. Sgarbi, JA; Villaca, FG; Garbeline, B; Villar, HE; Romaldini, JH. The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities. J Clin Endocrinol Metab 88 1672-1677 2003

33b Woeber KA.Observations concerning the natural history of subclinical hyperthyroidism.Thyroid. 2005 Jul;15(7):687-91

34. Lahey FH: Apathetic thyroidism. Ann Surg 93:1026, 1931.

35. Editorial: Apathetic thyrotoxicosis. Lancet 2:809, 1970.

35.1 Bartalena L., Chiovato L:, Vitti P. Menagement of hyperthyroidism due to Graves' disease: frequently asked questions and answers (if any) J Endocrinol Invest 2016

36. Philip JR, Harrison MT, Ridley EF, Crooks J: Treatment of thyrotoxicosis with ionizing radiation. Lancet 2:1307, 1968.

36.1. Franklyn, JA. The management of hyperthyroidism. New Engl J Med 330:1731-1738, 1994.

36.2. Torring O, Tallstedt L, Wallin G, Lundell G, Lunggren J-G, Taube A, Saaf M, Hamberger B, Thyroid Study Group. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine â€“ A prospective, randomized study. J Clin Endocrinol Metab 81:2986-2993, 1996.

36.3. Vitti P, Rago T, Chiovato L, Pallini S, Santini F, Fiore E, Rocchi R, Martino E, Pinchera A. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. Thyroid 7:369, 1997.

36.31 Burch HB[1], Cooper DS[2]. Management of Graves Disease: A Review.JAMA. 2015 Dec 15;314(23):2544-54. doi: 10.1001/jama.2015

36.4 Scholz, GH; Hagemann, E; Arkenau, C; Engelmann, L; Lamesch, P; Schreiter, D; Schoenfelder, M; Olthoff, D; Paschke, R. Is there a place for thyroidectomy in older patients with thyrotoxic storm and cardiorespiratory failure? Thyroid 13 933 2003

37. Glinoer D, Hesch D, LaGasse R, Laurberg P: The management of hyperthyroidism due to Graves' disease in Europe in 1986. Results of an international survey. Proceedings of the Symposium held during the 15th Annual Meeting of the European Thyroid Association in Stockholm, June - July, 1986, 37 pages.

38. Solomon B, Glinoer D, LaGasse R, Wartofsky L: Current trends in the management of Graves' disease. J Clin Endocrinol Metab 70:1518-1524, 1990.

39. Dobyns BM, Sheline GE, Workman JB, Tompkins EA, McConahey WM, Becker DV: Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the Cooperative Thyrotoxicosis Therapy Follow-up Study. J Clin Endocrinol Metabl 37:976-998, 1974.

40. Safa AM, Schumacher P, Rodriguez-Antunez A: Long-term follow-up results in children and adolescents treated with radioactive iodine (131-Iodine). N Engl J Med 292:167-171, 1975.

41. Holm LE, Dahlqvist I, Israelsson A, Lundell GM: Malignant thyroid tumors after 131-iodine therapy. N Engl J Med 303:188-191, 1980.

42. Hamburger JI: Management of hyperthyroidism in children and adolescents. J Clin Endocrinol Metab 60:1019, 1985.

43. Freitas JE, Swanson DP, Gross MD, Sisson JS: Iodine-131: Optimal therapy for hyperthyroidism in children and adolescents? J Nucl Med 20:847, 1979.

44. Hayek A, Chapman E, Crawford JD: Long-term results of treatment of thyrotoxicosis in children and adolescents with radioactive iodine. N Engl J Med 283:949, 1970.

44.1.Franklyn JA, Maisonneuve P, Sheppard M, Betteridge PB. Cancer indicdence and mortality after radioiodine treatment for hyperthyroidism: a population based cohort study. Lancet 353:2111-15, 1999

44.2 Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine.J Clin Endocrinol Metab. 2007 Mar;92(3):797-800.

44.3. Torring O, Tallstedt L, Wallin G, Lundell G, Ljunggren J-G, Taube A, Saaf M, Hamberger B, and The Thyroid Study Group. Graves' hyperthyroidism: Treatment with antithyroid drugs, surgery, or radioiodine-a prospective, randomized study. J Clin Endocrinol Metab 81:2986-2993,

44,4. Moleti M, Mattina F, Lo Presti VP, Baldari CS, Bonanno N, Trimarchi F, Vermiglio F. Role of residual thyroid tissue ablation after thyroidectomy for Graves' disease. Its effects on the course of related ophthalmopathy. J Endocrinol Invest 23:37, 2000.

44.5. De Bellis A204c. De Bellis A, Bizzarro A, Perrino S, Coronclla C, Iorio S, Pepe M, Guaglione M, Wall JR, Bellastella A. Improvement of severe ophthalmopathy and decrease of antibodies against extraocular muscles, G2s, and Fp subunit of succinate dehydrogenase after near-total thyroidectomy in Graves' disease. J Endocrinol Invest 23:14, 2000.

44.6. Marcocci C204d. Marcocci C, Bruno-Bossio G, Manetti L, Tanda ML, Miccoli P, Iacconi P, Bartolomei MP, Nardi M, Pinchera A, Bartalena L. The course of Graves' ophthalmopathy is not influenced by near-total thyroidectomy; a case-control study. Clin Endocrinol 51:503-508, 1999.

44.7 Moleti, M; Mattina, F; Salamone, I; Violi, MA; Nucera C; Baldari, S; Schiavo, MGL; Regalbuto, C; Trimarchi, F; Vermiglio, F. Effects of thyroidectomy alone or followed by radioiodine ablation of thyroid remnants on the outcome of Graves' ophthalmopathy. Thyroid 13 653-658 2003.

45. Chapman EM: History of the discovery and early use of radioactive iodine. J Amer Med Assn 250:2042-2044, 1983.

46. Chapman EM, Maloof F: The use of radioactive iodine in the diagnosis and treatment of hyperthyroidism: Ten years' experience. Medicine 34:261, 1955.

47. Blahd W, Hays MT: Graves' disease in the male. A review of 241 cases treated with an individually calculated dose of sodium iodide 131-I. Arch Intern Med 129:33, 1972.

47.1 Bajnok L, Mezosi E, Nagy E, Szabo J, Sztojka I, Varga J, et al. 1999 Calculation of the radioiodine dose for the treatment of Graves' hyperthyroidism: Is more than seven-thousand rad target dose necessary? Thyroid 9:865.

47.2 Leslie, WD; Ward, L; Salamon, EA; Ludwig, S; Rowe, RC; Cowden, EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab 88 978-983 2003

48. Hagen F, Ouelette RP, Chapman EM: Comparison of high and low dosage levels of 131-I in the treatment of thyrotoxicosis. N Engl J Med 277:559, 1967.

49. Cevallos JL, Hagen GA, Maloof F, Chapman EM: Low-dosage 131-I therapy of thyrotoxicosis (diffuse goiters). N Engl J Med 290:141, 1974.

50. Ross DS, Daniels GH, De Stafano P, Maloof F, Ridgway EC: Use of adjunctive potassium iodide after radioactive iodine (131-I) treatment of Graves' hyperthyroidism. J Clin Endocrinol Metab 57:250, 1983.

51. Reinwein D, Schaps D, Berger H, Hackenberg K, Horster FA, Klein E, Von Zur Muhlen A, Wendt RU, Wildmeister W: Hypothyreoserisyiko nach fraktionierter Radiojodtherapie. Dtsch Med Wochenschr 98:1789, 1973.

52. Rapoport B, Caplan R, DeGroot L: Low-dose sodium iodide 131-I therapy in Graves' disease. J Amer Med Assn 224:1610, 1973.

53. Roudebush CP, Hoye KE, DeGroot LJ: Compensated low-dose 131-I therapy of Graves' disease. Ann Intern Med 87:441, 1977.

54. Sridama V, McCormick M, Kaplan EL, Fauchet R, DeGroot LJ: Long-term follow-up study of compensated low-dose 131-I therapy for Graves' disease. N Engl J Med 311:426-432, 1984.

55. Glennon JA, Gordon ES, Sawin CT: Hypothyroidism after low- dose I131 treatment of hyperthyroidism. Ann Intern Med 76:721, 1972.

56. Saito S, Sakurada T, Yamamoto M, Yoshida K, Kaise K, Kaise N, Yoshinaga K: Long term results of radioiodine 131-I therapy in 331 patients with Graves' disease. Tokyo J Exp Med 132:1-10, 1980.

57. DeGroot LJ, Mangklabruks A, McCormick M: Comparison of RA 131-I treatment protocols for Graves' disease. J Endocrinol Invest 13:111-118, 1990.

57.1. Rini JN, Vallabhajosula S, Zanzonico P, Hurley JR, Becker DV, Goldsmith SJ. Thyroid uptake of liquid versus capsule 131-I tracers in hyperthyroid patients treated with liquid 131-I. Thyroid 9:347, 1999

57.2. Berg G, Michanek A, Holmberg E, Nystrom E. Clinical outcome of radioiodine treatment of hyperthyroidism: a follow-up study. J Intern Med 239:165-171, 1996.

57.3-Schiavo M, Bagnara MC, Calamia I, Bossert I, Ceresola E, Massaro F, Giusti M, Pilot A, Pesce G, Caputo M, Bagnasco M.A study of the efficacy of radioiodine therapy with individualized dosimetry in Graves' disease: need to retarget the radiation committed dose to the thyroid. J Endocrinol Invest. 2011 Mar;34(3):201-5. Epub 2010 Dec 15

57.4 Chen DY, Schneider PF, Zhang XS, He ZM, Jing J, Chen TH Striving for euthyroidism in radioiodine therapy of Graves' disease: a 12-year prospective, randomized, open-label blinded end point study. Thyroid. 2011 Jun;21(6):647-54. doi: 10.1089/thy.2010.0348. Epub 2011 May 12

58. Wise PH, Burnet RB, Ahmad A, Harding PE: Intentional radioiodine ablation in Graves' disease. Lancet 2:1231, 1975.

58.1 Sapienza MT[1], Coura-Filho GB, Willegaignon J, Watanabe T, Duarte PS, Buchpiguel CA. Clinical and Dosimetric Variables Related to Outcome After Treatment of Graves' Disease With 550 and 1110 MBq of 131I: Results of a Prospective Randomized Trial. Clin Nucl Med. 2015 Sep;40(9):715-9. doi: 10.1097

58.2. Allahabadia A, Daykin J, Sheppard MC, Gough SCL, Franklyn JA. Radioiodine treatment of hyperthyroidismâ€"prognostic factors for outcome. J Clin Endocrinol Metab 86:3611-3617, 2001.

58.3: Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism.J Clin Endocrinol Metab. 2003 Mar;88(3):978-83.

58.4 Santos RB, Romaldini JH, Ward LS A randomized controlled trial to evaluate the effectiveness of 2 regimens of fixed iodine (^{131}I) doses for Graves disease treatment.Clin Nucl Med. 2012 Mar;37(3):241-4.

58.5 Bogazzi F, Giovannetti C, Fessehatsion R, Tanda ML, Campomori A, Compri E, Rossi G, Ceccarelli C, Vitti P, Pinchera A, Bartalena L, Martino E. J Clin Endocrinol Metab. 2010 Jan;95(1):201-8 Impact of lithium on efficacy of radioactive iodine therapy for Graves' disease: a cohort study on cure rate, time to cure, and frequency of increased serum thyroxine after antithyroid drug withdrawal.

58.6 Bonnema SJ, Bennedbaek FN, Veje A, Marving J, Hegedus L.Continuous methimazole therapy and its effect on the cure rate of hyperthyroidism using radioactive iodine: an evaluation by a randomized trial. J Clin Endocrinol Metab. 2006 Aug;91(8):2946-51.

59. Marcocci C, Gianchecchi D, Masini I, Golia F, Ceccarelli C, Bracci E, Fenzi GF, Pinchera A: A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism. J Endocrinol Invest 13:513-520, 1990.

59.1. Glinoer D, Verelst J. Use of 131-Iodine for the treatment of hyperthyroidism in adults. Annales d Endocrinologie 57:177-185, 1996.

59.2 Nakazato N, Yoshida K, Mori K, Kiso Y, Sayama N, Tani J-I, et al. 1999 Antithyroid drugs inhibit radioiodine-induced increases in thyroid autoantibodies in hyperthyroid Graves' disease. Thyroid 9:775.

59.3. Andrade VA, Gross JL, Maia AL. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: one-year follow-up of a prospective, randomized study. J Clin Endocrinol Metab 86:3488-3493, 2001.

59.31. Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R. The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after 131-I ablation for Graves' disease. J Clin Endocrinol Metab 86:3016-3021, 2001.

59.4Zakavi SR[1], Khazaei G, Sadeghi R, Ayati N, Davachi B, Bonakdaran S, Jabbari Nooghabi M, Moosavi Z. Methimazole discontinuation before radioiodine therapy in patients with Graves' disease. Nucl Med Commun. 2015 Dec;36(12):1202-7. doi: 10.1097.

60. Greig WR, Gillespie FC, Thomson JA, McGirr EM: Iodine-125 treatment for thyrotoxicosis. Lancet 1:755, 1969.

61. Editorial: Radioiodine treatment of thyrotoxicosis. Lancet 1:23,1972.

62. Bremmer WF, Greig WR, McDougall IR: Results of treating 297 thyrotoxic patients with 125I. Lancet 2:281, 1973.

62.1. Liu B[1], Tian R[1], Peng W[1], He Y[1], Huang R[1], Kuang A[1].Radiation Safety Precautions in (131)I Therapy of Graves' Disease Based on Actual Biokinetic Measurements. J Clin Endocrinol Metab. 2015 Aug;100(8):2934-41. doi: 10.1210/jc.2015-1682

63. Benua RS, Dobyns BM: Isolated compounds in the serum, disappearance of radioactive iodine from the thyroid, and clinical response in patients treated with radioactive iodine. J Clin Endocrinol Metab 15:118, 1955.

63.1. Stensvold AD, Jorde R, Sundsfjord J. Late and transient increases in free T4 after radioiodine treatment for Graves' disease. J Endocrinol Invest 20:580-584, 1997.

64. Stanbury JB, Janssen MA: The iodinated albumin-like component of the plasma of thyrotoxic patients. J Clin Endocrinol Metab 22:978, 1962.

64.1. Dale J, Daykin J, Holder R, Sheppard MC, Franklyn JA. Weight gain following treatment of hyperthyroidism. Clin Endocrinol 55:233-239, 2001.

65. Goldsmith RE: Radioisotope therapy for Graves' disease. Mayo Clin Proc 47:953, 1972.

66. Slingerland WD, Hershman JM, Dell E, Burrows B: Thyrotropin and PBI in radioiodine-treated hyperthyroid patients. J Clin Endocrinol Metab 35:912, 1972.

67. Gordin A, Wagar G, Hernberg CA: Serum thyrotropin and response to thyrotrophin-releasing hormone in patients who are euthyroid after radioiodine treatment for hyperthyroidism. Acta Med Scand 194:335, 1973.

68. Baldwin WW: Graves' disease succeeded by atrophy. Lancet 1:145,1895.

69. Wood LC, Ingbar SH: Hypothyroidism as a late sequela in patients with Graves' disease treated with antithyroid drugs. J Clin Invest 64:1429, 1979.

69a. Tigas S, Idiculla J, Beckett G, Toft A. Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? Thyroid 10:1107, 2000.

70. Creutzig H, Kallfelz I, Haindl J, Thiede G, Hundeshagen H: Thyroid storm and iodine-131 treatment. Lancet 2:145, 1976.

71. Creutzig H, Kallfelz I, Haindl J, Thiede G, Hundeshagen H: Thyroid storm and iodine-131 treatment. Lancet 2:145, 1976.

72. Lamberg BA, Hernberg CA, Wahlberg P, Hakkila R: Treatment of toxic nodular goiter with radioactive iodine. Acta Med Scand 165:245, 1959.

73. McDermott MT, Kidd GS, Dodson Jr LE, Hofeldt FD: Radioiodine-induced thyroid storm. Case report and literature review. Amer J Med 75:353, 1983.

74. Townsend JD: Hypoparathyroidism following radioactive iodine therapy for intractable angina pectoris. Ann Intern Med 55:662, 1961.

75. Gilbert-Dreyfus MZ, Gali P: Cataract due to tetany following radioactive iodine therapy. Sem Hop Paris 34:1301, 1958.

76. Fulop M: Hypoparathyroidism after 131-I therapy. Ann Intern Med 75:808, 1971.

76.1 Ceccarelli C, Canale D, Battisti P, Caglieresi C, Moschini C, Fiore E, Grasso L, Pinchera A, Vitti P.Testicular function after 131-I therapy for hyperthyroidism.Clin Endocrinol (Oxf). 2006 Oct;65(4):446-52.

76.2. Franklyn JA, Sheppard MC, Maisonneuve P. Thyroid function and mortality in patients treated for hyperthyroidism. JAMA. 2005 Jul 6;294(1):71-80.

77. Fenzi G, Hashizume K, Roudebush C, DeGroot LJ: Changes in thyroid stimulating immunoglobulins during antithyroid therapy. J Clin Endocrinol Metab 48:572, 1979.

78. Teng CS, Yeung RTT, Khoo RKK, Alagaratnam TT: A prospective study of the changes in thyrotropin binding inhibitory immunoglobulins in Graves' disease treated by subtotal thyroidectomy or radioactive iodine. J Clin Endocrinol Metab 50:1005, 1980.

79. Sridama V, DeGroot LJ: Treatment of Graves' disease and the course of ophthalmopathy. Amer J Med 87:70-73, 1989.

80. Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren J-G, Blomgren H, Taube A. Occurrence of ophthalmopathy after treatment for Graves' disease. N Engl J Med 326:1733-1738, 1992.

80.1. Fernandez Sanchez JR, Rosell Pradas J, Carazo Martinez O, Torres Vela E, Escobar Jimenez F, Garbin Fuentes I, Vara Thorbeck R. Graves' ophthalmopathy after subtotal thyroidectomy and radioiodine therapy. Brit J Surg 80:1134-1136, 1993.

80.2 Vannucchi G, Campi I, Covelli D, Dazzi D, Currò N, Simonetta S, Ratiglia R, Beck-Peccoz P, Salvi M.
J Clin Endocrinol Metab. 2009 Sep;94(9):3381-6 Graves' orbitopathy activation after radioactive iodine therapy with and without steroid prophylaxis.
Eur J Endocrinol. 2016 Apr;174(4):491-502. doi: 10.1530/EJE-15-1099. Epub 2016 Jan 15.

80.3.Taïeb D[1], Bournaud C[2], Eberle MC[2], Catargi B[2], Schvartz C[2], Cavarec MB[2], Faugeron I[2], Toubert ME[2], Benisvy D[2], Archange C[2], Mundler O[2], Caron P[2], Abdullah AE[2], Baumstarck K[2]. Eur J Endocrinol. 2016 Apr;174(4):491-502. doi: 10.1530/EJE-15-1099. Quality of life, clinical outcomes and safety of early prophylactic levothyroxine administration in patients with Graves' hyperthyroidism undergoing radioiodine therapy: a randomized controlled study.

81. Gamstedt A, Wadman B, Karlsson A: Methimazole, but not betamethasone, prevents 131-I treatment-induced rises in thyrotropin receptor autoantibodies in hyperthyroid Graves' disease. J Clin Endocrinol Metab 62:773-777, 1986.

82. Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A: Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med 321:1349-1352, 1989.

82.1. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dellâ€™Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, Rossi G, Martino E, Pinchera A. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 338:73-78, 1998.

82.2 Jensen BE, Bonnema SJ, Hegedus L.Glucocorticoids do not influence the effect of radioiodine therapy in Graves' disease.Eur J Endocrinol. 2005 Jul;153(1):15-21.

82.3 Takamura Y, Nakano K, Uruno T, Ito Y, Miya A, Kobayashi K, Yokozawa T,Matsuzuka F, Kuma K, Miyauchi A. Changes in serum TSH receptor antibody (TRAb) values in patients with Graves' disease after total or subtotal thyroidectomy. Endocr J. 2003 Oct;50(5):595-601.

82.4 De Bellis A, Conzo G, Cennamo G, Pane E, Bellastella G, Colella C, Iacovo AD, Paglionico VA, Sinisi AA, Wall JR, Bizzarro A, Bellastella ATime course of Graves' ophthalmopathy after total thyroidectomy alone or followed by radioiodine therapy: a 2-year longitudinal study.Endocrine. 2012 Apr;41(2):320-6. Epub 2011 Nov 16.

82.5 Leo M, Marcocci C, Pinchera A, Nardi M, Megna L, Rocchi R, Latrofa F, Altea MA, Mazzi B, Sisti E, Profilo MA, Marinò M. Outcome of Graves' orbitopathy after total thyroid ablation and glucocorticoid treatment: follow-up of a randomized clinical trial.J Clin Endocrinol Metab. 2012 Jan;97(1):E44-8. Epub 2011 Oct 26.

82.6 Bojic T[1], Paunovic I[2,3], Diklic A[4,5], Zivaljevic V[6,7], Zoric G[8], Kalezic N[9,10], Sabljak V[11,12], Slijepcevic N[13], Tausanovic K[14], Djordjevic N[15,16], Budjevac D[17], Djordjevic L[18], Karanikolic A[19,20]. Total thyroidectomy as a method of choice in the treatment of Graves' disease - analysis of 1432 patients. BMC Surg. 2015 Apr 9;15:39. doi: 10.1186/s12893-015-0023-3.

83. DeGroot LJ, Paloyan E: Thyroid carcinoma and radiation. A Chicago endemic. J Amer Med Assn 225:487, 1973.

84. Clark DW: Association of irradiation with cancer of the thyroid in children and adolescents. J Amer Med Assn 159:1007, 1955.

85. Simpson CL, Hempelmann LH, Fuller LM: Neoplasia in children treated with x-rays in infancy for thymic enlargement. Radiology 64:840, 1955.

86. Doniach I: The effect of radioactive iodine alone and in combination with methylthiouracil upon tumor production in the rat's thyroid gland. Br J Cancer 7:181, 1953.

87. Sampson RJ, Key CR, Buncher CR, Iijuma S: Thyroid carcinoma in Hiroshima and Nagasaki. J Amer Med Assn 209:65, 1969.

88. Conard RA, Dobyns BM, Sutow W: Thyroid neoplasia as late effect of exposure to radioactive iodine in fallout. J Amer Med Assn 214:316, 1970.

89. Pacini F, Vorontsova T, Demidchik E, Molinaro E, Agate L, Romei C, Shavrova E, Cherstvoy E, Ivashkevitch Y, Kuchinskaya E, Schlumberger M, Rouga G, Felesi M, Pinchera A. Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. J Clin Endocrinol Metab 82:3563-3569, 1997.

89.2-Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, Drozdovitch V, Maceika E, Zvonova I, Vlassov O, Bouville A, Goulko G, Hoshi M, Abrosimov A, Anoshko J, Astakhova L, Chekin S, Demidchik E, Galanti R, Ito M, Korobova E,

Lushnikov E, Maksioutov M, Masyakin V, Nerovnia A, Parshin V, Parshkov E, Piliptsevich N, Pinchera A, Polyakov S, Shabeka N, Suonio E, Tenet V, Tsyb A, Yamashita S, Williams D. Risk of thyroid cancer after exposure to 131I in childhood.J Natl Cancer Inst. 2005 May 18;97(10):724-32.

90. Pochin EE: Leukemia following radioiodine treatment of thyrotoxicosis. Br Med J 2:1545, 1960.

91. Saenger EL, Thoma GE, Tompkins EA: Incidence of leukemia following treatment of hyperthyroidism. J Amer Med Assn 205:855, 1968.

92. Biological effects of ionizing radiation V. The health effects of exposure to low levels of ionizing radiation, report of the Advisory Committee on the Biological Effects of Ionizing Radiation, National Research Council, Washington, DC, Natl Acad Press, 1990.

93. Russell WL, Kelly EM: Mutation frequencies in male mice and the estimation of genetic hazards of radiation in men. Proc Natl Acad Sci USA 79:542, 1982.

94. Webster EW, Merrill OE: Radiation hazards: II. Measurements of gonadal dose in radiographic examination. N Engl J Med 257:811, 1957.

95. Robertson J, Gorman CA: Gonadal radiation dose and its genetic significance in radioiodine therapy of hyperthyroidism. J Nucl Med 17:826, 1976.

96. Sarkar SD, Bierwaltes WH, Gill SP, Cowley BJ: Subsequent fertility and birth histories of children and adolescents treated with 131-I for thyroid cancer. J Nucl Med 17:460, 197

97. Hollingsworth JW: Delayed radiation effects in survivors of the atomic bombings: A summary of the findings fo the Atomic Bomb Casualty Commission, 1947-1959. N Engl J Med 263:481, 1960.

98. Plummer HS: Results of administering iodine to patients having exophthalmic goiter. J Amer Med Assn 80:1955, 1923.

99. MacKenzie CG, MacKenzie JB: Effect of sulfonamides and thiourea on the thyroid gland and basal metabolism. Endocrinology 32:185, 1943.

100. Astwood EB: Treatment of hyperthyroidism with thiourea and thiouracil. J Amer Med Assn 122:78, 1943.

101. Marcocci C, Chiovato L, Mariotti S, Pinchera A: Changes of circula.1ing thyroid autoantibody levels during and after therapy with methi-mazole in patients with Graves' disease. J Endocrinol Invest 5:13, 1982.

102. Pinchera A, Liberti P, Martino E, Fenzi GF, Grasso L, Rovis I, Baschieri L: Effects of antithyroid therapy on the long-acting thyroid stimulator and the antithyroglobulin antibodies. J Clin Endocrinol Metab 29:231, 1969.

103. MacGregor AM, Ibbertson HK, Smith BR, Hall R: Carbimazole and autoantibody synthesis in Hashimoto's thyroiditis. Br Med J 281:968, 1980.

104. McGregor AM, Petersen MM, McLachlan SM, Rooke P, Smith BR, Hall R: Carbimazole and the autoimmune response in Graves' disease. N Engl J Med 303:302, 1980.

105. Hallengren B, Forsgren A, Melander A: Effects of antithyroid drugs on lymphocyte function in vitro. J Clin Endocrinol Metab 51:298, 1980.

105.1. Weetman AP. The immunomodulatory effects of antithyroid drugs. Thyroid 4:145-146, 1994.

106. Ludgate ME, McGregor AM, Weetman AP, Ratanachaiyavong S, Lazarus JH, Hall R, Middleton GW: Analysis of T cell subsets in Graves' disease: alterations associated with carbimazole. Br Med J 288:526, 1984.

107. Totterman TH, Karlsson FA, Bengtsson M, Mendel-Hartvig IB: Induction of circulating activated suppressor-like T cells by methimazole therapy for Graves' disease. N Engl J Med 316:15, 1987.

108. Sridama V, Pacini F, DeGroot LJ: Decreased suppressor T- lymphocytes in autoimmune thyroid diseases detected by monoclonal antibodies. J Clin Endocrinol Metab 54:316, 1982.

109. Volpe R. Evidence that the immunosuppressive effects of antithyroid drugs are mediated through actions on the thyroid cell, modulating thyrocyte-immunocyte signaling: A review. Thyroid 4:217-223, 1994.

109.1 Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, Laurberg P, McDougall IR, Rivkees SA, Ross D, Sosa JA, Stan MN. Thyroid. 2009 Jul;19(7):673-4. The Role of Propylthiouracil in the Management of Graves' Disease in Adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration.

110.Laurberg P, Hansen PEB, Iversen E, Jensen SE, Weeke J: Goiter size and outcome of medical treatment of Graves' disease. Acta Endocrinol 111:39-43, 1986.

110.1. Laurberg P[1], Krejbjerg A, Andersen SL. Relapse following antithyroid drug therapy for Graves' hyperthyroidism. Curr Opin Endocrinol Diabetes Obes. 2014 Oct;21(5):415-21. doi: 10.1097

111. Shizume K, Irie M, Nagataki S, Matsuzaki F, Shishiba Y, Suematsu H, Tsushima T: Long-term result of antithyroid drug therapy for Graves' disease: Follow-up after more than 5 years. Endocrinol Jpn 17:327, 1970.

112. Shizume K: Long term antithyroid drug therapy for intractable cases of Graves' disease. Endocrinol Jpn 25:377, 1978.

113. Wartofsky L: Low remission after therapy for Graves' disease. Possible relation of dietary iodine with antithyroid therapy results. J Amer Med Assn 226:1083, 1973.

114. Hedley AJ, Young RE, Jones SJ, Alexander WD, Bewsher PD: Antithyroid drugs in the treatment of hyperthyroidism of Graves' disease: Long-term follow-up of 434 patients. Clin Endocrinol 31:209-218, 1989.

115. Alexander WD, McG Harden R, Koutras DA, Wayne E: Influence of iodine intake after treatment with antithyroid drugs. Lancet 2:866, 1965.

116. McMurray JF Jr, Gilliland PF, Ratliff CR, Bourland PD: Pharmacodynamics of propylthiouracil in normal and hyperthyroid subjects after a single oral dose. J Clin Endocrinol Metab 41:362, 1975.

117. Cooper DS: Which antithyroid drug? Amer J Med 80:1165- 1168, 1986.

118. Cooper DS, Goldminz D, Levin AA, Ladenson PW, Daniels GH, Molitch ME, Ridgway EC: Agranulocytosis associated with antithyroid drugs. Ann Int Med 98:26-29, 1983.

119. Barnes V, Bledsoe T: A simple test for selecting the thioamide schedule in thyrotoxicosis. J Clin Endocrinol Metab 35:250, 1972.

120. Cooper DS, Saxe VC, Meskell M, Maloof F, Ridgway EC: Acute effects of propylthiouracil (PTU) on thyroidal iodide organification and peripheral iodothyronine deiodination: Correlation with serum PTU levels measured by radioimmunoassay. J Clin Endocrinol Metab 54:101, 1982.

121. Nabil N, Miner DJ, Amatruda JM: Methimazole: An alternative route of administration. J Clin Endocrinol Metab 54:180, 1982.

121.1. Zweig SB, Schlosser JR, Thomas SA, Levy CJ, Fleckman AM .Rectal administration of propylthiouracil in suppository form in patients with thyrotoxicosis and critical illness: case report and review of literature. Endocr Pract. 2006 Jan-Feb;12(1):43-47.

121.2Jongjaroenprasert W, Akarawut W, Chantasart D, Chailurkit L, Rajatanavin R. Rectal administration of propylthiouracil in hyperthyroid patients: comparison of suspension enema and suppository form. Thyroid 12:627-631, 2002

122. Greer MA, Meihoff WC, Studer H: Treatment of hyperthyroidism with a single daily dose of propylthiouracil. N Engl J Med 272:887, 1965.

123. Greer MA, Kammer H, Bouma DJ: Short-term antithyroid drug therapy for the thyrotoxicosis of Graves' disease. N Engl J Med 297:173, 1977.

124. Allannic H, Fauchet R, Orgiazzi J, Madec AM, Genetet B, Lorcy Y, Le Guerrier AM, Delambre C, Derennes V: Antithyroid drugs and Graves' disease: A prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab 70:675, 1990.

125. Romaldini JH, Bromberg N, Werner RS, Tanaka LM, Rodrigues HF, Werner MC, Farah CS, Reiss LCF: Comparison of high and low dosage regimens of antithyroid drugs. J Clin Endocrinol Metab 57:563, 1983.

126. Yamamoto M, Totsuka Y, Kojima I, Yamashita N, Togawa K, Sawaki N, Ogata E: Outcome of patients with Graves' disease after long-term medical treatment guided by triiodothyronine (T3) suppression test. Clin Endocrinol 19:467-476, 1983.

126.1 Azizi F, Ataie L, Hedayati M, Mehrabi Y, Sheikholeslami F.Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine.Eur J Endocrinol. 2005 May;152(5):695-701

126.2. Jodar E, Munoz-Torres M, Escobar-Jimenez F, Quesada M, Luna JD, Olea N. Antiresorptive therapy in hyperthyroid patients: Longitudinal changes in bone and mineral metabolism. J Clin Endocrinol Metab 82:1989-1994, 1997.

126.3 Majima T, Komatsu Y, Doi K, Takagi C, Shigemoto M, Fukao A, Morimoto T, Corners J, Nakao K.Clinical significance of risedronate for osteoporosis in the initial treatment of male patients with Graves' disease.J Bone Miner Metab. 2006;24(2):105-13.

127. Solomon DH, Beck JC, Vanderlaan WP, Astwood EB: Prognosis of hyper-thyroidism treated by antithyroid drugs. J Amer Med Assn 152:201, 1953.

128. McLarty DG, Alexander WD, McHarden R, Robertson JWK: Self-limiting episodes of recurrent thyrotoxicosis. Lancet 1:6, 1971.

129. Thalassinos NC, Fraser TR: Effect of potassium iodide on relapse rate of thyrotoxicosis treated with antithyroid drugs. Lancet 2:183, 1971.

130. Hashizume K, Ichikawa K, Sakurai A, Suzuki S, Takeda T, Kobayashi M, Miyamoto T, Arai M, Nagasawa T: Administration of thyroxine in treated Graves' disease. Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. N Engl J Med 324:947-953, 1991.

131. Hashizume K, Ichikawa K, Nishii Y, Kobayashi M, Sakurai A, Miyamoto T, Suzuki S, Takeda T. Effect of administration of thyroxine on the risk of postpartum recurrence of hyperthyroid Graves' disease. J Clin Endocrinol Metab 75:6-10, 1992.

131.1. Rittmaster RS, Zwicker H, Abbott EC, Douglas R, Givner ML, Gupta MK, Lehmann L, Reddy S, Salisbury SR, Shlossberg AH, Tan MH, York SE. Effect of methimazole with or without exogenous L-thyroxine on serum concentrations of thyrotropin receptor antibodies in patients with Graves' disease. J Clin Endocrinol Metab 81:3283-3288, 1996.

131.2. Lucas A, Salinas I, Rius F, Pizarro E, Granada ML, Foz M, Sanmarti A. Medical therapy of Graves' disease: does thyroxine prevent recurrence of hyperthyroidism? J Clin Endocrinol Metab 82:2410-2413, 1997.

132. Zakarija M, McKenzie JM, Banovac K: Clinical significance of assay of thyroid-stimulating antibody in Graves' disease. Ann Intern Med 93:28, 1980.

133. Werner RS, Romaldini JH, Farah CS, Werner MC, Bromberg N. Serum thyroid-stimulating antibody, thyroglobulin levels, and thyroid suppressibility measurement as predictors of the outcome of combined methimazole and triiodothyronine therapy in Graves' disease. Thyroid 1:293, 1991.

134. Schleusener H, Schwander J, Fischer C, Holle R, Holl G, Badenhoop K, Hensen J, Finke R, Bogner U, Mayr WR, Schernthaner G, Schatz H, Pickardt CR, Kotulla P: Prospective multicenter study on the prediction of relapse after antithyroid drug treatment in patients with Graves' disease. Acta Endocrinologica (Copenh) 120:689-701, 1989.

135. Farid NR (ed): HLA in Endocrine and Metabolic Disorders. New York, Academic Press, 1981, p 357.

136. Allannic H, Fauchet R, Lorcy Y, Gueguen M, Le Guerrier A- M, Genetet B: A prospective study of the relationship between relapse of hyperthyroid Graves' disease after antithyroid drugs and HLA haplotype. J Clin Endocrinol Metab 57:719, 1983.

136.1. Michelangeli V, Poon C, Taft J, Newnham H, Topliss D, Colman P. The prognostic value of thyrotropin receptor antibody measurement in the early stages of treatment of Graves’ disease with antithyroid drugs. Thyroid 8:119, 1998.

137. Irvine WJ, Gray RS, Toft AD, Lidgard FP, Seth J, Cameron EHD: Spectrum of thyroid function in patients remaining in remission after antithyroid drug therapy for thyrotoxicosis. Lancet 1:179, 1977.

138. Buerklin EM, Schimmel M, Utiger RD: Pituitary-thyroid regulation in euthyroid patients with Graves' disease previously treated with antithyroid drugs. J Clin Endocrinol Metab 43:419, 1976.

139. Lamberg BA, Salmi J, Wagar G, Makinen T: Spontaneous hypothyroidism after antithyroid treatment of hyperthyroid Graves' disease. J Endocrinol Invest 4:399, 1981.

140. Hirota Y, Tamai H, Hayashi Y, Matsubayashi S, Matsuzuka F, Kuma K, Kumagai LF, Nagataki S: Thyroid function and histology in forty-five patients with hyperthyroid Graves' disease in clinical remission more than ten years after thionamide drug treatment. J Clin Endocrinol Metab 62:165, 1986.

141. Kampmann JP, Johansen K, Hansen JM, Helwig J: Propylthiouracil in human milk: Revision of a dogma. Lancet 1:736, 1980.

141a. Azizi F, Khoshniat M, Bahrainian M, Hedayati M. Thyroid function and intellectual development of infants nursed by mothers taking methimazole. J Clin Endocrinol Metab 85:3233-3238, 2000.

142. Wiberg JJ, Nuttall FQ: Methimazole toxicity from high doses. Ann Intern Med 77:414, 1972.

143. Chevalley J, McGavack TH, Kenigsberg S, Pearson S: A four- year study of the treatment of hyperthyroidism with methimazole. J Clin Endocrinol Metab 14:948, 1954.

144. Tajiri J, Noguchi S, Murakami T, Murakami N. Antithyroid drug-induced agranulocytosis. The usefulness of routine white blood cell count monitoring. Arch Intern Med 150:621-624, 1990.

145. Tamai H, Takaichi Y, Morita T, Komaki G, Matsubayashi S, Kuma K, Walter Jr RM, Kumagai LF, Nagataki S: Methimazole- induced agranulocytosis in Japanese patients with Graves' disease. Clin Endocrinol 30:525-530, 1989.

146. Amrhein JA, Kenny F, Ross D: Granulocytopenia, lupus-like syndrome, and other complications of propylthiouracil therapy. J Pediatr 76:54, 1970.

147. Pacini F, Sridama V, Refetoff S: Multiple complications of propylthiouracil treatment: Granulocytopenia, eosinophilia, skin reaction, and hepatitis with lymphocyte sensitization. J Endocrinol Invest 5:403-407, 1982.

147.1 Darben T, Savige J, Prentice R, Paspaliaris B, Chick J. 1999 Pyoderma gangrenosum with secondary pyarthrosis following propylthiouracil. Australasian J Dermatol. 40:144-146.

148. Wall JR, Fang SL, Kuroki T, Ingbar SH, Braverman LE: In vitro immunoreactivity to propylthiouracil, methimazole, and carbimazole in patients with Graves' disease: A possible cause of antithyroid drug-induced agranulocytosis. J Clin Endocrinol Metab 58:868-872, 1984.

149. Biswas N, Ahn Y-H, Goldman JM, Schwartz JM: Case report: Aplastic anemia associated with antithyroid drugs. Am J Med Sci 301:190-194, 1991.

150. Escobar-Morreale HF, Bravo P, Garcia-Robles R, Garcia-Larana J, de la Calle H, Sancho JM. Methimazole-induced severe aplastic anemia: unsuccessful treatment with recombinant human granulocyte-monocyte colony-stimulating factor. Thyroid 7:67-70, 1997

151. Tamai H, Mukuta T, Matsubayashi S, Fukata S, Komaki G, Kuma K, Kumagai LF, Nagataki S. Treatment of methimazole-induced agranulocytosis using recombinant human granulocyte colony-stimulating factor (rhG-CSF). J Clin Endocrinol Metab 77:1356-1360, 1993

151.1 Gunton JE, Stiel J, Caterson RJ, McElduff A. Antithyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis. A case report and review of the literature. J Clin Endocrinol Metab 84:13-16, 1999

151.2 Guma M, Salinas I, Reverter JL, Roca J, Valls-Roc M, Juan M, Olive A. Frequency of antineutrophil cytoplasmic antibody in Graves' disease patients treated with methimazole. J Clin Endocrinol Metab 88:2141-2146, 2003.

151.3. Breier DV, Rendo P, Gonzalez J, Shilton G, Stivel M, Goldztein S. Massive plasmocytosis due to methimazole-induced bone marrow toxicity. Amer J Hematol 67:259-261, 2001.

151.4. Cooper DS: Antithyroid drugs. N Engl J Med 311:1353- 1362, 1984.

152. Weiss M, Hassin D, Bank H: Propylthiouracil-induced hepatic damage. Arch Intern Med 140:1184-1185, 1980.

152.1. Williams KV, Nayak S, Becker D, Reyes J, Burmeister LA. Fifty years of experience with propylthiouracil-associated hepatotoxicity: What have we learned? J Clin Endocrinol Metab 82:1727-1733, 1997.

153. Miyazono K, Okazaki T, Uchida S, Totsuka Y, Matsumoto T, Ogata E, Terakawa K, Kurihara N, Takeda T: Propylthiouracil-induced diffuse interstitial pneumonitis. Arch Intern Med 144:1764-1765, 1984.

.

153.1 Karlsson, FA; Axelsson, O; Melhus, H. Severe embryopathy and exposure to methimazole in early pregnancy. J Clin Endocrinol Metab 87 947-948 2002.

154. Sato S[1], Noh JY, Sato S, Suzuki M, Yasuda S, Matsumoto M, Kunii Y, Mukasa K, Sugino K, Ito K, Nagataki S, Taniyama M. Comparison of efficacy and adverse effects between methimazole 15 mg+inorganic iodine 38 mg/day and methimazole 30 mg/day as initial therapy for Graves' disease patients with moderate to severe hyperthyroidism. Thyroid. 2015 Jan;25(1):43-50. doi: 10.1089/thy.2014.0084.

155. Godley AF, Stanbury JB: Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate. J Clin Endocrinol Metab 14:70, 1954.

156. Krevans JR, Asper SP Jr, Rienhoff WF Jr: Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. J Amer Med Assn 181:162, 1962.

157. Georges JL, Normand JP, Lenormand ME, Schwob J. Life-threatening thyrotoxicosis induced by amiodarone in patients with benign heart disease. European Heart Journal 13:129-132, 1992.

158. Lazarus JH, Addison GM, Richards AR, Owen GM: Treatment of thyrotoxicosis with lithium carbonate. Lancet 2:1160, 1974.

159. Turner JG, Brownlie BEW, Rogers TGH: Lithium as an adjunct to radioiodine therapy for thyrotoxicosis. Lancet 1:614, 1976.

159.1. Mercado M, Mendoza-Zubieta V, Bautista-Osorio R, Espinoza-De Los Monteros AL. Treatment of hyperthyroidism with a combination of methimazole and cholestyramine. J Clin Endocrinol Metab 81:3191-3193, 1996.

160. Reinwein D, Klein E: Der Einfluss des anorganischen Blutjodes auf den Jodumstaz der menschlichen Schilddruse. Acta Endocrinol 35:485, 1960.

161. Thompson WO, Thorp EG, Thompson PK, Cohen AC: The range of effective iodine dosage in exophthalmic goiter. II. The effect on basal metabolism of the daily administration of one-half drop of compound solution of iodine. Arch Intern Med 45:420, 1930.

162. Friend DG: Iodide therapy and the importance of quantitating the dose. N Engl J Med 263:1358, 1960.

163. Emerson CH, Anderson AJ, Howard WJ, Utiger RD: Serum thyroxine and triiodothyronine concentrations during iodide treatment of hyperthyroidism. J Clin Endocrinol Metab 40:33, 1975.

164. Okamura K[1], Sato K, Fujikawa M, Bandai S, Ikenoue H, Kitazono T. Remission after potassium iodide therapy in patients with Graves' hyperthyroidism exhibiting thionamide-associated side effects. J Clin Endocrinol Metab. 2014 Nov;99(11):3995-4002. doi: 10.1210/jc.2013-4466.

165.. Uchida T[1], Goto H, Kasai T, Komiya K, Takeno K, Abe H, Shigihara N, Sato J, Honda A, Mita T, Kanazawa A, Fujitani Y, Watada H. Therapeutic effectiveness of potassium iodine in drug-naïve patients with Graves' disease: a single-center experience. Endocrine. 2014 Nov;47(2):506-11. doi: 10.1007/s12020-014-0171-8.

165.1. Yoshihara A[1], Noh JY[1], Watanabe N[1], Mukasa K[1], Ohye H[1], Suzuki M[1], Matsumoto M[1], Kunii Y[1], Suzuki N[1], Kameda T[1], Iwaku K[1], Kobayashi S[1], Sugino K[1], Ito K[1]. Substituting Potassium Iodide for Methimazole as the Treatment for Graves' Disease During the First Trimester May Reduce the Incidence of Congenital Anomalies: A Retrospective Study at a Single Medical Institution in Japan. Thyroid. 2015 Oct;25(10):1155-61. doi: 10.1089/thy.2014.058

166. Shanks RG, Hadden DR, Lowe DC, McDevitt DB, Montgomery DAD: Controlled trial of propranolol in thyrotoxicosis. Lancet 2:1969.

167. Mazzaferri EL, Reynolds JC, Young RL, Thomas CN, Parasi AF: Propranolol as primary therapy for thyrotoxicosis. Arch Intern Med 136:50, 1976.

168. Wiener L, Stout BD, Cox JW: Influence of beta sympathetic blockade with propranolol on the hemodynamics of hyperthyroidism. Am J Med 46:227, 1969.

.169. Saunders J, Hall SEH, Crowther A, Sonksen PH: The effect of propranolol on thyroid hormones and oxygen consumption in thyrotoxicosis. Clin Endocrinol 9:67, 1978.

170. Georges LP, Santangelo RP, Mackin JF, Canary JJ: Metabolic effects of propranolol in thyrotoxicosis. I. Nitrogen, calcium, and hydroxyproline. Metabolism 24:11, 1975.

171. Hadden DR, Montgomery DAD, Shanks RG, Weaver JA: Propranolol and iodine-131 in the management of thyrotoxicosis. Lancet 2:852, 1968.

172. Pimstone N, Marine N, Pimstone B: Beta-adrenergic blockade in thyrotoxic myopathy. Lancet 2:1219, 1968.

173. Smith CS, Howard NJ: Propranolol in treatment of neonatal thyrotoxicosis. J Pediatr 83:1046, 1973.

174. Rosenberg I: Thyroid storm. N Engl J Med 283:1052, 1970.

174.1. Fraser T, Green D. Weathering the storm: beta-blockade and the potential for disaster in severe hyperthyroidism. Emergency Med 13:376-380, 2001

174.2. Ikram H. Haemodynamic effects of beta-adrenergic blockade in hyperthyroid patients with and without heart failure. Br Med J 1:1505-1507, 1977.

175. Bewsher PD, Pegg CAS, Steward DJ, Lister DA, Michie W: Propranolol in the surgical management of thyrotoxicosis. Ann Surg 180:787, 1974.

176. Canary JJ, Schaaf M, Duffy BJ, Kyle LH: Effects of oral and intramuscular injection of reserpine in thyrotoxicosis. N Engl J Med 257:435, 1957.

177. Moncke C: Treatment of thyrotoxicosis with reserpine. Med Monatsschr Pharm 50:1742, 1955.

178. Lee WY, Bronsky D, Waldenstein SS: Studies of the thyroid and sympathetic nervous system interrelationships: Effect of guanethidine on manifestations of hyperthyroidism. J Clin Endocrinol Metab 22:879, 1962.

179. deGroot WJ, Leonard JJ, Paley HW, Johnson JE, Warren JV: The importance of autonomic integrity in maintaining the hyperkinetic circulatory dynamics of human hyperthyroidism. J Clin Invest 40:1033, 1961.

180. Dillion PT, Babe J, Meloni CR, Canary JJ: Reserpine in thyrotoxic crisis. N Engl J Med 283:1020, 1970.

181. DeGroot LJ, Hoye K: Dexamethasone suppression of serum T3 and T4. J Clin Endocrinol Metab 4:976, 1976.

182. Williams DE, Chopra IJ, Orgiazzi J, Solomon DH: Acute effects of corticosteroids on thyroid activity in Graves' disease. J Clin Endocrinol Metab 41:354, 1975.

183. Witztum JL, Jacobs LS, Schonfeld G: Thyroid hormone and thyrotropin levels in patients placed on colestipol hydrochloride. J Clin Endocrinol Metab 46:838-840, 1978.

184. Boehm TM, Burman KD, Barnes S, Wartofsky L: Lithium and iodine combination therapy for thyrotoxicosis. Acta Endocrinol 94:174, 1980.

185. Sharp B, Reed AW, Tamagna EI, Gefner DL, Hershman JM: Treatment of hyperthyroidism with sodium ipodate (oragraffin) in addition to propylthiouracil and propranolol. J Clin Endocrinol Metab 53:622, 1981. 186. Croxson MS, Hall TD, Nicoloff JT: Combination drug therapy for treatment of hyperthyroid Graves' disease. J Clin Endocrinol Metab 45:623, 1977.

187. Werner SC, Platman SR: Remission of hyperthyroidism (Graves' disease) and altered pattern of serum-thyroxine binding induced by prednisone. Lancet 2:752, 1965.

188. Wu S-Y, Shyh T-P, Chopra IJ, Solomon DH, Huang H-W, Chu P-C: Comparison of sodium ipodate (oragrafin) and propylthiouracil in early treatment of hyperthyroidism. J Clin Endocrinol Metab 54:630, 1982.

189. Shen D-C, Wu S-Y, Chopra IJ, Huang H-W, Shian L-R, Bian T-Y, Jeng C-Y, Solomon DH: Long term treatment of Graves' hyperthyroidism with sodium ipodate. J Clin Endocrinol Metab 61:723, 1985.189.1. Bal CS, Kumar A, Pandey RM. A randomized controlled trial to evaluate the adjuvant effect of lithium on radioiodine treatment of hyperthyroidism. Thyroid 12:399-405, 2002.

189.1 El Fassi D, Banga JP, Gilbert JA, Padoa C, Hegedüs L, Nielsen CH. Clin Immunol. 2009 Mar;130(3):252-8 Treatment of Graves' disease with rituximab specifically reduces the production of thyroid stimulating autoantibodies.

189.2 Heemstra KA, Toes RE, Sepers J, Pereira AM, Corssmit EP, Huizinga TW, Romijn JA, Smit JW.Eur J Endocrinol. 2008 Nov;159(5):609-15 Rituximab in relapsing Graves' disease, a phase II study.

189.3 El Fassi D, Nielsen CH, Junker P, Hasselbalch HC, Hegedüs L. Systemic adverse events following rituximab therapy in patients with Graves' disease.J Endocrinol Invest. 2011 Jul-Aug;34(7):e163-7.

189.4 Neumann S, Eliseeva E, McCoy JG, Napolitano G, Giuliani C, Monaco F, Huang W, Gershengorn MCA new small-molecule antagonist inhibits Graves' disease antibody activation of the TSH receptor.J Clin Endocrinol Metab. 2011 Feb;96(2):548-54. Epub 2010 Dec 1.

190. Klementschitsch P, Shen K-L, Kaplan EL: Reemergence of thyroidectomy as treatment for Graves' disease. Surg Clin North Am 59:35, 1979.

191. Palit TK, Miller CC, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: A meta-analysis. J Surg Res 90:161-165, 2000.

192. Winsa B, Rastad J, Akerstrom G, Johansson H, Westermark K, Karlsson FA. Retrospective evaluation of the effect of subtotal and total thyroidectomy in the treatment of Graves' disease with and without endocrine ophthalmopathy. Thesis, Brita Winsa, The University of Upsala, Upsala, Sweden, 1993.

193. Sundaresh V[1], Brito JP, Wang Z, Prokop LJ, Stan MN, Murad MH, Bahn RS. Comparative effectiveness of therapies for Graves' hyperthyroidism: a systematic review and network meta-analysis. J Clin Endocrinol Metab. 2013 Sep;98(9):3671-7. doi: 10.1210/jc.2013-1954.

194. Hamilton RD, Mayberry WE, McConahey WM, Hanson KC: Ophthalmopathy of Graves' disease: A comparison between patients treated surgically and patients treated with radioiodide. Mayo Clin Proc 42:812, 1967.

195. Stocker DJ, Foster SS, Solomon BL, Shriver CD, Burch HB. Thyroid cancer yield in patients with Graves' disease selected for surgery on the basis of cold scintiscan defects. Thyroid 12:305, 2002.

196. Bogazzi F, Miccoli P, Berti P, Cosci C, Brogioni S, Aghini-Lombardi F, Materazzi G, Bartalena L, Pinchera A, Braverman LE, Martino E. Preparation with iopanoic acid rapidly controls thyrotoxicosis in patients with amiodarone-induced thyrotoxicosis before thyroidectomy. Surgery 132:1114-1117, 2002.

197: Scholz GH, Hagemann E, Arkenau C, Engelmann L, Lamesch P, Schreiter D,Schoenfelder M, Olthoff D, Paschke R. Is there a place for thyroidectomy in older patients with thyrotoxic storm and cardiorespiratory failure?Thyroid. 2003 Oct;13(10):933-40.

198 Erbil Y, Ozluk Y, Giriş M, Salmaslioglu A, Issever H, Barbaros U, Kapran Y, Ozarmağan S, Tezelman S. Effect of lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease.J Clin Endocrinol Metab. 2007 Jun;92(6):2182-9

199. Feek CM, Stewart J, Sawers A, Irvine WJ, Beckett GJ, Ratcliffe WA, Toft AD: Combination of potassium iodide and propranolol in preparation of patients with Graves' disease for thyroid surgery. N Engl J Med 302:883, 1980.

200. Bewsher BD, Pegg CAS, Stewart DJ, Lister DA, Michie W: Propranolol in the surgical management of thyrotoxicosis. Ann Surg 180:787, 1974.

201. Toft AD, Irvine WJ, Campbell RWF: Assessment by continuous cardiac monitoring of minimum duration of preoperative propranolol treatment in thyrotoxic patients. Clin Endocrinol 5:195, 1976.

202. Kulkarni RS, Braverman LE, Patwardhan NA. Bilateral cervical plexus block for thyroidectomy and parathyroidectomy in healthy and high risk patients. J Endocrinol Invest 19:714-718, 1996.

203. Taylor GW, Painter NS: Size of the thyroid remnant in partial thyroidectomy for toxic goiter. Lancet 1:287, 1962.

204. Sugino K, Mimura T, Toshima K, Iwabuchi H, Kitamura Y, Kawano M, Ozaki O, Ito K. Follow-up evaluation of patients with Graves' disease treated by subtotal thyroidectomy and risk factor analysis for post-operative thyroid dysfunction. J Endocrinol Invest 16:195-199, 1993.

205. Ozaki O, Ito K, Mimura T, Sugino K, Ito K. Factors affecting thyroid function after subtotal thyroidectomy for Graves' disease: Case control study by remnant-weight matched-pair analysis. Thyroid 7:555, 1997.

206. Miccoli P, Vitti P, Rago T, Iacconi P, Bartalena L, Bogazzi F, Fiore E, Valeriano R, Chiovato L, Rocchi R, Pinchera A. Surgical treatment of Graves' disease: Subtotal or total thyroidectomy? Surgery 120:1020-1025, 1996

207. Menconi F, Marinò M, Pinchera A, Rocchi R, Mazzi B, Nardi M, Bartalena L, Marcocci C.Effects of total thyroid ablation versus near-total thyroidectomy alone on mild to moderate Graves' orbitopathy treated with intravenous glucocorticoids. J Clin Endocrinol Metab. 2007 May;92(5):1653-8.

208. Wilhelm SM, McHenry CR.World J Surg. 2009 Dec 23. [Total Thyroidectomy Is Superior to Subtotal Thyroidectomy for Management of Graves' Disease in the United States.

209. Sawyers JL, Martin CE, Byrd BF Jr, Rosenfield L: Thyroidectomy for hyperthyroidism. Ann Surg 175:939, 1972.

210. Farnell MB, van Heerden JA, McConahey WM, Carpenter HA, Wolff LH Jr: Hypothyroidism after thyroidectomy for Graves' disease. Amer J Surg 142:535, 1981

211 Buchanan WW, Koutras DA, Crooks J, Alexander WD, Brass W, Anderson JR, Goudie RB, Gray KG: The clinical significance of the complement-fixation test in thyrotoxicosis. J Endocrinol 24:115, 1962.

212. Yamashita H, Noguchi S, Tahara K, Watanabe S, Uchino S, Kawamoto H, Toda M, Murakami N. Postoperative tetany in patients with Graves' disease: A risk factor analysis. Clin Endocrinol 47:71-77, 1997.

213. Michie W, Duncan T, Hamer-Hodges DW, Bewsher PD, Stowers JM, Pegg CAS, Hems G, Hedley AJ: Mechanism of hypocalcemia after thyroidectomy for thyrotoxicosis. Lancet 1:508, 1971.

214. Hardisty CA, Talbot CH, Munro DS: The effect of partial thyroidectomy for Graves' disease on serum long-acting thyroid stimulator protector (LATS-P). Clin Endocrinol 14:181, 1981.

215. Bech K, Feldt-Rasmussen U, Bliddal H, Date J, Blichert-Toft M: The acute changes in thyroid stimulating immunoglobulins, thyroglobulin, and thyroglobulin antibodies following subtotal thyroidectomy. Clin Endocrinol 16:235, 1982.

216. Werga-Kjellman P, Zedenius J, Tallstedt L, Traisk F, Lundell G, Wallin G. Surgical treatment of hyperthyroidism: A ten year experience. Thyroid 11:187-192, 2001.

217. Fukino O, Tamai H, Fujii S, Ohsako N, Matsubayashi S, Kuma K, Nagataki S: A study of thyroid function after subtotal thyroidectomy for Graves' disease: particularly on TRH tests, T3 suppression tests and antithyroid antibodies in euthyroid patients. Acta Endocrinol 103:28-33, 1983.

218. Hedley AJ, Hall R, Amos J, Michie W, Crooks J: Serum-thyrotropin levels after subtotal thyroidectomy for Graves' disease. Lancet 1:455, 1971.

219 Segni M, Leonardi E, Mazzoncini B, Pucarelli I, Pasquino AM. 1999 Special features of Graves' disease in early childhood. Thyroid 9:871.

220. Perrild H, Jacobsen BB. Thyrotoxicosis in childhood. Europ J Endocrinol 134:678-679, 1996

221. Starr P, Jaffe HL, Oettinger L Jr: Late results of 131-I treatment of hyperthyroidism in seventy-three children and adosescents. J Nucl Med 5:81, 1964.

222. Kogut MD, Kaplan SA, Collipp PJ, Tiamsic T, Boyle D: Treatment of hyperthyroidism in children. N Engl J Med 272:217, 1965.

223: Read CH Jr, Tansey MJ, Menda Y. A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. J Clin Endocrinol Metab. 2004 Sep;89(9):4229-33

224. Rivkees SA, Sklar C, Freemark M. The management of Graves' disease in children, with special emphasis on radioiodine treatment. J Clin Endocrinol Metab 83:3767-3776.

224.1 Rivkees SA, Controversies in the management of Graves' disease in children. J Endocrinol Invest 2016 Nov;39(11):1247-1257

25. Barrio R, Lopez-Capape M, Martinez-Badas I, Carrillo A, Moreno JC, Alonso M.Graves' disease in children and adolescents: response to long-term treatment.Acta Paediatr. 2005 Nov;94(11):1583-9

226. Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C; French Childhood Graves' Disease Study Group Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study.J Clin Endocrinol Metab. 2012 Jan;97(1):110-9.

227. Jevalikar G, Solis J, Zacharin M. Long-term outcomes of pediatric Graves' disease. J Pediatr Endocrinol Metab. 2014 Nov;27(11-12):1131-6. doi: 10.1515/jpem-2013-0342.

228. Rudberg C, Johansson H, Akerstrom G, Tuvemo T, Karlsson FA. Graves' disease in children and adolescents. Late results of surgical treatment. Europ J Endocrinol 134:710-715, 1996.

229. Soreide JA, van Heerden JA, Lo CY, Grant CS, Zimmerman D, Ilstrup DM. Surgical treatment of Graves' disease in patients younger than 18 years. World J Surg 20:794-800, 1996

230 Sherman J, Thompson GB, Lteif A, Schwenk WF 2nd, van Heerden J, Farley DR, Kumar S, Zimmerman D, Churchward M, Grant CS.Surgical management of Graves disease in childhood and adolescence: an institutional experience.Surgery. 2006 Dec;140(6):1056-61

231. Okuno A, Yano K, Inyaku F, Suzuki Y, Sanae N, Kumai M, Naitoh Y. Pharmacokinetics of methimazole in children and adolescents with Graves' disease. Acta Endocrinol (Copenh) 115:112-118, 1987.

232. Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C; French Childhood Graves' Disease Study Group Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study.J Clin Endocrinol Metab. 2012 Jan;97(1):110-9.

233 Luton D, Le Gac I, Vuillard E, Castanet M, Guibourdenche J, Noel M, Toubert ME, Leger J, Boissinot C, Schlageter MH, Garel C, Tebeka B, Oury JF, Czernichow P, Polak M.Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring.J Clin Endocrinol Metab. 2005 Nov;90(11):6093-8

234. Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R. 1999 Methimazole embryopathy: delineation of the phenotype. Amer J Medical Genet. 83:43-46.

235. Cheek JH, Rezvani I, Goodner D, Hopper B: Prenatal treatment of thyrotoxicosis to prevent intrauterine growth retardation. Obstet Gynecol 60:122, 1982.

236. Zimmerman D. 1999 Fetal and neonatal hyperthyroidism. Thyroid 9:727.

237. Hollingsworth DR, Mabry CC, Eckerd JM: Hereditary aspects of Graves' disease in infancy and childhood. J Pediatr 81:446, 1972.